Wisconsin Department of Safety and Professional Services
Division of Policy Development
4822 Madison Yards Way, 2nd Floor
PO Box 8366
Madison WI 53708-8366

Phone: 608-266-2112
Web: http://dsps.wi.gov
Email: dsps@wisconsin.gov

Tony Evers, Governor
Dawn B. Crim, Secretary

VIRTUAL/TELECONFERENCE
PHARMACY RULES COMMITTEE
of the
PHARMACY EXAMINING BOARD
Virtual, 4822 Madison Yards Way, Madison, WI 53705
Contact: Christine Poleski (608) 266-2112
March 4, 2021

Notice: The following agenda describes the issues that the Committee plans to consider at the meeting. At the time of the meeting, items may be removed from the agenda. ***A quorum of the Board may be present during any committee meetings.***

AGENDA

8:30 A.M.

OPEN SESSION – CALL TO ORDER

A. Approval of Agenda (1)

B. Administrative Rule Matters – Discussion and Consideration (2)

1) Phar 8, Relating to Controlled Substances Requirements **(3-162)**
2) Phar 15, Relating to Compounding **(163-222)**
3) Pending or Possible Rulemaking Projects

C. Public Comments

ADJOURNMENT

****

MEETINGS AND HEARINGS ARE OPEN TO THE PUBLIC, AND MAY BE CANCELLED WITHOUT NOTICE.

Times listed for meeting items are approximate and depend on the length of discussion and voting. All meetings are held at 4822 Madison Yards Way, Madison, Wisconsin, unless otherwise noted. In order to confirm a meeting or to request a complete copy of the board's agenda, please call the listed contact person. The board may also consider materials or items filed after the transmission of this notice. Times listed for the commencement of disciplinary hearings may be changed by the examiner for the convenience of the parties. Requests for interpreters for the deaf or hard of hearing, or other accommodations, are considered upon request by contacting the Affirmative Action Officer, 608-266-2112, or the Meeting Staff at 608-266-5439.

State of Wisconsin
Department of Safety & Professional Services

AGENDA REQUEST FORM

1) Name and title of person submitting the request:	2) Date when request submitted:
Kassandra Walbrun	2/19/2021
	Items will be considered late if submitted after 12:00 p.m. on the deadline date which is 8 business days before the meeting

3) Name of Board, Committee, Council, Sections:

Pharmacy Examining Board – Rules Committee

4) Meeting Date:	5) Attachments:	**6)** How should the item be titled on the agenda page?
3/04/2021	☒ Yes ☐ No	Administrative Rule Matters – Discussion and Consideration 1. Phar 8, related to Controlled Substances Requirements 2. Phar 15, related to Compounding

7) Place Item in:	8) Is an appearance before the Board being scheduled? *(If yes, please complete Appearance Request for Non-DSPS Staff)*	9) Name of Case Advisor(s), if required:
☒ Open Session ☐ Closed Session	☐ Yes ☒ No	

10) Describe the issue and action that should be addressed:

1. Review draft rule. Discuss follow up questions regarding state authority and federal rules (2 docs - chart of differences, and draft rule changes, pdfs)
2. Review draft rule. (pdf)

11) Authorization

Kassandra Walbrun — *2/19/2021*

Signature of person making this request — Date

Supervisor (if required) — Date

Executive Director signature (indicates approval to add post agenda deadline item to agenda) Date

Chapter Phar 8
REQUIREMENTS FOR CONTROLLED SUBSTANCES

Phar 8.01 Federal registration and compliance with federal, state, and local laws and regulations. (1) FEDERAL REGISTRATION REQUIRED. In order to possess, manufacture, distribute, dispense, or conduct research with controlled substances in this state, pharmacies and pharmacists shall register with the drug enforcement administration as required under federal law.

(2) CONTROLLED SUBSTANCES AUTHORIZATION UNDER FEDERAL REGISTRATION. As provided under s. 961.32 (1m) (a), Stats., a pharmacy or pharmacist registered under federal law to manufacture, distribute, dispense, or conduct research with controlled substances may possess, manufacture, distribute, dispense, or conduct research with those substances in this state to the extent authorized by their federal registration and in conformity with the provisions of ch. 961, Stats.

(3) COMPLIANCE WITH LAWS AND REGULATIONS. Failure to register or otherwise comply with applicable federal, state, and local laws and regulations relating to possessing, manufacturing, distributing, dispensing, or conducting research with controlled substances constitutes unprofessional conduct for purposes of s. 450.10, Stats.

Phar 8.02 Notification of suspicious orders of controlled substances. A pharmacy shall, at the time of providing required notification to the drug enforcement administration of a suspicious order or series of orders for controlled substances, provide notification to the board. The notification to the board shall include all information provided in the notification to the drug enforcement administration.

Phar 8.03 Identification card requirements under s. 450.11 (1b), Stats. (1) DEFINITION. In s. 450.11 (1b) (e) 3., Stats., "health care facility" means a facility, as defined in s. 647.01 (4), Stats.; any hospital, nursing home, community−based residential facility, county home, county infirmary, county hospital, county mental health complex, or other place licensed or approved by the department of health services under s. 49.70, 49.71, 49.72, 50.03, 50.032, 50.033, 50.034, 50.35, 51.08, or 51.09, Stats.; a facility under s. 45.50, 51.05, 51.06, 233.40, 233.41, 233.42, or 252.10, Stats.; and a hospice facility under s. 50.90 (1) (c), Stats.

(2) RECORDKEEPING. Records required under s. 450.11 (1b) (bm), Stats., shall be maintained for at least 5 years from the date the drug was dispensed, or, for a record that is subject to s. 961.385, Stats., until the name of a person to whom a drug is dispensed is delivered to the controlled substances board under s. 961.385, Stats., whichever is sooner.

Phar 8.04 Dispensing schedule II controlled substances in emergency situations under s. 961.38 (2), Stats. (1) DEFINITION. For purposes of dispensing a schedule II controlled substance under s. 961.38 (2), Stats., "emergency situation" means a situation in which the prescribing practitioner determines all of the following:

(a) Immediate administration of the schedule II controlled substance is necessary for proper treatment of the patient.

(b) No appropriate alternative treatment is available, including the administration of a drug that is not a schedule II controlled substance.

(c) It is not reasonably possible for the prescribing practitioner to provide a written prescription order to be presented to the pharmacist prior to dispensing.

(2) RECORDKEEPING. Records of prescriptions for schedule II controlled substances dispensed under s. 961.38 (2), Stats., shall be retained and available for inspection by authorized persons for at least 5 years from the date of such records.

(3) REQUIRED NOTIFICATION. A dispensing pharmacist shall, at the time of providing required notification to the drug enforcement administration of the failure of a prescribing practitioner to deliver a written prescription within 7 days after authorizing an emergency oral prescription for a schedule II controlled substance, provide notification to the board. The notification to the board shall include all information provided in the notification to the drug enforcement administration.

Pharmacist's Manual

An Informational Outline of the Controlled Substances Act

Revised 2020

Timothy J. Shea
Acting Administrator
Drug Enforcement Administration

William T. McDermott
Assistant Administrator
Diversion Control Division

Loren T. Miller
Chief, Policy Section

This Pharmacist's Manual has been prepared by the Drug Enforcement Administration, Diversion Control Division, as a guide to assist pharmacists in their understanding of the Federal Controlled Substances Act and its implementing regulations as they pertain to the pharmacy profession.

The 2020 edition replaces all previous editions of the Pharmacist's Manual issued by the Drug Enforcement Administration, both hard copy and electronic.

Guidance documents, like this document, are not binding and lack the force and effect of law, unless expressly authorized by statute or expressly incorporated into a contract, grant, or cooperative agreement. Consistent with Executive Order 13891 and the Office of Management and Budget implementing memoranda, the Department will not cite, use, or rely on any guidance document that is not accessible through the Department's guidance portal, or similar guidance portals for other Executive Branch departments and agencies, except to establish historical facts. To the extent any guidance document sets out voluntary standards (e.g., recommended practices), compliance with those standards is voluntary, and noncompliance will not result in enforcement action. Guidance documents may be rescinded or modified in the Department's complete discretion, consistent with applicable laws.

EO-DEA154, October 8, 2020, DEA-DC-046

Table of Contents

SECTION I – INTRODUCTION

Disclaimer

This Pharmacist's Manual is intended to summarize and explain the basic requirements for prescribing, administering, and dispensing controlled substances under the Controlled Substances Act (CSA), Title 21, United States Code (21 U.S.C.) 801-971 and DEA regulations, Title 21, Code of Federal Regulations (21 CFR), Parts 1300 to End. This Pharmacist's Manual is not a legal document. It is a guidance document that provides statutory and regulatory requirements as well as recommended practices. Statutory and regulatory requirements use language such as "must," "shall," or "required" and will include statutory and/or regulatory citation(s). Recommended practices in this Pharmacist's Manual are voluntary and use language such as "should" or "recommend" to identify these suggestions. Readers should refer to the most current copy of the CSA, the Drug Addiction Treatment Act of 2000 (DATA), the Combat Methamphetamine Epidemic Act of 2005, the Ryan Haight Online Pharmacy Consumer Protection Act of 2008, the Secure and Responsible Drug Disposal Act of 2010, the Comprehensive Addiction and Recovery Act of 2016 (CARA), the SUPPORT for Patients and Communities Act of 2018 (the SUPPORT Act), the CFR, and Federal Register notices to obtain the most complete and accurate up-to-date statutory and regulatory information. These publications are available on the Internet through the U.S. Government Publishing Office website, https://www.govinfo.gov, which provides information by section, citation, and keywords. Any modifications to the law or regulations will be posted on DEA's Diversion Control Division website at www.DEAdiversion.usdoj.gov.

If there are errors in this Pharmacist's Manual, please send notification to the following:

ODLP@usdoj.gov

or

Drug Enforcement Administration
Diversion Control Division
Attn: Policy Section/DPY
8701 Morrissette Drive
Springfield, VA 22152

Inquiries regarding topics within this document may be addressed to your local DEA Diversion Field Office (Appendix K) or the address above.

Printed copies of the complete regulations implementing the CSA (21 CFR Part 1300 to End) may be obtained from:

Superintendent of Documents
U.S. Government Publishing Office
Washington, DC 20402

Both the CFR and the Federal Register (which includes proposed and final rules implementing the CSA) are available on the Internet through the U.S. Government Publishing Office website. This website, which provides information by section, citation, and keywords, can be accessed at:

https://www.govinfo.gov

Unofficial copies of pertinent CFR citations and this Pharmacist's Manual may be found on the internet at DEA's Diversion website (Click on "Resources" then "Publications and Manuals"):

www.DEAdiversion.usdoj.gov

Should any pertinent provisions of the law or regulations be modified in the future, DEA will issue a revised electronic version of this document, which will be posted at DEA's Diversion website.

Inquiries regarding topics within this document may be addressed to your local DEA Diversion Field Office (Appendix K) or the address above.

Authorization for Public Dissemination

Message from the Assistant Administrator

The Drug Enforcement Administration is pleased to provide you with the 2020 edition of the Pharmacist's Manual to assist you in understanding the provisions of the Controlled Substances Act (CSA) and its implementing regulations. This Pharmacist's Manual will answer questions you may encounter in the practice of pharmacy and provide guidance in complying with CSA regulations. This edition has been updated to include information on the Secure and Responsible Drug Disposal Act of 2010, the Comprehensive Addiction and Recovery Act of 2016, and the SUPPORT for Patients and Communities Act of 2018.

Your role in the proper dispensing of controlled substances is critical to the health of patients and helps protect society against drug abuse and diversion. Your compliance with the CSA and its objectives is a powerful resource for protecting the public health, assuring patient safety, and preventing the diversion of controlled substances and drug products containing listed chemicals.

Sincerely,

William T. McDermott
Assistant Administrator
Diversion Control Division

Preface

The Drug Enforcement Administration (DEA) was established in 1973 to serve as the primary agency responsible for the enforcement of federal drug laws. The Controlled Substances Act (CSA) and its implementing regulations establish federal requirements regarding both illicit and licit controlled substances. With respect to pharmaceutical controlled substances, DEA's responsibility is twofold: to prevent diversion and abuse of these substances while ensuring an adequate and uninterrupted supply is available to meet the country's legitimate medical, scientific, and research needs. In carrying out this mission, DEA works closely with state and local authorities and other federal agencies.

Under the framework of the CSA, all controlled substance transactions take place within a "closed system" of distribution established by Congress. Within this "closed system," all legitimate handlers of controlled substances—manufacturers, distributors, physicians, pharmacies, and others—must be registered with DEA (unless exempt) and maintain strict accounting for all controlled substance transactions.

To carry out this mission effectively, DEA seeks to educate its registrants regarding their legal obligations. It is DEA's goal to maintain a positive working relationship with all of its registrants, including pharmacies. DEA understands that it can best serve the public interest by working with the pharmacy community to prevent the diversion of pharmaceutical controlled substances and scheduled listed chemical products (SLCPs) into the illicit market.

Federal controlled substance laws are designed to function in tandem with state controlled substance laws. DEA works in cooperation with state professional licensing boards and state and local law enforcement officials to make certain that pharmaceutical controlled substances are prescribed, administered, and dispensed for a legitimate medical purpose in the usual course of professional practice. Within this framework, the majority of investigations into possible violations of controlled substance laws are carried out by state authorities. DEA focuses its investigations on cases involving violators of the highest level or most significant impact.

In the event a state board revokes the license of a pharmacy, DEA will request a voluntary surrender of the pharmacy's DEA registration. If the pharmacy refuses to surrender its registration, DEA will seek administrative action to revoke its DEA registration based on lack of state authorization. Additional administrative remedies that may be utilized to correct a lack of compliance include a letter of admonition or an administrative hearing. DEA may also pursue civil or criminal sanctions if there is sufficient evidence to justify a prosecution. All such actions are designed to protect the public health and safety.

In addition to the diversion of controlled substances, DEA is concerned with the diversion of certain chemicals used in the clandestine manufacture of controlled substances. Chemicals such as ephedrine and pseudoephedrine contained in over-the-counter and prescription substances are immediate precursors used in the illicit manufacture of methamphetamine and amphetamine. These products may be purchased or stolen from retail outlets, including pharmacies, for use in clandestine laboratories.

Pharmacies that sell over-the-counter products containing ephedrine and pseudoephedrine must be "self-certified" as required by the Combat Methamphetamine Epidemic Act of 2005 (CMEA). The CMEA created a new category of products designated as SLCPs. SLCPs are products containing ephedrine, pseudoephedrine, or phenylpropanolamine that may be marketed or distributed lawfully in the United States as a non-prescription drug under the Food, Drug, and Cosmetic Act. The retail provisions of the CMEA went into effect on September 30, 2006 and require, among other things, employee training, self-certification, placement of SLCPs out of customer reach, required identification, sales logbooks, and the use of sales and purchase limits.

DEA and the pharmacy profession have strong common interests in the appropriate use of controlled substances and SLCPs. An effective working relationship to ensure compliance with CSA requirements will continue to produce lasting benefits on a national scale.

SECTION II – SCHEDULES OF CONTROLLED SUBSTANCES

The drugs and other substances that are considered controlled substances under the CSA are divided into five schedules. A listing of the substances and their schedules is found in DEA regulations at 21 CFR 1308.11-15. A controlled substance is placed in its respective schedule based on whether it has a currently accepted medical use in treatment in the United States and its relative abuse potential and likelihood of causing dependence. 21 U.S.C. 812(b). Some examples of controlled substances in each schedule are outlined below.

NOTE: Drugs listed in schedule I have no currently accepted medical use in treatment in the United States and, therefore, may not be prescribed, administered, or dispensed for medical use. 21 U.S.C. 812(b)(1). In contrast, drugs listed in schedules II-V have some accepted medical use and may be prescribed, administered, or dispensed for medical use. 21 U.S.C. 812(b)(2)-(5).

Schedule I Controlled Substances

Substances in this schedule have a high potential for abuse, have no currently accepted medical use in treatment in the United States, and there is a lack of accepted safety for use of the drug or other substance under medical supervision. 21 U.S.C. 812(b)(1).

Some examples of substances listed in schedule I are: heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), peyote, methaqualone, and 3,4-methylenedioxymethamphetamine ("MDMA"). 21 U.S.C. 812(c), schedule I and 21 CFR 1308.11.

Schedule II Controlled Substances

Substances in this schedule have a high potential for abuse which may lead to severe psychological or physical dependence, and have a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. 21 U.S.C. 812(b)(2).

Examples of schedule II narcotics include morphine, codeine, and opium. Other schedule II narcotic substances and their common name brand products include: any combination products containing hydrocodone (Maxidone, Zydone, Vicodin, Lortab, Vicoprofen, Reprexain), hydromorphone (Dilaudid), methadone (Dolophine), meperidine (Demerol), oxycodone (OxyContin), and fentanyl (Sublimaze or Duragesic).

Examples of schedule II stimulants include: amphetamine (Dexedrine, Adderall), methamphetamine (Desoxyn), methylphenidate (Ritalin), and lisdexamfetamine

(Vyvanse). Other schedule II substances include: cocaine, amobarbital, and glutethimide. 21 U.S.C. 812(c), schedule II and 21 CFR 1308.12.

Schedule III Controlled Substances

Substances in this schedule have a potential for abuse less than substances in schedules I or II, have a currently accepted medical use in treatment in the United States, and abuse may lead to moderate or low physical dependence or high psychological dependence. 21 U.S.C. 812(b)(3).

Examples of schedule III narcotics include morphine combination products containing not more than 50 milligrams of morphine per 100 milliliters or per 100 grams, with one or more active, non-narcotic ingredients in recognized therapeutic amounts, and products containing not more than 90 milligrams of codeine per dosage unit with an equal or greater quantity of an isoquinoline alkaloid of opium (Tylenol with codeine). Also included are buprenorphine products used to treat opioid addiction.

Examples of schedule III non-narcotics include benzphetamine (Didrex), phendimetrazine, ketamine, and anabolic steroids such as oxandrolone (Oxandrin). 21 U.S.C. 812(c), schedule III and 21 CFR 1308.13.

Schedule IV Controlled Substances

Substances in this schedule have a low potential for abuse relative to substances in schedule III, have a currently accepted medical use in treatment in the United States, and abuse may lead to limited physical dependence or psychological dependence relative to substances in schedule III. 21 U.S.C. 812(b)(4).

An example of a schedule IV narcotic is Tramadol (Ultram).

Other schedule IV substances include: alprazolam (Xanax), clonazepam (Klonopin), clorazepate (Tranxene), diazepam (Valium), lorazepam (Ativan), midazolam (Versed), temazepam (Restoril), and triazolam (Halcion). 21 U.S.C. 812(c), schedule IV and 21 CFR 1308.14.

Schedule V Controlled Substances

Substances in this schedule have a low potential for abuse relative to substances listed in schedule IV, have a currently accepted medical use in treatment in the United States, and abuse may lead to limited physical dependence or psychological dependence relative to substances in schedule IV. They consist primarily of preparations containing limited quantities of certain narcotics. 21 U.S.C. 812(b)(5). These are generally used

for antitussive, antidiarrheal, and analgesic purposes. 21 U.S.C. 812(c), schedule V and 21 CFR 1308.15.

Examples include cough preparations containing not more than 200 milligrams of codeine per 100 milliliters or per 100 grams (Robitussin AC and Phenergan with Codeine).

Scheduled Listed Chemical Products (SLCP)

An SLCP is defined as a product that contains ephedrine, pseudoephedrine, or phenylpropanolamine and may be marketed or distributed lawfully in the United States under the Federal Food, Drug, and Cosmetic Act as a non-prescription drug. 21 U.S.C. 802(45) and 21 CFR 1300.02(b).

SECTION III – REGISTRATION REQUIREMENTS

New Pharmacy Registration

Every pharmacy that dispenses a controlled substance must be registered with DEA. 21 U.S.C. 823(f) and 21 CFR 1301.11(a). A state license must be obtained. 21 U.S.C. 823(f). Federal agencies are exempt from the state license requirement.

To register as a new pharmacy, the DEA Form 224 must be completed. 21 CFR 1301.13(e)(1)(iv). The cost of the application fee is indicated on the application form. The Certificate of Registration (DEA Form 223) must be maintained at the registered location and kept available for official inspection. 21 CFR 1301.35(c). If a person owns and operates more than one pharmacy, each place of business must be separately registered with DEA. 21 CFR 1301.12(a).

The DEA Form 224 should be completed online.

A paper version of the DEA Form 224 may be requested by writing to:

Drug Enforcement Administration
Diversion Control Division
Attn: Registration & Program Support Section/DRR
P.O. Box 2639
Springfield, VA 22152-2639

If a pharmacy needs a duplicate Certificate of Registration, a copy may be requested online, or by contacting DEA Headquarters at 1-800-882-9539, or via e-mail at DEA.Registration.Help@usdoj.gov.

Renewal of Pharmacy Registration

A pharmacy registration must be renewed every three years utilizing a DEA Form 224a. 21 CFR 1301.13(e)(1)(iv). The most expeditious method to renew a DEA registration is online, but it may be completed by paper application no earlier than 60 days prior to the current expiration date. 21 CFR 1301.13(b). The information from the existing DEA Form 223 is needed to login to initiate the renewal process. The cost of the non-refundable application fee is indicated on the application.

Pharmacies will receive a renewal notification at the mailing address associated with the current registration approximately 60 days prior to the expiration date in accordance with 21 CFR 1301.13(e)(3). DEA will subsequently send an electronic reminder to the email address associated with DEA registration approximately 20 days prior to the expiration date if the renewal has not been received or completed.

If a pharmacy wishes to obtain a paper DEA Form 224a, the pharmacy may send a request via email to DEA.Registration.Help@usdoj.gov or call 1-800-882-9539.

The completed renewal application should be mailed to the following address:

Drug Enforcement Administration
Diversion Control Division
Attn: Registration & Program Support Section/DRR
P.O. Box 2639
Springfield, VA 22152-2639

The following policy and procedures with respect to renewal and reinstatement of a DEA registration are as follows:

1. If a **renewal application** is submitted in a timely manner **prior to expiration**, the practitioner may continue operations, authorized by the registration, beyond the expiration date until final action is taken on the application. 21 CFR 1301.13(b), 1301.36(i).

2. DEA policy allows the reinstatement of an expired registration for one calendar month after the expiration date. If the registration is not renewed within that calendar month, an application for a new DEA registration is required.

3. Regardless of whether a registration is reinstated within the calendar month after expiration, federal law prohibits the handling of controlled substances for any period of time under an expired registration. 21 CFR 1301.13(a),(e).

For additional information or questions, contact DEA Registration Section at 1-800-882-9539 or DEA.Registration.Help@usdoj.gov.

Affidavit for Renewal of Retail Chain Pharmacy Registration

Corporations that own or operate a chain of pharmacies may submit a single DEA Form 224b, Retail Pharmacy Registration Affidavit for Chain Renewal. This affidavit, along with a list of the corporation's registrations, is provided in lieu of a separate registration application for each pharmacy registration. No registration may be issued unless the completed affidavit is received by DEA. The corporation should retain a copy of this affidavit with their readily retrievable records for the duration of the registrations covered by the affidavit. A responsible individual must answer the questions listed on the affidavit on behalf of the corporation as they pertain to each registrant.

DEA requests corporations with 50 or more retail pharmacy registrations to enroll the chain renewal program. The corporation would need to send a spreadsheet with their DEA registration information. Then DEA will create the chain indicator number and

send them back with the renewal letter and an affidavit. Chain renewal information can be found on the DEA website:
https://www.deadiversion.usdoj.gov/drugreg/chain_renewal.htm

The original affidavit along with the registration application fee and the list of registrations should be mailed to:

Registration Chain Renewal
Drug Enforcement Administration
Diversion Control Division
Attn: Registration & Program Support Section/DRR
P.O. Box 2639
Springfield, VA 22152-2639

Change of Business Address

Every registrant under 21 U.S.C. 801-904 shall be required to report any change of professional or business address in accordance with DEA regulations. 21 U.S.C. 827(h). Before moving to a new physical location, a pharmacy should first request a modification of registration. Modifications are handled in the same manner as applications and must be approved by DEA. 21 CFR 1301.51(a). A modification of registration can be requested online at www.DEAdiversion.usdoj.gov or in writing to the local DEA Registration Program Specialist (Appendix K) responsible for the area in which the pharmacy is or will be located. The request must contain the registrant's name, address, and registration number as printed on the Certificate of Registration; the new name or address; and a signature in accordance with 21 CFR 1301.13(j). If the change of address involves a change in state, the proper state issued license and, if applicable, controlled substances registration must be obtained prior to the approval of modification of the federal registration. 21 U.S.C. 823(f). If the modification is approved, DEA will issue an updated Certificate of Registration and, if requested, new schedule II order forms (DEA Form 222). The registrant should maintain the new certificate with the old certificate until expiration. A Renewal Application for Registration (DEA Form 224a) will only be sent to the registrant's mailing address on file with DEA. It will not be forwarded.

Termination of Registration

A pharmacy that discontinues business activities either completely, or only regarding controlled substances, must return its DEA registration certificate and unused official order forms (DEA Form 222) to the local DEA Registration Program Specialist (Appendix K). 21 CFR 1301.52(c). In addition, DEA may ask for the location where inventories, prescriptions, and other required controlled substance records will be stored during the requisite two-year retention period.

Unwanted controlled substances in the pharmacy's possession must be disposed of in accordance with DEA regulations (See *Section X, Transfer or Disposal of Controlled Substances.*)

Transfer of Business

Pursuant to 21 CFR 1301.52(d), a pharmacy registrant that desires to transfer its business operations to another pharmacy registrant must submit in person or by registered or certified mail, return receipt requested, to the Special Agent in Charge in his or her area, at least 14 days in advance of the date of the proposed transfer (unless the Special Agent in Charge waives this time limitation in individual instances), the following information:

1. The name, address, registration number, and authorized business activity of the registrant discontinuing the business (registrant-transferor);

2. The name, address, registration number, and authorized business activity of the person acquiring the business (registrant-transferee);

3. Whether the business activities will be continued at the location registered by the person discontinuing business, or moved to another location (if the latter, the address of the new location should be listed); and

4. The date on which the transfer of controlled substances will occur.

On the day the controlled substances are transferred, a complete inventory must be taken in accordance with 21 CFR 1304.11 which documents the drug name, dosage form, drug strength, quantity, and date transferred. 21 CFR 1301.52(e)(1). In addition, DEA Form 222 or the electronic equivalent must be prepared to document the transfer of schedule II controlled substances. 21 CFR 1301.52(e)(1), 1305.03. This inventory serves as the final inventory for the registrant going out of business and transferring the controlled substances. It also serves as the initial inventory for the registrant acquiring the controlled substances. A copy of the inventory must be included in the records of each pharmacy. It is not necessary to send a copy of the inventory to DEA unless requested by the Special Agent in Charge. 21 CFR 1301.52(e)(1). The pharmacy acquiring the controlled substances must maintain all records involved in the transfer of the controlled substances for two years. 21 U.S.C. 827(b) and 21 CFR 1304.04(a).

All controlled substance records required to be kept by the registrant-transferor shall be transferred to the registrant-transferee. Responsibility for the accuracy of records prior to the date of transfer remains with the transferor, but responsibility for custody and maintenance is the responsibility of the transferee. 21 CFR 1301.52(e)(2).

If the registrant acquiring the pharmacy owns at least one other pharmacy licensed in the same state as the pharmacy being transferred, the registrant may apply for a new DEA registration prior to the date of transfer. DEA may issue a registration which will authorize the registrant to obtain controlled substances at the time of transfer, but the registrant may not dispense controlled substances until the pharmacy has been issued a valid state pharmacy license. 21 CFR 1301.17(b).

A DEA registration application to transfer ownership of an existing pharmacy can be facilitated if the applicant includes an affidavit verifying that the pharmacy has been registered by the state licensing agency. The affidavit verifying the existence of the state license should be attached to the initial application for registration.

Denial of Registration in the Public Interest

A pharmacy may be denied DEA registration upon a finding that such registration is inconsistent with the public interest. 21 U.S.C. 823(f). In determining the public interest pursuant to 21 U.S.C. 823(f), the CSA provides that the following factors are to be considered:

1. The recommendation of the appropriate state licensing board or professional disciplinary authority.

2. The applicant's experience in dispensing controlled substances.

3. The applicant's conviction record under federal or state laws relating to the manufacture, distribution, or dispensing of controlled substances.

4. Compliance with applicable state, federal, or local laws relating to controlled substances.

5. Such other conduct which may threaten the public health and safety.

Suspension or Revocation of Registration

Under 21 U.S.C. 824(a), DEA has the authority to suspend or revoke a DEA registration upon a finding that the registrant:

1. Has materially falsified the application;

2. Has been convicted of a felony relating to a controlled substance or a List I chemical;

3. Had a state license or registration suspended, revoked, or denied by a competent state authority and is no longer authorized by state law to engage in the manufacturing, distribution, or dispensing of controlled substances or List I chemicals or has had the suspension, revocation, or denial of a registration recommended by competent state authority;

4. Has committed such acts as would render its registration inconsistent with the public interest as determined under 21 U.S.C. 823(f); or

5. Has been excluded (or directed to be excluded) from participation in a program pursuant to 42 U.S.C. 1320a-7(a).

Chemical Registration Requirements

Registration is not required for regulated sellers of scheduled listed chemical products (SLCPs). 21 U.S.C. 823(h) and 802(39)(A)(iv-v). However, a regulated seller must self-certify with DEA pursuant to federal law (See *Section XIII, Combat Methamphetamine Epidemic Act of 2005*.) 21 U.S.C. 830(e)(1)(B)(i), 21 CFR 1314.40(a). A regulated seller is a retail distributor (including a pharmacy or a mobile retail vendor) of SLCPs, except that the term does not include an employee or agent of the distributor. 21 CFR 1300.02 ("*Regulated seller*"). Examples of regulated sellers include grocery stores, general merchandise stores, drug stores, or other entities engaged in over-the-counter sales of ephedrine (both single entity and combination products), pseudoephedrine, or phenylpropanolamine products, directly to walk-in customers or in face-to-face transactions by direct sales.

If a pharmacy desires to engage in the distribution of bulk quantities of SLCPs, the pharmacy is required to register with DEA as a chemical distributor because these activities fall outside the definition of a regulated seller. 21 CFR 1309.21(a)(2). Therefore, the pharmacy would be subject to the registration requirements that apply to chemical distributors for those distribution activities, and subject to the pharmacy requirements for its pharmacy activities. To obtain a DEA chemical distributor registration, a pharmacy may complete the DEA Form 510 online. A paper version may be requested by writing to:

Drug Enforcement Administration
Diversion Control Division
Attn: Registration & Program Support Section/DRR
P.O. Box 2639
Springfield, VA 22152-2639

SECTION IV – ORDERING CONTROLLED SUBSTANCES

On September 30, 2019, DEA issued a final rule entitled *New Single-Sheet Format for U.S. Official Order Form for Schedule I and II Controlled Substances (DEA Form 222)*, which implements a new single-sheet format for DEA Form 222, used by DEA registrants to order schedule I and II controlled substances. 84 FR 51368. The rule became effective on October 30, 2019, and provides for a two-year transition period, during which the existing triplicate version of the forms may continue to be used. DEA registrants will be allowed to exhaust their supply of the current forms as part of the transition to using the new single-sheet form. When a registrant's supply of triplicate forms is depleted, DEA will issue new single-sheet forms to the registrant. This rule includes a "sunset date" of October 30, 2021—the date after which use of the triplicate forms will not be allowed.

Ordering Schedules I and II Controlled Substances

Only schedule I and II controlled substances are ordered with an official paper order form, DEA Form 222, or the electronic equivalent (See below, *Controlled Substance Ordering System (CSOS) - Electronic Order Forms.*) A DEA Form 222 is required for each distribution or transfer of a schedule I or schedule II controlled substance unless exempted. 21 CFR 1305.03, 1307.11(a)(1)(iii), 1301.52(e)(1).

When a controlled substance has been moved by DEA from schedule I or schedule II to another schedule at the federal level, in many states it may remain a schedule I or schedule II controlled substance pending any legislative or administrative action that may result from the federal action. States may require transactions that involve substances they classify as schedule I or schedule II to be made via DEA Form 222 or the electronic equivalent.

Requesting DEA Forms 222

DEA Forms 222 are issued in mailing envelopes containing a predetermined number of forms based on the business activity of the registrant, each form consisting of one single-sheet. A limit, which is based on the business activity of the registrant, will be imposed on the number of DEA Forms 222 that will be furnished upon a requisition for order forms unless additional forms are specifically requested and a reasonable need for such additional forms is shown. 21 CFR 1305.11(a).

Any person with an active registration that is authorized to order schedule I and II controlled substances is entitled to obtain a DEA Form 222, which will be supplied at any time after a DEA registration is granted. Any person holding a registration authorizing the person to obtain a DEA Form 222 may requisition the forms through a DEA secured network connection or by contacting a local DEA Diversion Field Office or

the Registration Section of the Administration through the customer service center. 21 CFR 1305.11(b). Each requisition must show the name, address, and registration number of the registrant and the number of DEA Forms 222 desired. 21 CFR 1305.11(c).

DEA Forms 222 have an order form number and are issued with the name, address, and registration number of the registrant, the authorized activity, and schedules of the registrant. This information cannot be altered or changed by the registrant; the registrant must report any errors to the local DEA Diversion Field Office or the Registration Section of the Administration to modify the registration. 21 CFR 1305.11(d).

Completing DEA Forms 222

A purchaser must prepare and execute a DEA Form 222 by use of a typewriter, computer printer, pen, or indelible pencil. 21 CFR 1305.12(a). Only one item may be entered on each numbered line. An item must consist of one or more commercial or bulk containers of the same finished or bulk form and quantity of the same substance. The number of lines completed must be noted on that form at the bottom of the form, in the space provided 21 CFR 1305.12(b). The purchaser should record the name and address from whom the controlled substances are being ordered must be entered on the form 21 CFR 1305.12(c). If the purchaser does not have this information then the supplier should ensure it is on the form. The purchaser must make a copy of the original DEA Form 222 for its records and then submit the original to the supplier. 21 CFR 1305.13(a). The purchaser does not have the option of retaining the original. The copy retained by the purchaser may be in paper or electronic form. 21 CFR 1305.13(a). Each DEA Form 222 must be signed and dated by a person authorized to sign a registration application or a person granted power of attorney (See below, *Power of Attorney to Sign an Official Order Form.*) 21 CFR 1305.12(d). When the items are received, the purchaser must document on the purchaser's copy the actual number of commercial or bulk containers received and the date received. 21 CFR 1305.13(e). The purchaser must retain a copy of each executed DEA Form 222 and all copies of unaccepted or defective forms with each statement attached. 21 CFR 1305.17(a). The supplier must retain the original DEA Form 222 for the supplier's files in accordance with 21 CFR 1305.17(c). Any supplier who is not required to report acquisition/disposition transactions to the Automation of Reports and Consolidated Orders System (ARCOS) under 1304.33(c) (such as a practitioner) must make and submit a copy of the original DEA Form 222 to DEA, either by mail to the Registration Section, or by email to DEA.Orderforms@usdoj.gov. The copy must be forwarded at the close of the month during which the order is filled. If an order is filled by partial shipments, the copy must be forwarded at the close of the month during which the final shipment is made or the 60-day validity period expires.

DEA Forms 222 must be maintained separately from all other records of the registrant. 21 CFR 1305.17(c). DEA Forms 222 are required to be kept available for inspection for a period of two years. 21 CFR 1305.17(c). If a purchaser has several registered locations, the purchaser must retain a copy of the executed DEA Form 222 and any attached statements or other related documents (not including unexecuted DEA Forms 222, which may be kept elsewhere under 21 CFR 1305.12(e)), at the registered location printed on the DEA Form 222. 21 CFR 1305.17(c).

Electronic copies of DEA Forms 222 do not need to be stored on a different server or electronic system from a registrant's other records. The requirement to store DEA Forms 222 separately from all other records may be met, for electronic copies, by storing them in such a way that they can be readily retrieved separately from all other records. 21 CFR 1305.17(e). Electronic copies of DEA Forms 222 may be stored on a system at a location different from the registered location, provided such copies are readily retrievable at the registered location. 21 CFR 1305.17(e). Purchasers must be able, during an inspection or upon other DEA requests, to readily retrieve their electronic copies of Forms 222, with any related statements or other documents, and without any other records.

Under 21 CFR 1305.15(a)(1), an order must not be filled if the Form 222 is not complete, legible, or properly prepared, executed, or endorsed, or if the Form 222 shows any alteration, erasure, or change of any description. For a discussion of the circumstances in which an electronic order must not be filled, see below, *Controlled Substance Ordering System (CSOS) - Electronic Order Forms*.

If a DEA Form 222 cannot be filled for any reason, the supplier must return the original DEA Form 222 to the purchaser with a statement explaining the reason the order could not be filled (e.g., illegible or altered). 21 CFR 1305.15(b). A supplier may refuse to accept an order for any reason. 21 CFR 1305.15(c). If a supplier refuses to accept an order, a statement that the order is not accepted is sufficient. 21 CFR 1305.15(c). For electronic orders, if the order cannot be filled, the supplier must notify the purchaser and provide a statement as to the reason; if the order is refused, a statement that the order is not accepted is sufficient (See below, *Controlled Substance Ordering System (CSOS) - Electronic Order Forms.*) 21 CFR 1305.25(b).

When a purchaser receives an unaccepted order, the original DEA Form 222 and the statement must be retained in the files of the purchaser. 21 CFR 1305.17. When a purchaser receives an unaccepted electronic order from a supplier, the purchaser must electronically link the statement of non-acceptance to the original order, and retain the original order and the statement in accordance with 21 CFR 1305.27.
21 CFR 1305.25(c). A defective DEA Form 222 may not be corrected; it must be replaced by a new DEA Form 222 for the order to be filled. 21 CFR 1305.15(d).

Power of Attorney to Sign DEA Forms 222

Any registrant (pharmacy) may authorize one or more individuals, whether or not they are located at the registered location, to obtain and execute DEA Forms 222 by granting a power of attorney to each such individual. 21 CFR 1305.05(a). Pursuant to 21 CFR 1305.05(d), the power of attorney must be signed by:

1. The registrant, if an individual; a partner of the registrant, if a partnership; or an officer of the registrant, if a corporation, corporate division, association, trust or other entity;
2. The person to whom the power of attorney is being granted; and
3. Two witnesses.

A power of attorney executed under this section may be signed electronically, by any or all of the persons required to sign. 21 CFR 1305.05(f).

The power of attorney may be revoked at any time by the person who signed the most recent application for DEA registration or reregistration and two witnesses. 21 CFR 1305.05(e). Only if the renewal application is signed by a different person is it necessary to grant a new power of attorney when the pharmacy completes a renewal registration. 21 CFR 1305.05(e). The power of attorney should be filed with executed DEA Forms 222 if applicable, and must be available for inspection. 21 CFR 1305.05(a). The power of attorney is not submitted to DEA.

Suggested formats for granting and revoking a power of attorney follow:

Power of Attorney for DEA Forms 222 and Electronic Orders

_____ (Name of registrant)
_____(Address of registrant)
_____(DEA registration number)

I, _____(name of person granting power), the undersigned, who am authorized to sign the current application for registration of the above named registrant under the Controlled Substances Act or Controlled Substances Import and Export Act, have made, constituted, and appointed, and by these presents, do make, constitute, and appoint _____(name of attorney-in-fact), my true and lawful attorney for me in my name, place, and stead, to execute applications for Forms 222 and to sign orders for schedule I and II controlled substances, whether these orders be on Form 222 or electronic, in accordance with 21 U.S.C. 828 and Part 1305 of Title 21 of the Code of Federal Regulations. I hereby ratify and confirm all that said attorney must lawfully do or cause to be done by virtue hereof.

_____

(Signature of person granting power)

I, _____(name of attorney-in-fact), hereby affirm that I am the person named herein as attorney-in-fact and that the signature affixed hereto is my signature.

_____
(Signature of attorney-in-fact)

Witnesses:
1. _____
2. _____

Signed and dated on the ___ day of _____ (year), at _____ .

Notice of Revocation

The foregoing power of attorney is hereby revoked by the undersigned, who is authorized to sign the current application for registration of the above-named registrant under the Controlled Substances Act or the Controlled Substances Import and Export Act. Written notice of this revocation has been given to the attorney-in-fact _____ this same day.

_____
(Signature of person revoking power)

Witnesses:
1. _____
2. _____

Signed and dated on the ___ day of _____ (year), at _____.

Cancellation and Voiding DEA Forms 222

A purchaser may cancel part or all of an order on a DEA Form 222 by notifying the supplier in writing of the cancellation. 21 CFR 1305.19(a). The supplier must indicate the cancellation on the original DEA Form 222 sent by the purchaser by drawing a line through the canceled items and printing "canceled" in the space provided for the number of items shipped. 21 CFR 1305.19(a).

For information regarding canceled electronic orders, see below, *Controlled Substance Ordering System (CSOS) - Electronic Order Forms*.

Lost or Stolen DEA Forms 222

If a purchaser ascertains that an unfilled DEA Form 222 has been lost, the purchaser must execute another and attach a statement containing the order form number and date of the lost form, and stating that the goods covered by the first DEA Form 222 were not received through loss of that DEA Form 222. 21 CFR 1305.16(a). A copy of the second form and a copy of the statement must be retained with a copy of the DEA Form 222 first executed. 21 CFR 1305.16(a). A copy of the statement must be attached to a copy of the second DEA Form 222 sent to the supplier. 21 CFR 1305.16(a). If the first DEA Form 222 is subsequently received by the supplier to whom it was directed, the supplier must mark upon the face "Not accepted" and return the original DEA Form 222 to the purchaser, who must attach it to the statement. 21 CFR 1305.16(a).

A pharmacy, upon discovery of the loss or theft of used or unused order forms, must immediately report the loss or theft to the local DEA Diversion Field Office (Appendix K) and provide the serial numbers of each lost or stolen order form. 21 CFR 1305.16(b).

If any DEA Forms 222 are lost or stolen, and the purchaser is unable to provide the order form numbers of DEA Forms 222, the purchaser must report, in lieu of numbers of the forms, the date or approximate date of issuance. 21 CFR 1305.16(d).

If an unused order form reported stolen or lost is later recovered or found, the pharmacy must immediately notify the local DEA Diversion Field Office (Appendix K). 21 CFR 1305.16(e).

Return of Unused DEA Forms 222

If the registration of any purchaser terminates (because the purchaser dies, ceases legal existence, discontinues business or professional practice, or changes the name or address as shown on the purchaser's registration) or is suspended or revoked under 21 CFR 1301.36 for all schedule I and II controlled substances for which the purchaser

is registered, the purchaser must return all unused DEA Forms 222 to the Registration Section. 21 CFR 1305.18.

Continued Use of Existing Stocks of Triplicate DEA Forms 222

Registrants may continue to use existing stocks of the triplicate DEA Form 222 until October 30, 2021. In any case, as soon as a registrant's supply of triplicate DEA Forms 222 is exhausted, the registrant must use the new single-sheet DEA Form 222. 21 CFR 1305.20.

Procedure for Obtaining Triplicate DEA Forms 222

DEA no longer issues triplicate forms. Triplicate DEA Forms 222 will not be accepted after October 30, 2021. 21 CFR 1305.20(a).

Completing Triplicate DEA Forms 222

A purchaser must prepare and execute a triplicate DEA Form 222 simultaneously by means of interleaved carbon sheets that are part of the triplicate DEA Form 222. Triplicate DEA Forms 222 must be prepared by use of a typewriter, pen, or indelible pencil. 21 CFR 1305.20(b)(1). Only one item may be entered on each numbered line. An item must consist of one or more commercial or bulk containers of the same finished or bulk form and quantity of the same substance. The number of lines completed must be noted on that form at the bottom of the form, in the space provided. 21 CFR 1305.20(b)(2). Each triplicate DEA Form 222 must be signed and dated by a person authorized to sign a registration application or a person granted power of attorney. 21 CFR 1305.20(b)(4). When the items are received, the purchaser must document on the purchaser's copy (copy three) the actual number of commercial or bulk containers received and the date received. 21 CFR 1305.20(c)(5).

The executed triplicate DEA Form 222 must be maintained separately from the pharmacy's other business records. 21 CFR 1305.20(g)(3). If a purchaser has several registered locations, the purchaser must retain Copy 3 of the executed triplicate DEA Form 222 and any attached statements or other related documents at the registered location printed on the triplicate DEA Form 222. 21 CFR 1305.20(g)(3).

Unaccepted and Defective Triplicate DEA Forms 222

21 CFR 1305.20(e) requires that, for orders using the triplicate DEA Form 222, an order must not be filled if the order is not complete, legible, or properly prepared, executed, or endorsed, or if the order shows any alteration, erasure, or change of any description. If an order cannot be filled, the supplier must return copies 1 and 2 of the triplicate DEA Form 222 to the purchaser with a statement explaining the reason the order could not be filled (e.g., illegible or altered). 21 CFR 1305.20(e)(2). A supplier may refuse to accept an order for any reason. 21 CFR 1305.20(e)(3). If a supplier refuses to accept an order, a statement that the order is not accepted is sufficient. 21 CFR 1305.20(e)(3). When a purchaser receives an unaccepted order, Copies 1 and 2 of the triplicate DEA Form 222 and the statement must be attached to Copy 3 and retained in the files of the purchaser. 21 CFR 1305.20(e)(4). A defective triplicate DEA Form 222 may not be corrected; it must be replaced by a new triplicate DEA Form 222 for the order to be filled. 21 CFR 1305.20(e)(4).

The purchaser must retain Copy 3 of each executed triplicate DEA Form 222 and all copies of unaccepted or defective forms with each statement attached. 21 CFR 1305.20(g)(1).

Cancellation and Voiding a Triplicate DEA Form 222

A purchaser may cancel an order (or part of an order) on a triplicate DEA Form 222 by notifying the supplier in writing. 21 CFR 1305.20(i)(1). The supplier must indicate the cancellation on Copies 1 and 2 of the triplicate DEA Form 222 by drawing a line through the canceled item(s) and printing "canceled" in the space provided for the number of items shipped. 21 CFR 1305.20(i)(1).

A supplier may void part or all of an order on a triplicate DEA Form 222 by notifying the purchaser in writing. 21 CFR 1305.20(i)(1). The supplier must indicate the voiding on Copies 1 and 2 of the triplicate DEA Form 222 by drawing a line through the canceled item(s) and printing "canceled" in the space provided for the number of items shipped. 21 CFR 1305.20(i)(1).

Lost or Stolen Triplicate DEA Forms 222

If a purchaser ascertains that an unfilled triplicate DEA Form 222 has been lost, the purchaser must execute another in triplicate and attach a statement containing the serial number and date of the lost form, and stating that the goods covered by the first triplicate DEA Form 222 were not received through loss of that triplicate DEA Form 222. 21 CFR 1305.20(f)(1). Copy 3 of the second form and a copy of the statement must be retained with Copy 3 of the triplicate DEA Form 222 first executed. 21 CFR 1305.20(f)(1). A copy of the statement must be attached to Copies 1 and 2 of the second triplicate DEA Form 222 sent to the supplier. 21 CFR 1305.20(f)(1). If the first triplicate DEA Form 222 is subsequently received by the supplier to whom it was

directed, the supplier must mark upon the face "Not accepted" and return Copies 1 and 2 to the purchaser, who must attach it to Copy 3 and the statement. 21 CFR 1305.20(f)(1). However, if the registrant no longer can use triplicate forms, then the registrant shall proceed by issuing a new single-sheet form in accordance with 21 CFR 1305.16. 21 CFR 1305.20(f)(1).

Whenever any used or unused triplicate DEA Forms 222 are stolen or lost (other than in the course of transmission) by any purchaser or supplier, the purchaser or supplier must immediately upon discovery of the theft or loss, report the theft or loss to the Special Agent in Charge of the Drug Enforcement Administration in the local DEA Diversion Field Office. 21 CFR 1305.20(f)(2).

Return of Unused Triplicate DEA Forms 222

If the registration of any purchaser terminates (because the purchaser dies, ceases legal existence, discontinues business or professional practice, or changes the name or address as shown on the purchaser's registration) or is suspended or revoked under 21 CFR 1301.36 of this chapter for all schedule I and II controlled substances for which the purchaser is registered, the purchaser must return all unused triplicate DEA Forms 222 to the Registration Section. 21 CFR 1305.20(h).

Controlled Substance Ordering System (CSOS) – Electronic Order Forms

Any registrant permitted to order schedule II controlled substances may do so electronically via the DEA's Controlled Substance Ordering System (CSOS) and maintain the records of these orders electronically for two years. 21 CFR 1311.60(a). The use of electronic orders is optional; registrants may continue to issue orders on a paper DEA Form 222. CSOS allows for secure electronic transmission of controlled substance orders without the supporting paper DEA Form 222. CSOS is the only electronic means of ordering schedule II controlled substances between controlled substance manufacturers, distributors, pharmacies, and other DEA authorized entities. CSOS uses Public Key Infrastructure (PKI) technology, which requires CSOS users to obtain a CSOS digital certificate for electronic ordering. The electronic orders must be signed using a digital signature issued by the Certification Authority (CA) run by DEA. 21 CFR 1305.21(a).

Digital certificates can be obtained only by the person who signed the most recent DEA registration application or renewal application, a person authorized to sign a registration application, or a person granted power of attorney by a DEA registrant to sign orders for one or more schedules of controlled substances. 21 CFR 1311.10(a) and (b). A registrant must appoint a CSOS coordinator who will serve as that registrant's recognized agent regarding issues pertaining to issuance of, revocation of, and changes to digital certificates issued under that registrant's DEA registration. 21 CFR

1311.20(a). A CSOS digital certificate is valid until the DEA registration under which it is issued expires or until the CSOS CA is notified that the certificate should be revoked. 21 CFR 1311.30(e), 1311.40(a). Certificates will be revoked if the certificate holder is no longer authorized to sign schedule II orders for the registrant, if the information on which the certificate is based changes, or if the digital certificate used to sign electronic orders has been compromised, stolen, or lost. 21 CFR 1311.30(e), 1311.40(a). A "Questions and Answers" page about the CSOS certificate is available on DEA's E-Commerce Program website at www.DEAecom.gov. Applicants can download the Diversion PKI CSOS Enrollment document and the CSOS Subscriber's Manual for assistance on the enrollment process. DEA maintains a support line to assist applicants and subscribers with issues pertaining to certificate enrollment, issuance, revocation, and renewal. Staff is available from 8:00 a.m. to 5:50 p.m. (Eastern Time), Monday through Friday at 1-877-332-3266 if further assistance is needed.

Unaccepted and Defective Electronic Orders

Under 21 CFR 1305.25(a), an electronic order for controlled substances may not be filled if any of the following occurs:

1. The required data fields have not been completed.
2. The order is not signed using a digital certificate issued by DEA.
3. The digital certificate used has expired or been revoked prior to signature.
4. The purchaser's public key will not validate the digital certificate.
5. The validation of the order shows that the order is invalid for any reason.

If an order cannot be filled, the supplier must notify the purchaser and provide a statement as to the reason (e.g., improperly prepared or altered). A supplier may, for any reason, refuse to accept any order. If a supplier refuses, a statement that the order is not accepted is sufficient. 21 CFR 1305.25(b).

When a purchaser receives an unaccepted electronic order from the supplier, the purchaser must electronically link the statement of non-acceptance to the original order. The original statement and all linked records for that order must be retained for two years. 21 CFR 1305.25(c), 1305.27(a). Neither a purchaser nor a supplier may correct a defective order. The purchaser must issue a new order for the order to be filled. 21 CFR 1305.25(d).

Cancellation and Voiding of Electronic Orders

A supplier may void all (or part) of an electronic order by notifying the purchaser of the voiding. If the entire order is voided, the supplier must make an electronic copy of the order and indicate "void" on the copy and return it to the purchaser. The supplier is not required to retain a record of orders that are not filled. 21 CFR 1305.28(a). The purchaser must retain an electronic copy of the voided order. 21 CFR 1305.28(b). Should a supplier partially void an order, the supplier must indicate in the linked record that nothing was shipped for each item voided. 21 CFR 1305.28(c).

Lost Electronic Orders

If a purchaser determines that an unfilled electronic order has been lost before or after receipt, the purchaser must provide, to the supplier, a signed statement. This statement must include the unique tracking number and date of the lost order and state that the goods covered by the first order were not received through loss of that order. 21 CFR 1305.26(a). If the purchaser executes a new order to replace the lost order, the purchaser must electronically link an electronic record of the second order and a copy of the statement with the record of the first order and retain them both. 21 CFR 1305.26(b). If the supplier to whom the order was directed subsequently receives the first order, the supplier must indicate that it is "Not Accepted" and return it to the purchaser. The purchaser must link the returned order to the record of that order and the statement. 21 CFR 1305.26(c).

Ordering Schedules III-V Controlled Substances

The registrant must keep a receipt (invoice or packing slip) on which it records the date the drugs were received and confirm that the order is accurate. 21 CFR 1304.21(a) and (d). Pursuant to 21 CFR 1304.22(c), 1304.22(a)(2), such receipts must also contain the following information:

1. The name of the substance;

2. Each finished form (e.g., 10-milligram tablet or 10-milligram concentration per fluid ounce or milliliter) and the number of units or volume of finished form in each commercial container (e.g., 100-tablet bottle or 3-milliliter vial);

3. The number of units of finished forms and/or commercial containers acquired from other persons, including the date of and number of units and/or commercial containers in each acquisition to inventory and the name, address, and registration number of the person from whom the units were acquired;

4. The number of commercial containers distributed to other persons, including the date of and number of containers in each reduction from inventory, and the name,

address, and registration number of the person to whom the containers were distributed;

5. The number of units of finished forms and/or commercial containers distributed or disposed of in any other manner by the registrant (e.g., by distribution of complimentary samples or by destruction), including the date and manner of distribution or disposal, the name, address, and registration number of the person to whom distributed, and the quantity in finished form distributed or disposed.

In addition, these receipts must be maintained either separately from all other records of the registrant or in such form that the information required is readily retrievable from the ordinary business records of the registrant. 21 CFR 1304.04(f)(2).

SECTION V – INVENTORY REQUIREMENTS

An "inventory" is a complete and accurate list of all stocks and forms of controlled substances in the possession of the registrant as determined by an actual physical count for schedule II controlled substances. 21 CFR 1300.01(b). With respect to inventories of a schedule III, IV, or V controlled substance, the registrant may, with respect to an open bottle which contains no more than 1,000 tablets, make an estimated count or measure of the contents, unless the container holds more than 1,000 tablets or capsules in which case an exact count of the contents must be made. 21 CFR 1304.11(e)(6)(i) and (ii). The CSA also requires that all inventory records be maintained at the registered location for at least two years for copying and inspection. 21 CFR 1304.04(a) and 21 U.S.C. 827(b). In addition, the inventory records of schedule II controlled substances must be kept separate from all other records of the pharmacy. 21 CFR 1304.04(h)(1). The inventory records of schedules III, IV, and V controlled substances must be maintained either separately from all other records of the pharmacy or in such form that the information required is readily retrievable from ordinary business records of the pharmacy. 21 CFR 1304.04(h)(3).

Initial Inventory

When issued a DEA registration, a registrant must take an initial inventory, which is an actual physical count of all controlled substances in their possession. 21 U.S.C. 827(a)(1). If there are no stocks of controlled substances on hand, the registrant should make a record showing a zero inventory. 21 CFR 1304.11(b). There is no requirement to submit a copy of the inventory to DEA. Under 21 CFR 1304.11(a), (b) and (e)(6), the inventory shall include:

1. The date of the inventory,
2. Whether the inventory was taken at the beginning or close of business,
3. The name of each controlled substance inventoried,
4. The finished form of each of the substances (e.g., 10 milligram tablet),
5. The number of dosage units or volume of each finished form in the commercial container (e.g., 100 tablet bottle or 3 milliliter vial),
6. The number of commercial containers of each finished form (e.g., four 100 tablet bottles), and
7. The total count of the substance.

Although the it is not required by law, DEA recommends that registrants keep an inventory record that includes the name, address, and DEA registration number of the registrant, and the signature of the person or persons responsible for taking the inventory.

Biennial Inventory

After the initial inventory, the registrant is required to take a new inventory at least every two years, which requires the same information as the initial inventory (see list above) of all controlled substances on hand. 21 CFR 1304.11(c). There is no requirement to submit a copy of the inventory to DEA.

Newly Scheduled Controlled Substance Inventory

When a drug not previously listed as a controlled substance is scheduled, the drug must be inventoried as of the effective date of scheduling, if possessed by the registrant. 21 CFR 1304.11(d).

Inventory for Damaged, Defective, or Impure Substances

For damaged, defective, or impure substances awaiting disposal, substances held for quality control purposes, or substances maintained for extemporaneous compoundings, the inventories, pursuant to 21 CFR 1304.11(e)(1)(iv), must include:

1. The name of the substance;

2. The total quantity of the substance to the nearest metric unit weight or the total number of units of finished form; and

3. The reason for the substance being maintained by the registrant and whether such substance is capable of use in the manufacture of any controlled substance in finished form.

SECTION VI – RECORDKEEPING REQUIREMENTS

Every pharmacy must maintain complete and accurate records on a current basis for each controlled substance received, sold, delivered, or otherwise disposed of. 21 CFR 1304.21(a). These records are required to provide accountability of all controlled substances from the manufacturing process through the dispensing pharmacy and to the ultimate user. The closed system reduces the potential for diversion of controlled substances.

All required records concerning controlled substances must be maintained for at least two years for inspection and copying by duly authorized DEA officials. 21 U.S.C. 827(b) and 21 CFR 1304.04(a). Records and inventories of schedule II controlled substances must be maintained separately from all other records of the registrant. 21 CFR 1304.04(h)(1). All records and inventories of schedules III, IV, and V controlled substances must be maintained either separately from all other records or in such a form that the information required is readily retrievable from the ordinary business records. 21 CFR 1304.04(h)(3). Recordkeeping requirements for prescriptions are detailed in Section VII, *Valid Prescription Requirements*.

Under 21 CFR 1300.01(b), readily retrievable is defined as:

1. Records kept by automatic data processing systems or other electronic or mechanized recordkeeping systems in such a manner that they can be separated out from all other records in a reasonable time, and/or

2. Records kept in such a manner that certain items are asterisked, redlined, or in some other manner visually identifiable apart from other items appearing on the records.

Required Records

Pursuant to 21 CFR 1304, the records which must be maintained by a pharmacy are:

1. Executed official order forms (DEA Form 222) or the electronic equivalent.

2. Power of Attorney authorization to sign order forms. 21 CFR 1305.05(a).

3. Receipts and/or invoices for schedules III, IV, and V controlled substances.

4. All inventory records of controlled substances, including the initial and biennial inventories, dated as of beginning or close of business.

5. Records of controlled substances distributed (i.e., sales to other registrants, returns to vendors, distributions to reverse distributors).

6. The Suspicious Orders Report System (SORS) should be accessed on-line and only be used by DEA registrants that distribute controlled substances to other DEA registrants. Reporting a suspicious order to SORS Online constitutes compliance with the reporting requirement under **21 U.S.C. 832**. Previously, only manufacturers and distributors were required to report suspicious orders. The SUPPORT Act requires that ALL DEA registrants that distribute controlled substances report suspicious orders to DEA. Reverse distributors and exporters are not affected by this SUPPORT Act requirement.

7. Records of controlled substances dispensed, to include prescriptions or a logbook of controlled substances which may be lawfully dispensed without a prescription.

8. Reports of Theft or Significant Loss (DEA Form 106), if applicable.

9. Registrant Record of Controlled Substances Destroyed (DEA Form 41), if applicable.

10. DEA registration certificate. 21 CFR 1301.35(c).

11. The self-certification certificate and logbook (or electronic equivalent) as required under the Combat Methamphetamine Epidemic Act of 2005. 21 CFR 1314.30.

Central Recordkeeping

A registrant desiring to maintain shipping and financial records (but not executed official order forms) at a central location rather than the registered location must submit written notification of its intention by registered or certified mail, return receipt requested, in triplicate, to the Special Agent in Charge of the local DEA Diversion Field Office in which the registrant is located (Appendix K). Unless the registrant is informed by DEA that permission to keep central records is denied, the registrant may begin maintaining central records 14 days after DEA receives this notification. Central recordkeeping requirements are described in 21 CFR 1304.04(a)(1). Central recordkeeping permits are no longer issued by DEA.

Prescription Records

Pharmacies have two options for filing paper prescription records and one option for electronic prescription records. Paper prescriptions for schedule II controlled substances shall be maintained at the registered location in a separate prescription file.

21 CFR 1304.04(h)(2). Prescriptions for schedules III, IV, and V controlled substances shall be maintained at the registered location either in a separate prescription file for schedules III, IV, and V, or in such form that they are readily retrievable from the other prescription records of the pharmacy. 21 CFR 1304.04(h)(4). Pursuant to 21 CFR 1304.04(h), controlled substance prescriptions must be filed in one of the following ways:

Paper Prescriptions Records Option 1:

1. A file for schedule II controlled substances dispensed.

2. A file for schedules III, IV and V controlled substances dispensed.

Paper Prescriptions Records Option 2:

1. A file for all schedule II controlled substances dispensed.

2. A file for all other drugs dispensed (non-controlled and those in schedules III, IV and V). If this method is used, a prescription for a schedule III, IV or V drug must be made readily retrievable by use of a red "C" stamp not less than one inch high. If a pharmacy has an electronic recordkeeping system for prescriptions which permits identification by prescription number and retrieval of original documents by prescriber's name, patient's name, drug dispensed, and date filled, the requirement to mark the hard copy with a red "C" is waived. 21 CFR 1304.04(h)(4).

Federal requirements for filling prescriptions shall not be construed as authorizing or permitting any person to do any act which such person is not authorized or permitted to do under other federal laws or obligations under international treaties, conventions or protocols, or under the law of the state in which he or she desires to do such act nor shall compliance with such parts be construed as compliance with other federal or state laws unless expressly provided in such other laws. 21 CFR 1307.02.

Electronic Prescription Records

1. If a prescription is created, signed, transmitted, and received electronically, all records related to that prescription must be retained electronically. 21 CFR 1311.305(a).

2. Electronic records must be maintained electronically for two years from the date of their creation or receipt. However, this record retention requirement shall not preempt any longer period of retention which may be required now or in the

future, by any other federal or state law or regulation, applicable to pharmacists or pharmacies. 21 CFR 1311.305(b).

3. Records regarding controlled substances must be readily retrievable from all other records. Electronic records must be easily readable or easily rendered into a format that a person can read. 21 CFR 1311.305(c).

Records of electronic prescriptions for controlled substances shall be maintained in an application that meets the requirements of 21 CFR Part 1311 and 21 CFR 1304.04(h)(5). The computers on which the records are maintained may be located at another location, but the records must be readily retrievable at the registered location if requested by a DEA or other law enforcement agent. The electronic application must be capable of printing out or transferring the records in a format that is readily understandable to a DEA or other law enforcement agent at the registered location. Electronic copies of prescription records must be sortable by prescriber name, patient name, drug dispensed, and date filled. 21 CFR 1304.04(h)(5).

SECTION VII – VALID PRESCRIPTION REQUIREMENTS

To dispense controlled substances, a pharmacist must know the requirements for a valid prescription which are described in this section. A prescription is an order for medication which is dispensed to or for an ultimate user. A prescription is not an order for medication which is dispensed for immediate administration to the ultimate user (i.e., an order to dispense a drug to an inpatient for immediate administration in a hospital is not a prescription). 21 CFR 1300.01(b) ("*prescription*").

A prescription for a controlled substance must be dated and signed on the date when issued. The prescription must include the patient's full name and address, and the practitioner's full name, address, and DEA registration number. 21 CFR 1306.05(a).

Under 21 CFR 1306.05(a), 1306.22(b), the prescription must also include:

1. Drug name
2. Drug strength
3. Dosage form
4. Quantity prescribed
5. Directions for use
6. Number of refills authorized (if any)

A paper prescription must be written in ink or indelible pencil or typewritten, or printed on a computer printer, and must be manually signed by the practitioner on the date when issued. 21 CFR 1306.05(d). An individual (i.e., secretary or nurse) may prepare prescriptions for the practitioner's signature. 21 CFR 1306.05(f). The practitioner is responsible for ensuring the prescription conforms to all requirements of the law and regulations, both federal and state. 21 CFR 1306.05(f). A corresponding liability rests upon the pharmacist, including a pharmacist employed by a central fill pharmacy, who fills a prescription not prepared in the form prescribed by DEA regulations. 21 CFR 1306.05(f).

Acceptable Changes to a Prescription

[Reserved]

Who May Issue

Under 21 CFR 1306.03, a prescription for a controlled substance may only be issued by a physician, dentist, podiatrist, veterinarian, mid-level practitioner, or other registered practitioner who is:

1. Authorized to prescribe controlled substances by the jurisdiction in which the practitioner is licensed to practice, and

2. Registered with DEA or exempted from registration (e.g., Public Health Service, Federal Bureau of Prisons, military practitioners), 21 CFR 1301.23(a), or

3. An agent or employee of a hospital or other institution acting in the normal course of business or employment under the registration of the hospital or other institution which is registered in lieu of the individual practitioner being registered, provided that additional requirements as set forth in 21 CFR 1301.22(c) are met.

Purpose of Issue

To be valid, a prescription for a controlled substance must be issued for a legitimate medical purpose by a practitioner acting in the usual course of professional practice. The practitioner is responsible for the proper prescribing and dispensing of controlled substances, but a corresponding responsibility rests with the pharmacist who fills the prescription. An order purporting to be a prescription that is not issued for a legitimate medical purpose in the usual course of professional treatment or in legitimate and authorized research is not a prescription within the meaning and intent of 21 U.S.C. 829. The person knowingly filling such a purported prescription, as well as the person issuing it, shall be subject to the penalties provided for violations of the provisions of law relating to controlled substances. 21 U.S.C. 841(a)(1) and 21 CFR 1306.04(a).

A prescription may not be issued in order for an individual practitioner to obtain controlled substances for supplying the individual practitioner for the purpose of general dispensing to patients. 21 CFR 1306.04(b).

Authorized Agent

An individual practitioner may authorize an agent to perform a limited role in communicating such prescriptions to a pharmacy in order to make the prescription process more efficient. 21 CFR 1306.03(b), 1306.11(a), 1306.21(a). Even though the CSA established a closed system in which all persons in the distribution chain are required to be registered and are held accountable for every controlled substance transaction, Congress recognized a role for agents under the Act. The CSA exempts agents of registrants, including practitioners, from the requirement of registration.

21 U.S.C. 822(c)(1). The statute defines an "agent" as "an authorized person who acts on behalf of or at the direction of a manufacturer, distributor, or dispenser." 21 U.S.C. 802(3). The CSA does not permit a prescribing practitioner, however, to delegate to an agent or any other person the practitioner's authority to issue a prescription for a controlled substance. A practitioner acting in the usual course of his or her professional practice must determine that there is a legitimate medical purpose for a controlled substance prescription; an agent may not make this determination. 21 CFR 1306.04(a). The common means to communicate a prescription to a pharmacy include hand delivery, facsimile, phone call, or an electronic transmission. The proper role of an agent is fact specific and depends upon the schedule of the controlled substance prescribed, the circumstances of the ultimate user, and the method of communication, among other things.

Summary of the acts that an agent may execute in connection with controlled substance prescriptions:

1. An authorized agent of an individual practitioner may prepare a written prescription for the signature of the practitioner, provided that the practitioner, in the usual course of professional practice, has determined that there is a legitimate medical purpose for the prescription and has specified to the agent the required elements of the prescription. 21 CFR 1306.03(b), 1306.04(a).

2. Where a DEA registered individual practitioner has made a valid oral prescription for a controlled substance in schedules III-V by conveying all the required prescription information to the practitioner's authorized agent, that agent may telephone the pharmacy and convey that prescription information to the pharmacist. 21 CFR 1306.03(b), 1306.21(a).

3. In those situations in which an individual practitioner has issued a valid written prescription for a controlled substance, and the regulations permit the prescription to be transmitted by facsimile to a pharmacy, the practitioner's agent may transmit the practitioner-signed prescription by facsimile. 21 CFR 1306.11(a),(f),(g), 1306.21(a).

DEA believes it is in the best interest of the practitioner, the agent, and the dispensing pharmacist that the designation of those persons authorized to act on behalf of the practitioner and the scope of any such authorization be reduced to writing. A signed copy should also be provided to the practitioner's designated agent, the agent's employer (if other than the practitioner), and any pharmacies that regularly receive communications from the agent pursuant to the agreement. Providing a copy to pharmacies likely to receive prescriptions from the agent on the practitioner's behalf may assist those pharmacists with their corresponding responsibility regarding the dispensing of controlled substances. However, even where the pharmacist has a copy of an agency agreement, the pharmacist may also have a duty to inquire further

depending upon the particular circumstances. (See Federal Register: October 6, 2010, Volume 75, Number 193, page 61613-61617, for the complete policy statement on the *Role of Authorized Agents in Communicating Controlled Substance Prescriptions to Pharmacies*.)

Corresponding Responsibility

A pharmacist has a corresponding responsibility for the proper dispensing of controlled substances . An order purporting to be a prescription that is not issued for a legitimate medical purpose in the usual course of professional treatment or in legitimate and authorized research is an invalid prescription within the meaning and intent of the CSA. The person knowingly filling such a purported prescription, as well as the person issuing it, shall be subject to the penalties provided for violations of the provisions of law relating to controlled substances. 21 U.S.C. 841(a)(1), 21 U.S.C. 842(a)(1), and 21 CFR 1306.04(a).

A pharmacist is required to exercise sound professional judgment, and to adhere to professional standards, when making a determination about the legitimacy of a controlled substance prescription. 21 CFR 1306.04(a), 21 CFR 1306.06. Such a determination is made before the prescription is dispensed. The law does not require a pharmacist to dispense a prescription of doubtful, questionable, or suspicious medical legitimacy. To the contrary, the pharmacist who deliberately ignores the high probability that a prescription was not issued for a legitimate medical purpose and fills the prescription, may be prosecuted along with the issuing practitioner, for knowingly and intentionally distributing controlled substances. *United States v. Veal*, 23 F.3d 985 (6th Cir.1994). Such action is a felony offense, which upon conviction, may result in a term of imprisonment and a fine. 21 U.S.C. 841(b). Unlawful dispensing of controlled substances by a pharmacist may also be subject to criminal actions against the pharmacy or pharmacist, and to civil enforcement actions against the pharmacy or pharmacist for money penalties or injunctions. 21 U.S.C. 842, 843. Moreover, DEA may revoke a pharmacy's registration based on a finding that its pharmacists have violated the corresponding responsibility rule and both the pharmacy and pharmacists may be the subject of proceedings against their state licenses. *Jones Total Healthcare, L.L.C., v. DEA*, 881 F.3d 823 (11th Cir. 2018).

Electronic Prescriptions

On March 31, 2010, DEA published in the Federal Register an interim final rule *Electronic Prescriptions for Controlled Substances* which became effective June 1, 2010. 75 FR 16235-16319 (Mar. 31, 2010). The rule revises DEA regulations to provide practitioners with the option of writing prescriptions for controlled substances electronically. The regulations also permit pharmacies to receive, dispense, and archive these electronic prescriptions. These regulations are an addition to, not a replacement of, the existing rules.

Persons who wish to dispense controlled substances using electronic prescriptions must select software that meets the requirements of this rule. 21 CFR 1311.120(a). As of June 1, 2010, only those electronic pharmacy applications that comply with all of DEA's requirements as set forth in 21 CFR Part 1311 may be used by DEA registered pharmacies to electronically receive and archive controlled substances prescriptions and dispense controlled substances based on those prescriptions.

Pursuant to 21 CFR 1306.08, a registered pharmacy may fill electronic prescriptions for controlled substances only if the following conditions are met:

1. The pharmacy uses a pharmacy application that meets all of the applicable requirements of 21 CFR 1311.205, and

2. The prescription is otherwise in conformity with the requirements of the CSA and 21 CFR Part 1311.

A pharmacy cannot process electronic prescriptions for controlled substances until its pharmacy application provider obtains a third party audit or certification review that determines that the application complies with DEA's requirements and the application provider provides the audit/certification report to the pharmacy. 21 CFR 1311.200(a). The audit report the pharmacy receives from the pharmacy application provider indicates if the application is capable of importing, displaying, and storing DEA-required prescription information accurately and consistently. If the third-party auditor or certification organization finds that a pharmacy application does not accurately and consistently import, store, and display the information related to the name, address, and registration number of the practitioner, patient name and address, and prescription information (drug name, drug strength, quantity, directions for use), the indication of signing, the number of refills, and the practitioner's digital signature, where applicable, the pharmacy must not accept electronic prescriptions for the controlled substance. 21 CFR 1311.200(b) and (c).

If the third-party auditor or certification organization finds that a pharmacy application does not accurately and consistently import, store, and display other information required for prescriptions, the pharmacy must not process electronic prescriptions for controlled substances that are subject to the additional information requirements. 21 CFR 1311.200(b). (For example: 21 CFR 1306.11(d)(4) requires practitioners to submit a prescription with the phrase "Authorization for Emergency Dispensing" written on its face in addition to conforming to the requirements of 21 CFR 1306.05. 21 CFR 1306.11(g) requires the practitioner or the practitioner's agent to note on the prescription that the patient is a hospice patient. 21 CFR 1306.05(c) requires the practitioner to note on the face of the prescription the medical need of the patient for the prescription.)

The pharmacy must determine which employees are authorized to enter information regarding the dispensing of controlled substance prescriptions and annotate or alter records of these prescriptions (to the extent such alterations are permitted under DEA regulations). The pharmacy must ensure that logical access controls in the pharmacy application are set so that only such employees are granted access to perform these functions. 21 CFR 1311.200(e).

When a pharmacist fills a prescription in a manner that would require, under 21 CFR Part 1306, the pharmacist to make notation on the prescription if the prescription were a paper prescription, the pharmacist must make the same notation electronically when filling an electronic prescription and retain the annotation electronically in the prescription record or linked files. 21 CFR 1306.08(b) and (c) and 21 CFR 1311.200(f). When a prescription is received electronically, the prescription and all required annotations must be stored electronically. 21 CFR 1311.305(a) and 21 CFR 1311.200(f).

When a pharmacist receives a paper or oral prescription that indicates that it was originally transmitted electronically to the pharmacy, the pharmacist must check the pharmacy's records to ensure that the electronic version was not received and the prescription dispensed. 21 CFR 1311.200(g). If both prescriptions were received, the pharmacist must mark one as void. 21 CFR 1311.200(g).

When a pharmacist receives a paper or oral prescription that indicates that it was originally transmitted electronically to another pharmacy, the pharmacist must check with that pharmacy to determine whether the prescription was received and dispensed. 21 CFR 1311.200(h). If the pharmacy that received the original electronic prescription had not dispensed the prescription, the pharmacy must mark the electronic version as void or cancelled. 21 CFR 1311.200(h). If the pharmacy that received the original electronic prescription dispensed the prescription, the pharmacy with the paper version must not dispense the paper prescription and must mark the prescription as void. 21 CFR 1311.200(h).

Construction of a Valid DEA Registration Number for Practitioners

A pharmacist has a responsibility to ensure that a prescription has been issued by an appropriately registered or exempt practitioner (See above, *Who May Issue.*) Knowing how a DEA registration number is constructed can be a useful tool for recognizing a forged prescription (See Appendix D, *Pharmacist's Guide to Prescription Fraud*). Prior to October 1, 1985, DEA policy provided that DEA registration numbers for physicians, dentists, veterinarians, and other practitioners started with the letter A. New registration numbers issued to practitioners after that date begin with the letter B or F. Registration numbers issued to mid-level practitioners begin with the letter M. The first letter of the registration number is almost always followed by the first letter of the registrant's last name (e.g., J for Jones or S for Smith) and then a computer generated sequence of

seven numbers (such as MJ3614511). A registrant (pharmacy) may verify a practitioner's DEA number by using the following link:

https://apps.deadiversion.usdoj.gov/webforms/validateLogin.jsp.

Practitioner's Use of a Hospital's DEA Registration Number

Pursuant to 21 CFR 1301.22(c), practitioners (e.g., intern, resident, staff physician, mid-level practitioner) who are agents or employees of a hospital or other institution, may, when acting in the usual course of business or employment, administer, dispense, or prescribe controlled substances under the registration of the hospital or other institution in which he or she is employed, in lieu of individual registration, provided that:

1. The dispensing, administering, or prescribing is in the usual course of professional practice.

2. The practitioner is authorized to do so by the state in which he or she is practicing.

3. The hospital or institution has verified that the practitioner is permitted to administer, dispense, or prescribe controlled substances within the state.

4. The practitioner acts only within the scope of employment in the hospital or institution.

5. The hospital or institution authorizes the practitioner to administer, dispense, or prescribe under its registration and assigns a specific internal code number for each practitioner.

A current list of internal codes and the corresponding individual practitioners is to be maintained by the hospital or other institution. This list is to be available at all times to other registrants and law enforcement agencies upon request for the purpose of verifying the authority of the prescribing individual practitioner. 21 CFR 1301.22(c)(6). Pharmacists should contact the hospital or other institution for verification if they have any doubts in filling prescriptions issued under a hospital's DEA registration.

Unique Identification Number

The Unique Identification Number (UIN) or "X" number authorizes a DEA registered, Qualified Practitioner (e.g., a physician) under the Drug Addiction Treatment Act of 2000 or Qualifying Other Practitioner (i.e., nurse practitioner, physician's assistant, clinical nurse specialists, certified registered nurse anesthetists, or certified nurse midwives) under the Comprehensive Addiction and Recovery Act of 2016 and the SUPPORT for

Patients and Communities Act of 2018, to prescribe schedule III-V narcotic controlled substances approved by the Food and Drug Administration specifically for maintenance and detoxification treatment. The Qualifying Practitioner or the Qualifying Other Practitioner will be issued only one UIN. The UIN can be used with multiple DEA registration numbers in any state as long as the DEA registration number with which it is associated remains valid. Pursuant to DEA policy, the UIN number consists of two letters and seven numbers; the first letter is always an X, and is commonly referred to as the "X" number. For example, AB1234567 would have a UIN of XB1234567. 21 U.S.C. 823(g)(2)(D)(ii). For more information on prescription requirements for UINs please see Section XII, *Prescriptions for Maintenance and Detoxification Treatment*.

Exemption of Federal Government Practitioners from Registration

The requirement of registration is waived for any official of the U.S. Army, Navy, Marine Corps, Air Force, Coast Guard, Public Health Service, or Bureau of Prisons, who is authorized to administer, dispense, or prescribe, but not to procure or purchase controlled substances in the course of his or her official duties. 21 CFR 1301.23(a). Such officials must follow procedures set forth in 21 CFR Part 1306 regarding prescriptions, but must also state the branch of service or agency (e.g., "U.S. Army" or "Public Health Service") and the service identification number of the issuing official in lieu of the registration number required on prescription forms. The service identification number for a Public Health Service employee is his or her Social Security identification number. 21 CFR 1301.23(a).

If Federal Government practitioners wish to maintain a DEA registration for a private practice, which would include prescribing for private patients, these practitioners must obtain a registration for such private activities. 21 CFR 1301.23(c) and 21 U.S.C. 823(f).

Registration Requirements for Mid-Level Practitioners

Mid-level practitioners (MLPs) are registered and authorized by DEA and the state in which they practice to dispense, administer, and prescribe controlled substances in the course of professional practice (See Appendix B, *Definitions.*) Examples of MLPs include, but are not limited to, nurse practitioners, nurse midwives, nurse anesthetists, clinical nurse specialists, physician assistants, optometrists, ambulance services, animal shelters, euthanasia technicians, nursing homes, and homeopathic physicians. 21 CFR 1300.01(b).

MLPs may apply for an individual DEA registration granting controlled substance privileges. 21 CFR 1301.13(a). However, such registration is contingent upon the authority granted by the state in which they are licensed. 21 CFR 1300.01(b) ("*Mid-level practitioner*"). DEA may register MLPs whose states clearly authorize them to prescribe,

dispense, and administer controlled substances in one or more schedules. 21 U.S.C. 823(f).

For electronic prescriptions written by mid-level practitioners, if required by state law, it is DEA policy that a supervisor's name and DEA number may be listed on the prescription, provided the prescription clearly indicates which is the supervisor, and which is the prescribing practitioner. 75 FR 16257 (Mar. 31, 2010).

Schedule II Controlled Substances

Schedule II controlled substances require a written prescription which must be manually signed by the practitioner or an electronic prescription that meets all DEA requirements for electronic prescriptions for controlled substances. 21 CFR 1306.11(a), 1306.08, 1311.100(b). There is no federal time limit within which a schedule II prescription must be filled after being signed by the practitioner. However, the pharmacist must determine that the prescription is still needed by the patient, and the amount dispensed must be consistent with the requirement that a prescription for a controlled substance be issued only for a legitimate medical purpose by a practitioner acting in the usual course of professional practice. 21 CFR 1306.04(a). Some states and many insurance carriers limit the quantity of controlled substances dispensed to a 30-day supply. Other states and pharmacies have limited the initial prescribing of opioids. Though there are no express federal limits with respect to the quantities of drugs dispensed via a prescription, to be valid, a prescription for controlled substances must only be for a legitimate medical purpose by a practitioner acting in the usual course of professional practice. 21 CFR 1306.04(a). For a schedule II controlled substance, an oral order is only permitted in an emergency situation. 21 CFR 1306.11(d). Within 7 days after authorizing an emergency oral prescription, the prescribing individual practitioner shall cause a written prescription for the emergency quantity prescribed to be delivered to the dispensing pharmacist.
21 CFR 1306.11(d)(4). The prescribing individual practitioner must personally communicate the emergency oral prescription to the pharmacist. An agent may not call in an oral prescription for a schedule II controlled substance on behalf of a practitioner even in an emergency circumstance. *Role of Authorized Agents in Communicating Controlled Substance Prescriptions to Pharmacies*, 75 FR 61613, 61615 (October 6, 2010). (See Section VIII, *Emergency Dispensing.*)

Refills

The refilling of a prescription for a controlled substance listed in schedule II is prohibited. 21 U.S.C. 829(a).

Issuance of Multiple Prescriptions for Schedule II Controlled Substances

Under 21 CFR 1306.12(b)(1), an individual practitioner may issue multiple prescriptions authorizing the patient to receive a total of up to a 90-day supply of a schedule II controlled substance provided the following conditions are met:

1. Each separate prescription must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of professional practice. 21 CFR 1306.12(b)(1)(i).

2. The individual practitioner must provide written instructions on each prescription (other than the first prescription, if the prescribing practitioner intends for that prescription to be filled immediately) indicating the earliest date on which a pharmacy may fill each prescription. 21 CFR 1306.12(b)(1)(ii).

3. The individual practitioner concludes that providing the patient with multiple prescriptions in this manner does not create an undue risk of diversion or abuse. 21 CFR 1306.12(b)(1)(iii).

4. The issuance of multiple prescriptions is permissible under applicable state laws. 21 CFR 1306.12(b)(1)(iv).

5. The individual practitioner complies fully with all other applicable requirements under the CSA and CFR, as well as any additional requirements under state law. 21 CFR 1306.12(b)(1)(v).

It should be noted that this regulation should not be construed as encouraging individual practitioners to issue multiple prescriptions or to see their patients only once every 90 days when prescribing schedule II controlled substances. Rather, individual practitioners must determine on their own, based on sound medical judgment, and in accordance with established medical standards, whether it is appropriate to issue multiple prescriptions and how often to see their patients when doing so. 21 CFR 1306.12(b)(2).

Facsimile Prescriptions for Schedule II Controlled Substances

In order to expedite the filling of a prescription, a prescriber may transmit a schedule II prescription to the pharmacy by facsimile. The original schedule II prescription must be presented to the pharmacist and verified against the facsimile prior to the actual dispensing of the controlled substance. 21 CFR 1306.11(a). The pharmacist must make sure the original document is properly annotated and filed with the records that are required to be kept. 21 CFR 1306.11(a), 1304.04(h).

Exceptions for Schedule II Facsimile Prescriptions

DEA has granted three exceptions to the facsimile prescription requirements for schedule II controlled substances. The facsimile of a schedule II prescription may serve as the original prescription as follows:

1. A practitioner prescribing a schedule II narcotic controlled substance to be compounded for the direct administration to a patient by parenteral, intravenous, intramuscular, subcutaneous or intraspinal infusion may transmit the prescription by facsimile. The facsimile serves as the original written prescription and no further documentation is required. All normal requirements of a legal prescription must be followed. 21 CFR 1306.11(e).

2. Practitioners prescribing schedule II controlled substances for residents of Long-Term Care Facilities may transmit, or direct their authorized agent to transmit, a prescription to the dispensing pharmacy by facsimile. The facsimile prescription serves as the original written prescription for the pharmacy. No further documentation is required. 21 CFR 1306.11(f).

3. A practitioner prescribing a schedule II narcotic controlled substance for a patient enrolled in a hospice care program certified and/or paid for by Medicare under Title XVIII or a hospice program which is licensed by the state, may transmit, or direct his or her authorized agent to transmit, a prescription to the dispensing pharmacy by facsimile. The practitioner will note on the prescription that it is for a hospice patient. The facsimile serves as the original written prescription. No further documentation is required. 21 CFR 1306.11(g).

Schedules III-V Controlled Substances

A pharmacist may dispense directly a controlled substance listed in schedule III, IV, or V only pursuant to either a paper prescription signed by a practitioner, a facsimile of a signed paper prescription transmitted by the practitioner or the practitioner's agent to the pharmacy, an electronic prescription that meets DEA's requirements for such prescriptions, or a call-in prescription which is promptly reduced to writing by the pharmacist. 21 CFR 1306.21(a). (See *Section VII, Oral Authorization for Schedules III-V Controlled Substances.*)

Refills

Schedules III and IV controlled substances may be refilled if authorized on the prescription. However, the prescription may only be refilled up to five times within six months after the date of issue. After five refills or after six months, whichever occurs first, a new prescription is required. 21 U.S.C. 829(b) and 21 CFR 1306.22(a).

When a prescription for any controlled substance in schedules III or IV is refilled, the following information must be entered on either the back of the prescription, another appropriate document, or an electronic prescription record: the dispensing pharmacist's initials, the date the prescription was refilled, and the amount of drug dispensed on the refill. 21 CFR 1306.22(b) and (c). If the pharmacist only initials and dates the back of the prescription, the pharmacist will be deemed to have dispensed a refill for the full face amount of the prescription. 21 CFR 1306.22(d).

Electronic Recordkeeping of Schedules III-IV Refill Information

A pharmacy is permitted to use an electronic recordkeeping system as an alternative to the manual method for the storage and retrieval of refill information for original paper prescription orders for schedules III and IV controlled substances. 21 CFR 1306.22(f).

The electronic system must provide online retrieval of original prescription information for those prescriptions which are currently authorized for refill. The information must include, but is not limited to: the original prescription number; date of issuance; full name and address of the patient; the prescriber's name, address, and DEA registration number; the name, drug strength, dosage form and quantity of the controlled substance prescribed (and quantity dispensed if different from the quantity prescribed); and the total number of refills authorized by the prescriber. 21 CFR 1306.22(f)(1).

In addition, the electronic system must provide online retrieval of the current refill history for schedules III or IV controlled substance prescriptions. This information must include, but is not limited to: the name of the controlled substance, the date of refill, the quantity dispensed, the dispensing pharmacist's identification code or name/initials for each refill, and the total number of refills dispensed to date for that prescription. 21 CFR 1306.22(f)(2).

The pharmacist must verify and document that the refill data entered into the system is correct. 21 CFR 1306.22(f)(3). All computer generated prescription/refill documentation must be stored in a separate file at the pharmacy and must be maintained for a period of two years from the dispensing date. Under 21 CFR 1306.22(f), the pharmacy's electronic system must comply with the following guidelines:

1. If the system provides a hard copy printout of each day's controlled substance prescription refills, each pharmacist who refilled those prescriptions must verify the accuracy of the data by signing and dating the printout as he or she would sign a check or legal document. 21 CFR 1306.22(f)(3).

2. The printout must be provided to each pharmacy that uses the computer system within 72 hours of the date on which the refill was dispensed. The printout must be verified and signed by each pharmacist who dispensed the refills. 21 CFR 1306.22(f)(3).

3. In lieu of such a printout, the pharmacy must maintain a bound logbook or a separate file in which each pharmacist involved in the day's dispensing signs a statement, verifying that the refill information entered into the computer that day has been reviewed by him or her and is correct as shown. 21 CFR 1306.22(f)(3).

4. A pharmacy's electronic system must have the capability of printing out any refill data which the pharmacy must maintain under the CSA. For example, this would include a refill-by-refill audit trail for any specified strength and dosage form of any controlled substance, by either brand or generic name or both, dispensed by the pharmacy. Such a printout must include:

    a. Prescribing practitioner's name

    b. Patient's name and address

    c. Quantity and date dispensed on each refill

    d. Name or identification code of the dispensing pharmacist

    e. Original prescription number

    In any electronic system employed by a user pharmacy, the central recordkeeping location must be capable of providing a printout to a requesting pharmacy of the above information within 48 hours. 21 CFR 1306.22(f)(4).

5. In case a pharmacy's electronic system experiences downtime, the pharmacy must have a back-up procedure to document in writing refills of schedules III or IV controlled substances. This procedure must ensure that refills are authorized by the original prescription, that the maximum number of refills has not been exceeded, and that all required data is retained for online entry as soon as possible. 21 CFR 1306.22(f)(5).

A pharmacy may use only one of the two methods described (i.e., manual or electronic) for storage and retrieval of prescription order refill information of schedules III or IV controlled substances. 21 CFR 1306.22(g).

Facsimile Prescriptions for Schedules III-V Controlled Substances

Prescriptions for schedules III-V controlled substances may be transmitted by facsimile from the practitioner or the practitioner's agent to the dispensing pharmacy. The facsimile is considered to be equivalent to an original prescription as long as the practitioner has manually signed the prescription. 21 CFR 1306.21(a),(c).

Oral Authorization for Schedules III-V Prescriptions

A pharmacist may dispense a controlled substance listed in schedules III, IV, or V pursuant to an oral prescription made by an individual practitioner and communicated by the practitioner or their authorized agent, and promptly reduced to writing by the

pharmacist containing all information required for a valid prescription except for the signature of the practitioner. 21 CFR 1306.03(b),1306.21(a). (See Appendix D, *Pharmacist's Guide to Prescription Fraud*.)

Transfer of Schedules III-V Prescription Information

A DEA registered pharmacy may transfer original prescription information for schedules III, IV, and V controlled substances to another DEA registered pharmacy for the purpose of refill dispensing between pharmacies, on a one-time basis only. 21 CFR 1306.25. Neither the CSA nor DEA's regulations permit the transfer of any original unfilled prescription received in paper (including fax) or oral form to another pharmacy; however, after the original prescription is filled, the refills may be transferred, subject to the conditions placed on prescription transfers in 21 CFR 1306.25.

Transfers are subject to the following requirements:

Under 21 CFR 1306.25(b)(1), the transfer must be communicated directly between two licensed pharmacists and the transferring pharmacist must record the following information:

1. Write the word "VOID" on the face of the invalidated prescription; for electronic prescriptions, information that the prescription has been transferred must be added to the prescription record. 21 CFR 1306.25(b)(2)(i).

2. Record on the reverse of the invalidated prescription the name, address, and DEA registration number of the pharmacy to which it was transferred and the name of the pharmacist receiving the prescription information; for electronic prescriptions, such information must be added to the prescription record. 21 CFR 1306.25(b)(2)(ii).

3. Record the date of the transfer and the name of the pharmacist transferring the information. 21 CFR 1306.25(b)(2)(iii).

Under 21 CFR 1306.25(b)(3), for paper prescriptions and prescriptions received orally and reduced to writing by the pharmacist, the pharmacist receiving the transferred prescription information must write the word "transfer" on the face of the transferred prescription and reduce to writing all information required to be on a prescription and include:

1. Date of issuance of original prescription.

2. Original number of refills authorized on original prescription.

3. Date of original dispensing.

4. Number of valid refills remaining and date(s) and locations of previous refill(s).

5. Pharmacy's name, address, DEA registration number, and prescription number from which the prescription information was transferred.

6. Name of pharmacist who transferred the prescription.

7. Pharmacy's name, address, DEA registration number, and prescription number from which the prescription was originally filled.

Transferring Electronic Prescriptions for Controlled Substances (EPCS)

[Reserved]

Under 21 CFR 1306.25(b)(4), for electronic prescriptions being transferred electronically, the transferring pharmacist must provide the receiving pharmacist with the following information in addition to the original electronic prescription data:

1. The date of the original dispensing.

2. The number of refills remaining and the date(s) and locations of previous refills.

3. The transferring pharmacy's name, address, DEA registration number, and prescription number for each dispensing.

4. The name of the pharmacist transferring the prescription.

5. The name, address, DEA registration number, and prescription number from the pharmacy that originally filled the prescription, if different.

The pharmacist receiving a transferred electronic prescription must create an electronic record for the prescription that includes the receiving pharmacist's name and all of the information transferred with the prescription (listed above). 21 CFR 1306.25(b)(5).

The original and transferred prescription(s) must be maintained for a period of two years from the date of last refill. 21 CFR 1306.25(c).

Pharmacies electronically accessing the same prescription record must satisfy all information requirements of a manual mode for prescription transferal. 21 CFR 1306.25(d).

The procedure allowing the transfer of prescription information for refill purposes is permissible only if allowable under existing state or other applicable law. 21 CFR 1306.25(e).

Prescription Monitoring Programs

A prescription monitoring program is a state-administered data collection system used to gather prescription information. This information may be made available to state and federal investigators on a need-to-know basis.

Many states have established an electronic prescription drug monitoring program because it has proven to be an effective tool for detecting pharmaceutical diversion and for developing pharmacist and physician medical education programs. These programs heighten awareness about diversion, prescription drug abuse, drug trends, and are useful for tracking prescription medication dispensed within a state. In some states, the data can be used by pharmacists to identify potential "doctor shoppers" and those who attempt to obtain controlled substances by fraud, forgery, or deceit.

In the states that have adopted these programs, a large part of their success has been attributed to the pharmacists' participation. DEA strongly endorses prescription monitoring programs.

SECTION VIII – DISPENSING REQUIREMENTS

Required Information for Prescription Labels

The pharmacist dispensing a prescription for a controlled substance listed in schedules II, III, IV, or V must affix to the package a label showing date of filling, the pharmacy name and address, the serial (prescription) number, the name of the patient, the name of the prescribing practitioner, and directions for use and cautionary statements, if any, contained in such prescription as required by law. 21 CFR 1306.14(a), 1306.24(a). In addition to this information, if a prescription is filled at a central fill pharmacy, the central fill pharmacy must affix to the package a label showing the retail pharmacy name and address and a unique identifier (i.e., the central fill pharmacy's DEA registration number) indicating that the prescription was filled at the central fill pharmacy. 21 CFR 1306.14(b), 1306.24(b).

Federal Food and Drug Administration (FDA) regulations found in 21 CFR 290.5 require that the label of any drug listed as a "controlled substance" in schedules II, III, or IV of the CSA must, when dispensed to or for a patient, contain the following warning: "*CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.*" In addition, a pharmacist who receives a prescription for a controlled substance must dispense that prescription to the patient or a member of the patient's household. 21 U.S.C. 802(10) and (27). To deliver the controlled substance to anyone other than the patient or a member of the patient's household is distributing, not dispensing. 21 U.S.C. 802(10) and (11).

Schedule II Controlled Substance Prescriptions

A pharmacist may dispense a schedule II controlled substance, which is a prescription drug as determined under the Federal Food, Drug, and Cosmetic Act, only pursuant to a written prescription signed by the practitioner, except in an emergency situation as defined in the FDA regulations, and as described below. 21 CFR 1306.11(a).

Emergency Oral Schedule II Prescriptions

Under FDA and DEA regulations, an "emergency situation" in this context means that the prescribing practitioner has determined that immediate administration of the drug is necessary for proper treatment of the intended ultimate user, that no appropriate alternative treatment is available (including a drug which is not a schedule II controlled substance), and it is not reasonably possible for the prescribing practitioner to provide a written prescription for the drug at that time. 21 CFR 1306.11(d) and 21 CFR 290.10. In a bona fide emergency, a practitioner may telephone a schedule II prescription to the pharmacist who may then dispense the prescription. Under 21 CFR 1306.11(d), the prescribing practitioner must provide a written and signed prescription to the pharmacy within seven days and meet the below requirements:

1. The drug prescribed and dispensed must be limited to the amount needed to treat the patient during the emergency period. Prescribing or dispensing beyond the emergency period must be pursuant to a paper or electronic prescription signed by the prescribing individual practitioner. 21 CFR 1306.11(d)(1).

2. The prescription order must be immediately reduced to writing by the pharmacist and must contain all required information, except for the prescribing practitioner's signature. 21 CFR 1306.11(d)(2).

3. If the prescribing individual practitioner is not known to the pharmacist, he or she must make a reasonable effort to determine that the oral authorization came from a registered individual practitioner, which may include a call back to the prescribing individual practitioner using his or her telephone number as listed in the telephone directory and/or other good faith efforts to insure his or her identity. 21 CFR 1306.11(d)(3).

4. Within seven days after authorizing an emergency oral prescription, the prescribing practitioner must furnish the pharmacist a written, signed prescription for the emergency quantity of the controlled substance prescribed. 21 CFR 1306.11(d)(4). The prescription must have written on its face "Authorization for Emergency Dispensing" and the date of the oral order. 21 CFR 1306.11(d)(4). The written prescription may be delivered to the pharmacist in person or by mail, but if delivered by mail, it must be postmarked within the seven day period. 21 CFR 1306.11(d)(4).

5. Upon receipt, the dispensing pharmacist must attach this written prescription to the oral emergency prescription which had earlier been reduced to writing by the pharmacist. 21 CFR 1306.11(d)(4).

6. By regulation, the pharmacist must notify the local DEA Diversion Field Office (Appendix K) if the prescriber fails to provide a written prescription within seven days. 21 CFR 1306.11(d)(4). Failure of the pharmacist to do so will void the authority conferred on the pharmacy to dispense the controlled substance without a written prescription of a prescribing practitioner.

7. For electronic prescriptions, the pharmacist must annotate the record of the electronic prescription with the original authorization and date of the oral order. 21 CFR 1306.11(d)(4).

Partial Dispensing of Schedule II Controlled Substances

A prescription for a schedule II controlled substance may be partially dispensed if the pharmacist is unable to supply the full quantity of a written or emergency oral (telephone) prescription, provided the pharmacist notes the quantity supplied on the front of the written prescription, on a written record of the emergency oral prescription, or in the electronic prescription record. The remaining portion may be dispensed within 72 hours of the first partial dispensing. However, if the remaining portion is not or cannot be filled within the 72 hour period, the pharmacist must notify the prescribing practitioner. No further quantity may be supplied beyond 72 hours without a new prescription. 21 CFR 1306.13(a).

It is the position of DEA that the pharmacy must have the balance of the prescription ready for dispensing prior to the 72-hour limit, but the patient is not required to pick up the balance of the prescription within that 72-hour limit.

On July 22, 2016, the Comprehensive Addiction and Recovery Act of 2016 (CARA) was enacted and provided an addition to the schedule II partial fill allowances under 21 CFR 1306.13 (above). CARA Section 702 amended 21 U.S.C. 829 by adding subsection (f), which permits a prescription for a controlled substance in schedule II to be partially filled at the request of the patient or the prescribing practitioner if:

1. The partial filling is not prohibited by state law;

2. The prescription is written and filled in accordance with the CSA, DEA regulations, and state law;

3. The total quantity dispensed in all partial fillings does not exceed the total quantity prescribed; and

4. The remaining portions of a partially filled prescription in schedule II, if filled, shall be filled not later than 30 days after the date on which the prescription was written.

DEA views CARA's partial fill exception to be in addition to the exceptions currently listed under 21 CFR 1306.13. A pharmacist needs to check with their state to determine if its laws or regulations have been changed to parallel CARA. If the state regulations have not changed, and they still only allow the partial filling of a schedule II controlled substance under the conditions outlined in 21 CFR 1306.13(a), then the stricter state law applies until such time as the state makes a change.

Partial Filling of Schedule II Prescriptions for Terminally Ill or Long-Term Care Facility (LTCF) Patients

An LTCF is defined in the CFR as a nursing home, retirement care, mental care, or other facility or institution, which provides extended health care to resident patients. 21 CFR 1300.01(b) ("*Long-Term Care Facility (LTCF)*").

A prescription for a schedule II controlled substance written for a patient in an LTCF or for a patient with a medical diagnosis documenting a terminal illness, may be filled in partial quantities to include individual dosage units. 21 CFR 1306.13(b). If there is any question whether a patient may be classified as having a terminal illness, the pharmacist must contact the practitioner prior to partially filling the prescription. 21 CFR 1306.13(b). Both the pharmacist and the prescribing practitioner have a corresponding responsibility to assure that the controlled substance is for a terminally ill patient. 21 CFR 1306.13(b).

The pharmacist must record on the prescription whether the patient is "terminally ill" or an "LTCF patient." 21 CFR 1306.13(b). A prescription that is partially filled and does not contain the notation "terminally ill" or "LTCF patient" must be deemed to have been filled in violation of the CSA. 21 CFR 1306.13(b). For each partial filling, the dispensing pharmacist must record on the back of the prescription (or on another appropriate record, uniformly maintained, and readily retrievable) the date of the partial filling, quantity dispensed, remaining quantity authorized to be dispensed, and the identification of the dispensing pharmacist. 21 CFR 1306.13(b). The total quantity of schedule II controlled substances dispensed in all partial fillings must not exceed the total quantity prescribed. 21 CFR 1306.13(b). Schedule II prescriptions for patients in an LTCF or terminally ill patients are valid for a period not to exceed 60 days from the issue date unless sooner terminated by the discontinuance of medication. 21 CFR 1306.13(b).

Schedules III-V Controlled Substance Prescriptions

A pharmacist may dispense a controlled substance in schedules III, IV, or V having received either a paper prescription signed by a practitioner, a facsimile of that prescription transmitted by the practitioner or their agent to the pharmacy, an electronic prescription that meets DEA's requirements for such prescriptions, or an oral prescription made by an individual practitioner and communicated by the practitioner or their authorized agent. 21 CFR 1306.21(a). The pharmacist must promptly reduce the oral prescription to writing, including all required information except the signature of the prescribing practitioner. 21 CFR 1306.21(a).

Partial Dispensing Schedule III-V Controlled Substances

A pharmacist may partially dispense a prescription for schedules III-V controlled substances provided that each partial filling is recorded in the same manner as a

refilling, the total quantity dispensed in all partial fillings does not exceed the total quantity prescribed, and no dispensing occurs beyond six months from the date on which the prescription was issued. 21 CFR 1306.23.

Dispensing Without a Prescription

Dispensing a controlled substance without a prescription is governed by 21 CFR 1306.26. The regulation states that a controlled substance listed in schedules II, III, IV, or V which is not a prescription drug as determined under the Federal Food, Drug, and Cosmetic Act, may be dispensed by a pharmacist without a prescription to a purchaser at retail, provided that:

1. Such dispensing is made only by a pharmacist and not by a non-pharmacist employee even if under the supervision of a pharmacist (although after the pharmacist has fulfilled his or her professional and legal responsibilities, the actual cash, credit transaction, or delivery, may be completed by a non-pharmacist). 21 CFR 1306.26(a).

2. Not more than 240 cc. (8 ounces) of any such controlled substance containing opium, nor more than 120 cc. (4 ounces) of any other such controlled substance, nor more than 48 dosage units of any such controlled substance containing opium, nor more than 24 dosage units of any other such controlled substance, may be dispensed at retail to the same purchaser in any given 48-hour period. 21 CFR 1306.26(b).

3. The purchaser is at least 18 years of age. 21 CFR 1306.26(c).

4. The pharmacist requires every purchaser of a controlled substance not known to him to furnish suitable identification (including proof of age where appropriate). 21 CFR 1306.26(d).

5. A bound record book must be maintained in accordance with the recordkeeping requirement of 21 CFR 1304.04. (See *Section VI - Recordkeeping Requirements*.) It is maintained by the pharmacist, and contains the name and address of the purchaser, the name and quantity of the controlled substance purchased, the date of each purchase, and the name or initials of the pharmacist who dispensed the substance to the purchaser. 21 CFR 1306.26(e).

6. A prescription is not required for distribution or dispensing of the substance pursuant to any other federal, state or local law. 21 CFR 1306.26(f).

7. Central fill pharmacies may not dispense controlled substances at the retail level to a purchaser. 21 CFR 1306.26(g).

Delivery of a Controlled Substance to Persons in Other Countries

Controlled substances that are dispensed pursuant to a legitimate prescription may not be delivered or shipped to individuals in other countries without proper authorization. 21 CFR 1312.21(a). Any such delivery or shipment is an export under the CSA and cannot be conducted unless the person sending the controlled substances:

1. Has registered with DEA as an "exporter" (or is exempt from registration). 21 U.S.C. 957(a) & (b); 21 CFR 1312.21(a), (b), 1301.13(e)(1)(ix).

2. Has obtained the necessary permit(s), or submitted the necessary declaration(s) for export. 21 CFR 1312.21(c), 1312.22(a), 1312.23(a-c), 1312.27(a) & (b).

SECTION IX – SECURITY REQUIREMENTS

Requests for Employment Waivers for Certain Pharmacy Employees

A registrant must not employ in a position which allows access to controlled substances any person who has been convicted of a felony relating to controlled substances, or who, at any time, has had an application for a DEA registration denied, had a DEA registration revoked, or has surrendered a DEA registration for cause. 21 CFR 1301.76(a) "For cause" means surrendering a registration in lieu of, or as a consequence of, any federal or state administrative, civil, or criminal action resulting from an investigation of the individual's handling of controlled substances. 21 CFR 1301.76(a).

However, 21 CFR 1307.03 does permit registrants desiring to employ an individual who meets this definition to request an exception to this requirement. The employer must have a waiver approved before allowing such an employee or prospective employee to have access to controlled substances. A waiver request should be sent by the employer to the following address:

Drug Enforcement Administration
Diversion Control Division
Attn: Assistant Administrator
8701 Morrissette Drive
Springfield, VA 22152

A waiver will not be considered unless there are valid reasons to believe that diversion is unlikely to occur. In determining whether there is a valid reason to belive that diversion is unlikely to occur, DEA will consider, among other things:

1. A detailed description of the nature and extent of the individual's past controlled substances violations, including all pertinent documentation;

2. Current status of the individual's state licensure;

3. Extent of individual's proposed access to controlled substances. "Access" is not limited to only physical access to controlled substances, but includes any influence over the handling of controlled substances;

4. Registrant's proposed physical and professional safeguards to prevent diversion by the individual;

5. Status of employing registrant regarding handling of controlled substances;

6. Other pertinent information uncovered by DEA in its investigation of the individual's or registrant's handling of controlled substances; and

7. All other relevant factors or materials.

Controlled Substance Theft or Significant Loss

Under 21 CFR 1301.76(b), should a theft or significant loss of any controlled substance occur at a pharmacy, the following procedures must be implemented within one business day of the discovery of the theft or loss.

A. Notify DEA and Local Police

The theft of controlled substances from a registrant is a criminal act and a source of diversion that requires notification to DEA. A pharmacy must notify in writing the local DEA Diversion Field Office (Appendix K) within one business day of discovery of a theft or significant loss of a controlled substance. 21 CFR 1301.76(b). Although not specifically required by federal law or regulations, the registrant should also notify local law enforcement and state regulatory agencies. Prompt notification to law enforcement agencies will allow them to investigate the incident and prosecute those responsible for the diversion. If there is a question as to whether a theft has occurred or a loss is significant, a registrant should err on the side of caution and report it to DEA and local law enforcement authorities. (See below, *D. Registrant's Responsibility for Identifying "Significant Loss"*.)

DEA must be notified directly. 21 CFR 1301.76(b). This requirement is not satisfied by reporting the theft or significant loss in any other manner. For example, a corporation which owns or operates multiple registered sites and wishes to channel all notifications through corporate management or any other internal department responsible for security must still provide notice directly to their local DEA Diversion Field Office in writing within one business day upon discovery and keep a copy of that notice for its records.

B. Complete a DEA Form 106 (Report of Theft or Loss of Controlled Substances)

The DEA Form 106 is used to document the actual circumstances of the theft or significant loss and the quantities of controlled substances involved. A pharmacy must complete a DEA Form 106 (Report of Theft or Loss of Controlled Substances) (21 CFR 1301.76(b)) which can be found online at www.DEAdiversion.usdoj.gov under the Quick Links section. A pharmacy could download a fillable pdf version from this page.

A paper version of the form can be obtained by writing to:

Drug Enforcement Administration
Diversion Control Division
Attn: Registration & Program Support Section/DRR
8701 Morrissette Drive
Springfield, VA 22152

If completing the paper version, the pharmacy should send the original DEA Form 106 to the local DEA Diversion Field Office (Appendix K) and keep a copy for its records. Please see the *Guidelines for Completing the DEA Form 106* (Appendix I) for additional guidance, or email DEA's regulatory section at DRG@dea.usdoj.gov. If the theft or loss involves listed chemicals, please see page 91 for information on how to complete a DEA Form 107 (Theft or Loss of Listed Chemicals).

The DEA Form 106 must include the following information:

1. Name and address of the firm (pharmacy),
2. DEA registration number,
3. Date of theft or loss (or when discovered if not known),
4. Name and telephone number of local police department (if notified),
5. Type of theft (e.g., night break-in, armed robbery),
6. List of identifying marks, symbols, or price codes (if any) used by the pharmacy on the labels of the containers, and
7. A listing of controlled substances missing, including the strength, dosage form, and size of container (in milliliters if liquid form) or corresponding National Drug Code numbers.

C. If Investigation Finds No Theft or Loss

If, after the initial notification to DEA, the investigation of the theft or loss determines no such theft or loss of controlled substances occurred, a DEA Form 106 does not need to be filed. However, for complete and accurate records, it is strongly recommended that the registrant notify DEA in writing of this fact in order to resolve the initial report and

explain why no DEA Form 106 was filed regarding the incident. 21 CFR 1301.76, 1304.21(a), 21 U.S.C. 827(a)(3).

D. Registrant's Responsibility for Identifying "Significant Loss"

Although the CSA and the regulations do not define the term "significant loss," it is the responsibility of the registrant to use his or her best judgment to take appropriate action. Whether a "significant loss" has occurred depends, in large part, on the business of the pharmacy and the likelihood of a rational explanation for a particular occurrence. What would constitute a significant loss for a pharmacy may be viewed as comparatively insignificant for a hospital or manufacturer.

Further, the loss of a small quantity of controlled substances, repeated over a period of time, may indicate a significant problem for a registrant, which must be reported. Pursuant to 21 CFR 1301.76(b), the burden of responsibility is on the registrant to identify what is a significant loss and make the required report to DEA.

When determining whether a loss is significant, a registrant should consider, among others, the following factors:

1. The actual quantity of controlled substances lost in relation to the type of business;

2. The specific controlled substances lost;

3. Whether the loss of the controlled substances can be associated with access to those controlled substances by specific individuals, or whether the loss can be attributed to unique activities that may take place involving the controlled substances;

4. A pattern of losses over a specific time period, whether the losses appear to be random, and the results of efforts taken to resolve the losses; and, if known

5. Whether the specific controlled substances are likely candidates for diversion; and

6. Local trends and other indicators of the diversion potential of the missing controlled substances.

If it is determined that the loss is not significant, DEA recommends that the registrant place a record of the occurrence in a theft and loss file for future reference. Miscounts

or adjustments to inventory involving clerical errors on the part of the pharmacy should not be reported on a DEA Form 106, but rather should be noted in a separate log at the pharmacy management's discretion.

In-Transit Loss

When all or part of an in-transit shipment of controlled substances fails to reach its intended destination, the supplier is responsible for reporting the in-transit loss of controlled substances to DEA. 21 CFR 1301.74(c). The purchaser is responsible for reporting any loss of controlled substances after they have signed for or taken custody of a shipment. The purchaser must then submit a DEA Form 106. 21 CFR 1301.76(b). Otherwise, if the purchaser does not take custody of the shipment it is the supplier's responsibility for reporting any loss of controlled substances in the original shipment.

In-Transit Loss from Central Fill Pharmacy

Central fill pharmacies must comply with 21 CFR 1301.74(e) when selecting private, common, or contract carriers to transport filled prescriptions to a retail pharmacy for delivery to an ultimate user. 21 CFR 1301.76(d). Pursuant to 21 CFR 1301.76(d), when a central fill pharmacy contracts with private, common or contract carriers to transport filled prescriptions to a retail pharmacy, the central fill pharmacy is responsible for reporting the in-transit loss upon discovery of such loss by use of a DEA Form 106. In addition, when a retail pharmacy contracts with private, common, or contract carriers to retrieve filled prescriptions from a central fill pharmacy, the retail pharmacy is responsible for reporting in-transit losses upon discovery using a DEA Form 106. 21 CFR 1301.76(d).

Breakage and Spillage

While neither the CSA nor DEA's regulations specifically address the breakage and/or spillage of a controlled substance, DEA offers the following guidance, which was also published in the 2003 Notice of Proposed Rulemaking and guidance document, *Reports by Registrants of Theft or Significant Loss of Controlled Substances*, 68 FR 40576, 40578 (Jul. 8, 2003). The witnessed breakage or spillage of a controlled substance does not constitute a loss of controlled substances because the registrant can account for the controlled substances. These types of incidents do not require notification to DEA. If there is breakage, spillage, or other damage to controlled substances, but the controlled substances are still recoverable, there are **options** for disposing of them:

1. Promptly destroy that controlled substance in accordance with 21 CFR 1317.90 using an on-site method of destruction. 21 CFR 1317.05.

2. Send those controlled substances to an entity registered with DEA to handle returns/disposals (known as a reverse distributor). 21 CFR 1317.05(a)(2).

3. Contact the local DEA Diversion Field Office to request assistance to dispose of the controlled substances pursuant to 21 CFR 1317.05(a), 1304.21(e).

If the breakage or spillage is clearly observed, but the controlled substances are not recoverable, the registrant should document the circumstances of the event in his or her records. It is DEA's position that in order to maintain complete and accurate records in accordance with 21 CFR 1304.21(a) that non-recoverable breakage or spillage must be recorded on a DEA Form 41 and, as with any other form of disposal under 21 CFR Part 1317, should be signed by two individuals who can testify that a breakage or spillage occurred. These records must be maintained in the registrant's files and contain such information as required by 21 CFR 1304.22(c).

Robberies and Burglaries Involving Controlled Substances

The Controlled Substance Registrant Protection Act of 1984 (CSRPA) was enacted to protect DEA registrants against certain crimes. (See Title 18 U.S.C. 2118 for a complete text of CSRPA.) The CSRPA provides for the federal investigation of controlled substance burglaries and robberies (or attempts) if any of the following conditions are met:

1. The replacement cost of the controlled substances taken or attempted to be taken is $500 or more.

2. Interstate or foreign commerce was involved in the execution of the crime.

3. A person was killed or suffered significant bodily injury as a result of the crime.

The perpetrator(s) convicted of violating CSRPA's provisions may be subject to fines and/or imprisonment under Title 18, United States Code (18 U.S.C.).

SECTION X – TRANSFER OR DISPOSAL OF CONTROLLED SUBSTANCES

Transfer of Controlled Substances

A pharmacy may hire an outside firm to inventory, package, and arrange for the transfer of its controlled substances to another pharmacy, the original supplier, or the original manufacturer. The pharmacy is responsible for the actual transfer of the controlled substances and for the accuracy of the inventory and records. (See *Section XII*, Controlled Substance Distribution by a Pharmacy–"Five Percent Rule.") The records involving the transfer of controlled substances must be kept readily available by the pharmacy for two years for inspection by DEA. 21 U.S.C. 827(a) and (b), 21 CFR 1304.04(a), 1307.11(a)(1)(ii),(iii), 1305.17(c).

To transfer schedule II controlled substances, the receiving registrant must issue an official order form (DEA Form 222) or an electronic equivalent to the registrant transferring the drugs. 21 CFR 1307.11(a)(1)(iii), 1305.03. The transfer of schedules III-V controlled substances must be recorded by the distributing practitioner in accordance with 21 CFR 1304.22(c) and must be recorded by the receiving practitioner in accordance with 21 CFR 1304.22(c). 21 CFR 1307.11(a)(1)(ii). The document must include the names, addresses, and DEA registration numbers of the parties involved in the transfer of the controlled substances. 21 CFR 1304.22(c). (See *Section IV, Ordering Schedules III-V Controlled Substances*.)

Transfer to a Pharmacy

If a pharmacy goes out of business or is acquired by a new pharmacy, it may transfer the controlled substances to another pharmacy. On the day the controlled substances are transferred, a complete inventory must be taken in accordance with 21 CFR 1304.11 which documents the drug name, dosage form, drug strength, quantity, and date transferred. 21 CFR 1301.52(e)(1). In addition, DEA Form 222 or the electronic equivalent must be prepared to document the transfer of schedule II controlled substances. 21 CFR 1305.03. This inventory will serve as the final inventory for the registrant going out of business and transferring the controlled substances. It will also serve as the initial inventory for the registrant acquiring the controlled substances. A copy of the inventory must be included in the records of each pharmacy. It is not necessary to send a copy of the inventory to DEA. 21 CFR 1301.52(e)(1). The pharmacy acquiring the controlled substances must maintain all records involved in the transfer of the controlled substances for two years. 21 U.S.C. 827(b), 21 CFR 1304.04(a).

Transfer to the Original Supplier or Original Manufacturer

Any pharmacy may transfer controlled substances to the original supplier or the original manufacturer that is appropriately registered with DEA. Pursuant to 21 CFR 1317.10, 21 CFR 1304.22(c), the pharmacist must maintain a written record showing:

1. The date of the transaction.

2. The name, strength, dosage form, and quantity of the controlled substance.

3. The supplier or manufacturer's name, address, and registration number.

The DEA Form 222 or the electronic equivalent will be the official record for the transfer of schedule II controlled substances. 21 CFR 1317.10(b).

Disposal of Controlled Substances

All controlled substances to be destroyed by a registrant, or caused to be destroyed by a registrant pursuant to 21 CFR 1317.95(c), shall be destroyed in compliance with applicable federal, state, tribal, and local laws and regulations and shall be rendered non-retrievable. 21 CFR 1317.90(a). A pharmacy registrant may dispose of its controlled substances inventory in the following manner pursuant to 21 CFR 1317.05:

1. Promptly destroy that controlled substance in accordance with 21 CFR 1317.90 and 21 CFR 1317.95 using an on-site method of destruction. 21 CFR 1317.05.

2. Promptly deliver that controlled substance to a reverse distributor's registered location by common or contract carrier pick-up or by reverse distributor pick-up at the registrant's registered location. 21 CFR 1317.05(a)(2).

3. For the purpose of return or recall, promptly deliver that controlled substance by common or contract carrier pick-up or pick-up by other registrants at the registrant's registered location to: The registered person from whom it was obtained, the registered manufacturer of the substance, or another registrant authorized by the manufacturer to accept returns or recalls on the manufacturer's behalf. 21 CFR 1317.05(a)(3).

4. Request assistance from the Special Agent in Charge of the Administration in the area in which the practitioner is located. 21 CFR 1317.05(a)(4).

The pharmacy should contact the local DEA Diversion Field Office (Appendix K) for an updated list of DEA registered reverse distributors. In no case should drugs be forwarded to DEA unless the registrant has received prior approval from DEA.

Reverse Distributors Authorized to Dispose of Controlled Substances

A pharmacy may transfer controlled substances to a DEA registered reverse distributor who handles the disposal of controlled substances. 21 CFR 1317.05(a)(2). When a pharmacy transfers schedule II controlled substances to a reverse distributor for destruction, the reverse distributor must issue an official order form (DEA Form 222) or the electronic equivalent to the pharmacy. 21 CFR 1305.03, 1317.10(b). When schedules III-V controlled substances are transferred to a reverse distributor for destruction, the pharmacy must maintain a record of distribution that lists the drug name, dosage form, drug strength, quantity, and date transferred. 21 CFR 1317.10(a), 1304.22(a)(2)(iv). The DEA registered reverse distributor who destroys the controlled substances is responsible for submitting a DEA Form 41 (Registrants Inventory of Drugs Surrendered) to DEA when the controlled substances have been destroyed. 21 CFR 1304.21(e). A DEA Form 41 should **not** be used to record the transfer of controlled substances between the pharmacy and the reverse distributor disposing of the drugs.

An PDF version of the DEA Form 41 may be obtained online at www.DEAdiversion.usdoj.gov under the Reporting tab or by the following link: https://www.deadiversion.usdoj.gov/21cfr_reports/surrend/index.html#privacy.

A paper version of the DEA Form 41 may be requested by writing to:

Drug Enforcement Administration
Diversion Control Division
Attn: Registration Section/DRR
P.O. Box 2639
Springfield, VA 22152-2639

SECTION XI- AUTHORIZED COLLECTORS

On October 12, 2010, the President signed the ''Secure and Responsible Drug Disposal Act of 2010'' (the Act). This Act amended the CSA to allow authorized manufacturers, distributors, reverse distributors, narcotic treatment programs, hospitals/clinics with an on-site pharmacy, and retail pharmacies to collect pharmaceutical controlled substances from ultimate users by voluntarily administering mail-back programs and maintaining collection receptacles. 21 U.S.C. 822(g)(1), 21 CFR 1317.30(a), 1317.40(a). In addition, the regulations allow authorized hospitals/clinics and retail pharmacies to voluntarily maintain collection receptacles at LTCFs. 21 CFR 1317.75(d)(2)(iii). Ultimate users are thus able to deliver unused pharmaceutical controlled substances to appropriate entities for disposal in a safe and effective manner consistent with effective controls against diversion.

Authorized Collectors

Authorized collectors may receive a controlled substance for the purpose of destruction from an ultimate user, a person lawfully entitled to dispose of an ultimate user decedent's property, or an LTCF on behalf of an ultimate user who resides or has resided at that facility. 21 CFR 1300.01(b)("collector," "collection"), 1317.30(a)(1) & (b),1301.51(b).

Retail pharmacies and hospitals/clinics with on-site pharmacies may modify their registrations to obtain authorization to be a collector. 21 CFR 1301.51(b), 1317.40(a). Once authorized, such entities are "authorized collectors." There is no fee for a modification of registration. 21 CFR 1301.51(b)-(c).

Authorization to be a collector is subject to renewal. (See Section III, *Renewal of Pharmacy Registration*). Pursuant to 21 CFR 1301.52(f), if an authorized retail pharmacy or an authorized hospital/clinic with an on-site pharmacy desires to cease activities as an authorized collector, such pharmacy shall notify DEA of its intent by submitting a written notification to the Registration Unit, Drug Enforcement Administration at:

Drug Enforcement Administration
Diversion Control Division
Attn: Registration Section/DRR
P.O. Box 2639
Springfield, VA 22152

Notice may also be submitted on-line at

https://www.DEAdiversion.usdoj.gov/drugreg/index.html.

Authorized Collection Locations

Under 21 CFR 1317.40(b),1317.75(d), collection by an authorized retail pharmacy or an authorized hospital/clinic with an on-site pharmacy shall only occur:

1. Inside the registered location of the authorized retail pharmacy or authorized hospital/clinic with an on-site pharmacy; and

2. At long-term care facilities at which authorized hospitals/clinics with on-site pharmacies or retail pharmacies are authorized to maintain collection receptacles.

Authorized Collection Receptacle Locations

A. Authorized Retail Pharmacy

At an authorized retail pharmacy, collection receptacles shall be securely placed and maintained inside the registered location, or at an authorized LTCF. 21 CFR 1317.75(d)(1). If placed at an authorized retail pharmacy's registered location, the collection receptacle shall be located in the immediate proximity of a designated area where controlled substances are stored and at which an employee is present (e.g., can be seen from the pharmacy counter.) 21 CFR 1317.75(d)(2).

B. Authorized Hospital/Clinic

At an authorized hospital/clinic with an on-site pharmacy, collection receptacles shall be located in an area regularly monitored by employees, and shall not be located in the proximity of any area where emergency or urgent care is provided. 21 CFR 1317.75(d)(2)(i).

C. Long-Term Care Facility

At an LTCF, a collection receptacle shall be located in a secured area regularly monitored by LTCF employees. 21 CFR 1317.75(d)(2)(iii).

In the preamble of the final rule titled *Disposal of Controlled Substances* published by DEA in the Federal Register on September 9, 2014, DEA stated that the term "regularly" has its ordinary meaning "to generally be considered as being on a routine basis or at routine intervals." 79 FR 53520, 53528 (Sept. 9, 2014).

Authorized Collection Activities

Under 21 CFR 1317.40(c), authorized collectors with no on-site method of destruction may conduct the following activities:

1. Install, manage, and maintain collection receptacles located at their authorized collection location(s) pursuant to 21 CFR 1317.75, 1317.80. (See below.)

2. Promptly dispose of sealed inner liners and their contents as provided for in 21 CFR 1317.05(c)(2). (See Section X.)

Collection Receptacles

DEA regulations allow authorized collectors to maintain collection receptacles at their authorized collection location(s). 21 CFR 1317.40(c)(2). Thus, ultimate users are able to carry their unwanted pharmaceutical controlled substances to an authorized retail pharmacy, authorized hospital clinic with an on-site pharmacy, or other authorized collector location and deposit their unwanted or expired controlled substances in a secure container for disposal. Hospitals/clinics with on-site pharmacies and retail pharmacies that are authorized to be collectors may also maintain collection receptacles at LTCFs. 21 CFR 1317.40(b)(2).

Only those controlled substances listed in schedule II, III, IV, or V that are lawfully possessed by an ultimate user or other authorized non-registrant person may be collected. 21 CFR 1317.75(b). Controlled and non-controlled substances may be collected together and be comingled, although comingling is not required. 21 CFR 1317.75(b).

Authorized collectors shall only allow ultimate users and other authorized non-registrant persons in lawful possession of a controlled substance in schedule II, III, IV, or V to deposit such substances in a collection receptacle at a registered location. 21 CFR 1317.75(c). Authorized collectors shall not permit an ultimate user to transfer such substance to any person for any reason. 21 CFR 1317.75(c). Once a substance has been deposited into a collection receptacle, the substances shall not be counted, sorted, inventoried, or otherwise individually handled. 21 CFR 1317.75(c).

Collection Receptacle Design Specifications

Under 21 CFR 1317.75(e), a controlled substance collection receptacle shall meet the following design specifications:

1. Be securely fastened to a permanent structure so that it cannot be removed;

2. Be a securely locked, substantially constructed container with a permanent outer container and a removable inner liner as specified in 21 CFR 1317.60 (see Inner Liner Requirements, below);

3. The outer container shall include a small opening that allows contents to be added to the inner liner, but does not allow removal of the inner liner's contents;

4. The outer container shall prominently display a sign indicating that only schedule II-V controlled and non-controlled substances, if a collector chooses to comingle substances, are acceptable substances (schedule I controlled substances, controlled substances that are not lawfully possessed by the ultimate user, and other illicit or dangerous substances are not permitted); and

5. A small opening in the outer container of the collection receptacle shall be locked or made otherwise inaccessible to the public when an employee is not present (e.g., when the pharmacy is closed), or when the collection receptacle is not being regularly monitored by LTCF employees. This requirement does not apply to collection receptacles placed at narcotic treatment programs. 21 CFR 1317.75(f). However, at a narcotic treatment program, a collection receptacle shall be located in a room that does not contain any other controlled substances and is securely locked with controlled access. 21 CFR 1317.75(d)(2)(ii).

6. The installation and removal of the inner liner of the collection receptacle shall be performed by or under the supervision of at least two employees of the authorized collector.

7. For a collection receptacle at an LTCF: The installation, removal, transfer, and storage of inner liners shall be performed either: By or under the supervision of one employee of the authorized collector and one supervisor-level employee of the LTCF (e.g., a charge nurse or supervisor) designated by the authorized collector; or, by or under the supervision of two employees of the authorized collector. 21 CFR 1317.80(c).

Inner Liner Requirements

Under 21 CFR 1317.60(a)-(c), an inner liner shall meet the following requirements:

1. The inner liner shall be waterproof, tamper-evident, and tear-resistant;

2. The inner liner shall be removable and sealable immediately upon removal without emptying or touching the contents;

3. The contents of the inner liner shall not be viewable from the outside when sealed;

4. The size of the inner liner shall be clearly marked on the outside of the liner (e.g., 5-gallon, 10-gallon, etc.); and

5. The inner liner shall bear a permanent, unique identification number that enables the inner liner to be tracked.

6. Access to the inner liner shall be restricted to employees of the collector.

7. The inner liner shall be sealed by two employees immediately upon removal from the permanent outer container and the sealed inner liner shall not be opened, x-rayed, analyzed, or otherwise penetrated.

Inner Liner Recordkeeping

Pursuant to 21 CFR 1304.22(f)(2), each authorized hospital/clinic with an on-site pharmacy and each authorized retail pharmacy shall maintain the following records with regards to collection receptacle inner liners:

1. Date each unused inner liner is acquired, unique identification number and size (e.g., 5-gallon, 10-gallon, etc.) of each unused inner liner acquired.

2. Date each inner liner is installed, the address of the location where each inner liner is installed, the unique identification number and size (e.g., 5-gallon, 10-gallon, etc.) of each installed inner liner, the registration number of the collector, and the names and signatures of the two employees that witnessed each installation.

3. Date each inner liner is removed and sealed, the address of the location from which each inner liner is removed, the unique identification number and size (e.g., 5-gallon, 10-gallon, etc.) of each inner liner removed, the registration number of the collector, and the names and signatures of the two employees that witnessed each removal.

4. Date each sealed inner liner is transferred to storage, the unique identification number and size (e.g., 5-gallon, 10-gallon, etc.) of each sealed inner liner stored, and the names and signatures of the two employees that transferred each sealed inner liner to storage.

5. Date each sealed inner liner is transferred for destruction, the address and registration number of the reverse distributor or distributor to whom each sealed inner liner was transferred, the unique identification number and the size (e.g., 5-gallon, 10-gallon, etc.) of each sealed inner liner transferred, and the names and

signatures of the two employees that transferred each sealed inner liner to the reverse distributor or distributor.

Collection Receptacles at Long-Term Care Facilities

An LTCF may dispose of controlled substances in schedules II, III, IV, and V on behalf of an ultimate user who resides, or has resided, at such LTCF by transferring those controlled substances into an authorized collection receptacle located at that LTCF. 21 CFR 1317.80(a). When disposing of such controlled substances by transferring those substances into a collection receptacle, such disposal shall occur immediately, but no longer than three business days after the discontinuation of use by the ultimate user. Discontinuation of use includes a permanent discontinuation of use as directed by the prescriber, as a result of the resident's transfer from the LTCF, or as a result of death. 21 CFR 1317.80(a).

Only authorized retail pharmacies and authorized hospitals/clinics with an on-site pharmacy may install, manage, and maintain collection receptacles at LTCFs and remove, seal, transfer, and store, or supervise the removal, sealing, transfer, and storage of sealed inner liners at LTCFs. 21 CFR 1317.80(b). Such authorized retail pharmacies and authorized hospitals/clinics shall comply with all of the requirements of 21 CFR 1317.60, 1317.75, 1317.80. 21 CFR 1317.80(b).

The installation, removal, transfer, and storage of inner liners shall be performed either: By or under the supervision of one employee of the authorized retail pharmacy or authorized hospital/clinic with an on-site pharmacy, and one supervisor-level employee of the LTCF (e.g., a charge nurse or supervisor) designated by the authorized collector; or, by or under the supervision of two employees of the authorized collector. 21 CFR 1317.80(c).

Upon removal, sealed inner liners may only be stored at the LTCF for up to three business days in a securely locked, substantially constructed cabinet or a securely locked room with controlled access until transfer in accordance with 21 CFR 1317.05(c)(2)(iv). 21 CFR 1317.80(d).

Neither an authorized hospital/clinic with an on-site pharmacy nor an authorized retail pharmacy shall operate a collection receptacle at an LTCF until its registration has been modified in accordance with 21 CFR 1301.51. 21 CFR 1317.80(e).

Mail-Back Packages

A hospital/clinic with an on-site pharmacy or a retail pharmacy can partner with an authorized reverse distributor who conducts a mail-back program by providing empty mail-back packages to patients. 21 CFR 1317.70(c). This does not require modification of a DEA registration, and there are no recordkeeping requirements.

SECTION XII – OTHER PHARMACY OPERATIONS

Central Fill Pharmacy

A "central fill pharmacy" (See Appendix B, *Definitions*) fills prescriptions for controlled substances on behalf of retail pharmacies with which it has a contractual agreement to provide such services or with pharmacies who share a common owner. When one retail pharmacy receives a prescription and a second pharmacy prepares and subsequently delivers the controlled substance medication to the first retail pharmacy for dispensing to the patient, the second pharmacy is engaging in a "central fill" activity. 21 CFR 1300.01(b). Records must be maintained by both the central fill pharmacy and the retail pharmacy that completely reflect the disposition of all controlled substance prescriptions dispensed. 21 CFR 1306.15, 1306.27. Central fill pharmacies are required to comply with the same security and recordkeeping requirements applicable to retail pharmacies including the general requirement to maintain effective controls and procedures to guard against theft and diversion of controlled substances. 21 CFR 1301.71(a), 1301.75-76, 1304.04(h), and 21 U.S.C. 827(b). Retail pharmacies that also perform central fill activities are allowed to do so without a separate DEA registration. 21 CFR 1301.13(e)(1)(iv)(table).

Central fill pharmacies are permitted to prepare both initial and refill prescriptions, subject to all applicable state and federal regulations. Only a licensed pharmacist may fill the prescription. 21 CFR 1306.06. Both the retail and central fill pharmacists have a corresponding responsibility to ensure that the prescription was issued for a legitimate medical purpose by an individual practitioner acting in the usual course of professional practice and otherwise in the manner specified by DEA regulations. 21 CFR 1306.04(a).

Prescription information may be provided to an authorized central fill pharmacy by a retail pharmacy for dispensing purposes. 21 CFR 1306.15, 1306.27. Prescriptions for controlled substances listed in schedules II, III, IV, or V may be transmitted electronically from a retail pharmacy to a central fill pharmacy including via facsimile. 21 CFR 1306.15(a), 1306.27(a). For electronic prescriptions, the name, address, and the DEA registration number of the central fill pharmacy to which the prescription has been transmitted, the name of the retail pharmacy pharmacist transmitting the prescription, and the date of transmittal must be added to the electronic prescription record. 21 CFR 1306.15(a)(1), 1306.27(a)(1).

Under 21 CFR 1306.15(a), 1306.27(a), the retail pharmacy transmitting the prescription information must:

1. Write the words "CENTRAL FILL" on the face of the original prescription and record the name, address, and DEA registration number of the central fill pharmacy to which the prescription has been transmitted and the name

of the retail pharmacy pharmacist transmitting the prescription, and the date of transmittal;

2. Ensure that all information required to be on a prescription is transmitted to the central fill pharmacy (either on the face of the prescription or in the electronic transmission of information);

3. Maintain the original prescription for a period of two years from the date the prescription was last filled (for schedule II prescriptions) or refilled (for schedules III-V prescriptions);

4. Keep a record of receipt of the filled prescription, including the date of receipt, the method of delivery (private, common, or contract carrier) and the name of the retail pharmacy employee accepting delivery;

5. For schedules III-V prescriptions, indicate in the information transmitted the number of refills already dispensed and the number of refills remaining (refills for schedule II prescriptions are not permitted).

Under 21 CFR 1306.15(b) and 1306.27(b), the central fill pharmacy receiving the transmitted prescription must:

1. Keep a copy of the prescription (if sent via facsimile) or an electronic record of all the information transmitted by the retail pharmacy, including the name, address, and the DEA registration number of the retail pharmacy transmitting the prescription;

2. Keep a record of the date of receipt of the transmitted prescription, the name of the licensed pharmacist filling the prescription, and dates of filling or refilling of the prescription; and

3. Keep a record of the date the filled prescription was delivered to the retail pharmacy and the method of delivery (i.e., private, common, or contract carrier).

Central fill pharmacies must affix to the package a label showing the date of filling, the serial number of the prescription, the name of the patient, the name of the prescribing practitioner, the retail pharmacy name and address, and a unique identifier (i.e., the central fill pharmacy's DEA registration number) indicating that the prescription was filled at the central fill pharmacy and directions for use and cautionary statements, if any, contained in such prescription or required by law. 21 CFR 1306.14(a),(b), 1306.24(a),(b). Central fill pharmacies must comply with the provisions of 21 CFR 1301.74(e) when selecting private, common, or contract carriers to transport filled prescriptions to a retail pharmacy (and likewise for retail pharmacies retrieving filled

prescriptions from a central fill pharmacy) for delivery to the ultimate user 21 CFR 1301.76(d).

The requirement under 21 CFR 1306.27, to write "CENTRAL FILL" applies to the retail pharmacy transmitting prescription information to a central fill pharmacy; DEA regulations do not require that a central fill pharmacy write "CENTRAL FILL" on the prescriptions that it fills or refills.

Long-Term Care Facilities

An LTCF is defined in the CFR as a nursing home, retirement care, mental care, or other facility or institution, which provides extended health care to resident patients. 21 CFR 1300.01(b) ("*Long-Term Care Facility (LTCF)*"). In most cases, these facilities are not registered with DEA, yet these health care facilities routinely maintain controlled substances issued via prescription to their residents. These controlled substances are already outside the CSA's closed drug distribution system since they have been dispensed to the ultimate user.

LTCFs frequently need to dispose of unused medications due to a change in the resident's medication or the resident's death. Accordingly, LTCFs should contact the local DEA Diversion Field Office (Appendix K) for drug disposal instructions. DEA is aware of issues currently facing LTCFs concerning the dispensing and handling of controlled substances, which are affected by a variety of state laws and circumstances. Pharmacists should check with their state agency for guidelines concerning controlled substances at LTCFs.

Regulations concerning LTCFs can also be found under:

1. Section VII, *Exceptions for Schedule II Facsimile Prescriptions*
2. Section VIII, *Partial Filling of Schedule II Prescriptions for Terminally Ill or Long-Term Care Facility Patients*
3. Section XI, *Collection Receptacles at Long-Term Care Facilities*

Use of Automated Dispensing Systems by Retail Pharmacies at Long-Term Care Facilities

Automated dispensing system means a mechanical system that performs operations or activities, other than compounding or administration, relative to the storage, packaging, counting, labeling, and dispensing of medications, and which collects, controls, and maintains all transaction information. 21 CFR 1300.01(b) ("*Automated dispensing system*").

If state law and regulations permit, DEA will allow a retail pharmacy to register at the site of the LTCF and store controlled substances in an Automated Dispensing System (ADS) as outlined in 21 CFR 1301.27. In an ADS, a pharmacy stores bulk drugs in the machine in separate bins or containers. The pharmacy programs and controls the ADS remotely. Authorized LTCF staff are allowed access to its contents, which are dispensed on a single-dose basis at the time of administration pursuant to a valid prescription. The ADS electronically records each dispensing, thus maintaining dispensing records for the pharmacy. Because the drugs are not considered dispensed until the system provides them, drugs in the ADS are counted as pharmacy stock. 21 CFR 1300.01(b) ("*Inventory*"). A registered retail pharmacy that possesses additional registrations for ADS machines at LTCFs may keep most records required for those additional registered sites at the retail pharmacy or other approved central location. 21 CFR 1304.04(a)(2) and 21 CFR 1304.04(b)(1).

DEA registered pharmacies wishing to operate an ADS at an LTCF must contact the DEA Office of Diversion Control, Registration Section, at 1-800-882-9539 for registration instructions. An affidavit which meets the requirement of 21 CFR 1301.17(c) must also be submitted with DEA. 21 CFR 1301.27(a).

Emergency Kits for Long-Term Care Facilities

DEA has issued a policy statement which provides individual state licensing and regulatory boards with general guidelines for establishing specific rules concerning controlled substances used in emergency kits at LTCFs. 45 FR 24128 (Apr. 9, 1980) (See Appendix H, *Guidelines for Emergency Kits in Long-Term Care Facilities*.)

All emergency kits (whether or not they are electronic) remain subject to the policy statement in Appendix H, provided they satisfy the criteria of that policy statement at all times. 45 FR 24128 (Apr. 9, 1980). Among other things, it is crucial to bear in mind that an emergency kit is for use in emergencies as defined by the state. It also bears emphasis that, in accordance with the CSA and DEA regulations, a controlled substance may only be dispensed for emergency purposes (or otherwise) pursuant to a valid prescription or medical order. 21 U.S.C. 841(a)(1), 21 CFR 1306.04(a), 21 CFR 1300.01(b) ("*prescriptions*"). Thus, where the kit is maintained at the LTCF by a pharmacy, controlled substances may not be dispensed from the kit for emergencies prior to receipt by the pharmacist of a valid prescription in accordance with the requirements of 21 CFR 1306.11, 1306.21. As these sections of the regulations indicate, such prescriptions may, depending on the circumstances, be issued in writing (paper or electronic in accordance with Part 1311), orally, or by fax. In addition, to be valid, a prescription for a controlled substance must be issued for a legitimate medical purpose by a practitioner acting in the usual course of his professional practice, and the pharmacist bears a corresponding responsibility therefor. 21 CFR 1306.04(a). If, at any time, a kit is used to administer or dispense controlled substances for a purpose other

than in emergencies as defined by the state, the kit thereafter ceases to be an emergency kit and, as a result, the separate registration requirement applies.

Opioid (Narcotic) Addiction Treatment Programs

The Narcotic Addict Treatment Act of 1974, the Drug Addiction Treatment Act (DATA) of 2000, the Comprehensive Addiction and Recovery Act of 2016 (CARA) and the SUPPORT for Patients and Communities Act of 2018 amended the CSA with respect to the use of controlled substances in the medical treatment of opioid addiction. These laws established the procedures for approving and licensing practitioners involved in the treatment of opioid addiction as well as improving the quality and delivery of that treatment to the segment of society in need.

Practitioners wishing to dispense FDA approved schedule II controlled substances (e.g., methadone) for maintenance and detoxification treatment must obtain a separate DEA registration as a Narcotic Treatment Program via a DEA Form 363 which may be completed online. 21 U.S.C. 823(f),(g)(1), and 21 CFR 1306.07(a)(1). In addition to obtaining this separate DEA registration, this type of activity also requires the approval and certification by the Center for Substance Abuse Treatment (CSAT) within the Substance Abuse and Mental Health Services Administration (SAMHSA) of the U.S. Department of Health and Human Services (HHS).

Qualifying Practitioners

NOTE: For the purposes of this manual, the term "Qualifying Practitioner" will replace the terms "Qualifying Physician" and "DATA-Waived Physician," and will not include Qualifying Other Practitioners. Also, the term "Qualifying Other Practitioner" will be used for nurse practitioners and physician assistants, and until October 1, 2023, or until this sunset provision in the 2018 SUPPORT for Patients and Communities Act is removed by law, clinical nurse specialists, certified registered nurse anesthetists, or certified nurse midwives.

A "Qualifying Practitioner" is a practitioner who is licensed under state law; who is registered with DEA under 21 U.S.C. 823(f) to dispense controlled substances as defined under 21 U.S.C. 802(10); and, who is qualified by specified training and/or certification. 21 U.S.C. 823(g)(2)(G)(ii),(iii) and 21 CFR 1301.28(b)(1)(i). In order to obtain a waiver from the requirement of obtaining a separate registration as a Narcotic Treatment Program under 21 U.S.C 823(g)(1), a practitioner must be capable of providing directly, by referral, or in such other manner as determined by the Secretary of HHS, appropriate counseling and other appropriate ancillary services. 21 U.S.C. 823(g)(2)(B)(ii) and 21 CFR 1301.28(b)(1)(ii).

If a practitioner wishes to become a Qualifying Practitioner, the practitioner must submit notification to the Secretary of HHS stating the individual's intent to prescribe or dispense schedules III, IV, or V narcotic controlled drugs or combinations of narcotic controlled drugs approved by the FDA for maintenance or addiction treatment (i.e., buprenorphine or buprenorphine combination products). 21 CFR 1301.28(b)(1). The notice must contain all of the certification required in 21 CFR 1301.28(b)(1)(i). After receiving the notification submitted under 21 CFR 1301.28(b)(1), the Secretary of HHS will forward a copy of the notification to the Administrator of DEA. 21 CFR 1301.28(d)(1).

Upon notification from SAMHSA that the individual practitioner has been issued a written waiver, qualifies under DATA, and has the appropriate DEA registration, DEA will issue a UIN as well as a new DEA Form 223 bearing their DEA registration number, a UIN, a corresponding business activity, and their authorized patient limit. 21 U.S.C. 823(g)(2)(D)(ii). Pursuant to 21 CFR 1301.28(d)(3), the practitioner is required to include the UIN on all prescriptions when prescribing FDA approved schedules III, IV, or V narcotic controlled drugs for use in maintenance or detoxification treatment. 21 CFR 1306.05(b). The listing of the UIN on a prescription is in addition to all other information required on a valid prescription to include the practitioner's DEA registration number (See Section VII, *Valid Prescription Requirements*.)

Qualifying Other Practitioners

Under federal law, the term "Qualifying Other Practitioner" means a nurse practitioner, physician assistant, clinical nurse specialist, certified registered nurse anesthetist, certified nurse midwife, or physician assistant who satisfies each of the following criteria:

(1) "is licensed under state law to prescribe schedule III, IV, or V medications for the treatment of pain"; (2) "has completed not fewer than 24 hours of initial training addressing each of the topics listed in" 21 U.S.C. 823(g)(2)(G)(ii)(IV), "or has such other training or experience as the Secretary of HHS determines will demonstrate the ability of the nurse practitioner, clinical nurse specialist, certified registered nurse anesthetist, certified nurse midwife, or physician assistant to treat and manage opiate-dependent patients"; and (3) "[t]he nurse practitioner, clinical nurse specialist, certified nurse anesthetist, certified nurse midwife, or physician assistant is supervised by, or works in collaboration with, a qualifying physician, or physician assistant is supervised by, or works in collaboration with, a qualifying physician, if the nurse practitioner, clinical nurse specialist, certified registered nurse anesthetist, certified nurse midwife, or physician assistant is required by State law to prescribe medications for the treatment of opioid use disorder in collaboration with or under the supervision of a physician." 21 U.S.C. 823(g)(2)(G)(iv).

The Secretary may, by regulation, revise the requirements for being a Qualifying Other Practitioner. A nurse practitioner, clinical nurse specialist, certified registered nurse anesthetist, certified nurse midwife, or physician assistant who meets the requirements

can now be authorized to prescribe FDA-approved schedule III-V narcotic controlled substances for maintenance and detoxification treatment. 21 U.S.C. 823(g)(2)(A)-(B), (G)(iii)-(iv).

Prescriptions for Maintenance and Detoxification Treatment

A Qualifying Practitioner or Qualifying Other Practitioner needs one DEA registration and a Unique Identification Number (UIN) to prescribe FDA approved schedule III-V narcotics within a state for the purpose of treating opioid addiction. 21 CFR 1301.28(a). The prescription must be issued by the individual practitioner for a legitimate medical purpose in the usual course of their professional practice and be compliant with all associated federal and state laws and regulations. 21 CFR 1306.04(a).

If a Qualifying Practitioner or Qualifying Other Practitioner is practicing at multiple locations within the same state and is only prescribing FDA-approved schedule III-V narcotic controlled drugs for maintenance and detoxification treatment, then they must affix to the prescription the DEA registration number that they has been assigned in that jurisdiction along with the UIN. 21 CFR1306.05(a) and (b). As mentioned previously, a Qualifying Other Practitioner may be required by state law to be supervised by, or work in collaboration with, a Qualifying Practitioner. 21 U.S.C. 823(g)(2)(G)(iv)(III).

If a Qualifying Practitioner is practicing at multiple locations within the same state and is administering or dispensing FDA-approved schedule III-V narcotic controlled drugs for maintenance or detoxification treatment, then they must affix to the prescription, and on all records when dispensing, the DEA registration number that is assigned to that specific registered location in that state along with the UIN. 21 CFR 1301.28(d)(3), 1301.12(a) & (b)(3), 1306.05(a)-(b).

If a Qualifying Practitioner is prescribing FDA-approved schedule III-V narcotic controlled drugs for maintenance and detoxification treatment in multiple states, then he or she must affix to the prescription the DEA registration number that is assigned to that specific registered location in that state along with the UIN. 21 CFR 1306.05(a)-(b), 1301.12(a), 1301.28(d)(3).

The UIN must be used in each jurisdiction where the Qualifying Practitioner or Qualifying Other Practitioner is registered with DEA, and is administering or dispensing FDA-approved schedule III-V narcotic controlled drugs for maintenance or detoxification treatment. 21 CFR 1301.28(d)(3).

Delivery of a Controlled Substance by a Pharmacy to an Administering Practitioner

The SUPPORT for Patients and Communities Act of 2018 (the SUPPORT Act) amended the CSA to allow a pharmacy to deliver a controlled substance to a practitioner in accordance with a prescription that meets the requirements of 21 U.S.C.

829 and 21 CFR Part 1306 for the purpose of administering the controlled substance by the practitioner if:

1. The controlled substance is delivered by the pharmacy to the prescribing practitioner or the practitioner administering the controlled substance, as applicable, at the location listed on the practitioner's certificate of registration; 21 U.S.C. 829a(a)(1);

2. The controlled substance is to be administered for the purpose of maintenance or detoxification treatment under 21 U.S.C. 823(g)(2) and

    a. The practitioner who issued the prescription is a "Qualifying Practitioner" or "Qualifying Other Practitioner" per 21 U.S.C. 823(g)(2)(G); and

    b. The controlled substance is to be administered by injection or implantation; 21 U.S.C. 829a(a)(2);

3. The pharmacy and the practitioner are authorized to conduct the activities specified in this section under the law of the state in which such activities take place; 21 U.S.C. 829a(a)(3);

4. The prescription is not issued to supply any practitioner with a stock of controlled substances for the purpose of general dispensing to patients; 21 U.S.C. 829a(a)(4);

5. The controlled substance is to be administered only to the patient named on the prescription not later than **14 days*** after the date of receipt of the controlled substance by the practitioner; 21 U.S.C. 829a(a)(5); and

6. Notwithstanding any exceptions under 21 U.S.C. 827, the prescribing practitioner, and the practitioner administering the controlled substance, as applicable, maintain complete and accurate records of all controlled substances delivered, received, administered, or otherwise disposed of under this section, including the persons to whom controlled substances were delivered and such other information as may be required by the CSA and DEA regulations (i.e., 21 CFR Part 1304). 21 U.S.C. 829a(a)(6).

***NOTE**: During a 2-year period which began on the date of enactment of the SUPPORT Act, October 24, 2018, the Attorney General, in coordination with the Secretary for Health and Human Services, may reduce the number of days described in "5" above, if the Attorney General determines that such reduction will reduce the risk of diversion or protect the public health. Any such modification shall be for a period not less than 7 days.

Prescribing Buprenorphine for Pain

Neither the CSA nor its implementing regulations expressly prohibit the prescribing and dispensing of buprenorphine or other opiate products for the treatment of pain. Federal regulations do require that controlled substances be prescribed for a legitimate medical purpose by a DEA registered practitioner acting in the usual course of his or her professional practice. 21 CFR 1306.04(a). If a DEA registered practitioner issues a prescription for a buprenorphine drug product approved by the FDA for the treatment of pain, or off-label prescribes a buprenorphine drug product approved by the Food and Drug Administration (FDA) for maintenance or detoxification treatment for the treatment of pain, then the UIN or "X" Number is not required. Please note that the specific prescribing or dispensing of certain buprenorphine products for pain may be considered "off-label" use. DEA cannot address any possible consequences under the Food, Drug, and Cosmetic Act (FD&C) for dispensing for unapproved (off-label) uses.

Dispensing Controlled Substances for the Treatment of Pain

On September 6, 2006, DEA published in the Federal Register a Policy Statement, *Dispensing Controlled Substances for the Treatment of Pain*. 71 FR 52716 (Sept. 6, 2006). The purpose of the Policy Statement was to make clear the longstanding requirement under the law that physicians may prescribe controlled substances only for a legitimate medical purpose in the usual course of professional practice. 21 CFR 1306.04. In no way should this interfere with the legitimate practice of medicine or cause any physician to be reluctant to provide legitimate pain treatment. The second purpose of the Policy Statement was for DEA to dispel the mistaken notion among a small number of medical professionals that the agency has embarked on a campaign to "target" physicians who prescribe controlled substances for the treatment of pain or that physicians must curb their legitimate prescribing of pain medications to avoid legal liability.

To achieve these aims, the document summarized the relevant legal principles and provided an explanation of DEA's role with respect to the regulation of controlled substances. The document also addressed specific issues and questions that have been raised on a recurring basis by physicians who seek guidance on the subject of dispensing controlled substances for the treatment of pain.

For additional guidance on the responsibilities of the pharmacist where it pertains to the treatment of pain. (See Section VII, *Corresponding Responsibility*.)

Compounding and Other Manufacturing Activities Involving Controlled Substances

The term "manufacture" means the production, preparation, propagation, compounding, or processing of a drug or other substance, either directly or indirectly or by extraction from substances of natural origin, or independently by means of chemical synthesis or by a combination of extraction and chemical synthesis, and includes any packaging or repackaging of such substance or labeling or relabeling of its container; except that such term does not include the preparation, compounding, packaging, or labeling of a drug or other substance in conformity with applicable state or local law by a practitioner as an incident to his administration or dispensing of such drug or substance in the course of his professional practice. The term "manufacturer" means a person who manufactures a drug or other substance. 21 U.S.C. 802(15).

Controlled Substance Distribution by a Pharmacy – "Five Percent Rule"

Pursuant to 21 CFR 1307.11(a), a pharmacy registered to dispense controlled substances may distribute such substances (without being registered as a distributor) to another pharmacy or to a registered practitioner for the purpose of general dispensing by the practitioner to patients, provided that the following conditions are met:

1. The pharmacy or practitioner that will receive the controlled substance is registered under the CSA to dispense that controlled substance;

2. The distribution is recorded by the distributing practitioner in accordance with 21 CFR 1304.22(c) and the receipt is recorded by the receiving practitioner in accordance with 21 CFR 1304.22(c);

3. If the pharmacy distributes a schedule II controlled substance in response to an official order form (DEA Form 222) submitted by a practitioner in accordance with 21 CFR 1305.12, it must document the transfer on an official order form (DEA Form 222) or the electronic equivalent. The distributing pharmacy must retain the original copy (if using single sheet DEA Form 222), or Copy 1 (if using the triplicate DEA Form 222). Any supplier who is not required to report acquisition/disposition transactions to the Automation of Reports and Consolidated Orders System (ARCOS) under **1304.33(**c) (such as a practitioner) must make and submit a copy of the original DEA Form 222 to DEA, either by mail to the Registration Section, or by email to DEA.Orderforms@usdoj.gov. For instructions on completing this form, see Section IV, *Ordering Controlled Substances*. In addition, pharmaices must have a system to identify any suspicious orders, which when identified must be reported online to SORS.

4. **"Five Percent Rule"** – The total number of dosage units of all controlled substances distributed by a pharmacy may not exceed five percent of the total number of dosage units of all controlled substances dispensed by the pharmacy

during a calendar year. If at any time during the calendar year the total number of dosage units of controlled substances distributed exceed five percent of the total number of dosage units of controlled substances distributed and dispensed, the pharmacy is required to register as a distributor.

United States Postal Service Mailing Requirements for Controlled Substances

United States Postal Services issued guidance permiting the mailing of controlled substances by drug manufacturers or their agents, pharmacies, or other authorized handlers when distribution is lawful under DEA regulations and if the mailer or the addressee meets one of the following conditions:

1. The mailer or the addressee is registered with DEA.

2. The mailer or the addressee is exempt from DEA registration as permissible by law.

United States Postal Service issued guidance permiting the mailing of any controlled substance, provided it is not outwardly dangerous and will not cause injury to a person's life or health, and if the following preparation and packaging standards are met:

1. The inner packaging of any parcel containing controlled substances is marked and sealed as required by the provisions of the CSA and its implementing regulations, and is placed in a plain outer container or securely wrapped in plain paper.

2. If the controlled substance consists of a prescription medicine, the inner container is also labeled to show the name and address of the pharmacy, practitioner, or other person dispensing the prescription.

3. The outside wrapper or packaging is free of markings that would indicate the nature of the contents.

For additional guidance on this issue please see the United States Postal Service's Publication 52, *Hazardous, Restricted, and Perishable Mail,* 453 Controlled Substances and Drugs.

Patients Bringing Medications from Home to the Hospital

DEA is aware that many pharmacies operate in a hospital setting.

If a patient is admitted to a hospital via ambulance/emergency medical services (EMS), and there is no family present, and the patient has in his or her possession dispensed medications, including controlled substances, it is DEA's position that:

1. If the treating practitioner deems that it is medically appropriate for the patient to continue to take any controlled substance medications brought from the patient's residence to the DEA registered hospital, the hospital could secure the controlled substances with the patient's effects in his or her hospital room (e.g., small safe or secured lock box). Thus, the hospital has not taken possession of the controlled substances and it would not be considered an unlawful distribution by the ultimate user under 21 U.S.C. 841(a).

2. If the treating practitioner deems that it would be medically inappropriate for the patient to continue taking any controlled substance medication(s) brought from the patient's residence to the DEA registered hospital, or it is the hospital's policy not to permit patients to bring already dispensed controlled medications into the hospital, then the hospital has the following options:

    a. If a member of the patient's household arrives at the hospital, the hospital can turn over the patient's medications, including controlled substances, to him or her. The member of the patient's household can take the controlled medications back to the household and/or dispose of them in a manner that is in accordance with federal, state, local and tribal laws and regulations.

    b. If a hospital has modified its DEA registration to become an authorized collector and has placed a collection receptacle at its registered location, then a member of the patient's household may dispose of the patient's medications, including controlled substances, in the hospital's collection receptacle.

    c. If a hospital has empty mail-back packages (no modification of the hospital's DEA registration is required), then the hospital may provide one or more of the mail-back packages to a member of the patient's household to place the medications, including controlled substances, into the mail-back package(s) and seal the package(s) for mailing to the authorized DEA registered reverse distributor for disposal purposes.

    d. If there is no member of the patient's household present, " DEA understands that there may be circumstances where there is no authorized person to dispose of the controlled substances, such as when controlled substances are

abandoned ... and return to the ultimate user is not feasible. In such instances, the affected entities should contact local law enforcement or their local DEA Diversion Field Office for guidance on proper disposal procedures." 79 FR 53546.

e. If your state has passed a law or regulation authorizing a hospital to dispose of controlled substances that have been dispensed to a patient admitted to the hospital and are considered abandoned (e.g., the patient left the controlled substance medications and they cannot be returned; or the patient is deceased and the state has authorized that the hospital can dispose of the decedent's personal property to include controlled substance medications), then a hospital may dispose of the abandoned controlled substance medications in accordance with federal, state, local, tribal laws and regulations.

SECTION XIII – COMBAT METHAMPHETAMINE EPIDEMIC ACT OF 2005

Summary of the Act's Major Provisions

On March 2006, the President signed the *Combat Methamphetamine Epidemic Act of 2005* (CMEA). As a result of this law, DEA issued an Interim Final Rule in the Federal Register on September 26, 2006, which outlined the retail provisions of the CMEA. 71 FR 56008 (Sept. 26, 2006).

The CMEA includes requirements that regulated sellers must follow for retail sales of over-the-counter products containing the List I chemicals ephedrine, pseudoephedrine, and phenylpropanolamine (PPA), which can be used to manufacture methamphetamine illegally. The CMEA defined "*regulated seller*" to mean a retail distributor (including a pharmacy and mobile retail vendors) and "*at retail*" to mean sale or purchase for personal use. 21 U.S.C. 802(46) and (48), 21 CFR 1300.02(b) ("*regulated seller*" and "*at retail*").

Scheduled Listed Chemical Products

The CMEA created a new category of products called "scheduled listed chemical products*"*(SLCPs). It includes any product that may be marketed or distributed lawfully in the United States under the Federal Food, Drug, and Cosmetic Act as a non-prescription drug, and that contains ephedrine, pseudoephedrine, or phenylpropanolamine (PPA) (including salts, optical isomers, and salts of optical isomers). 21 U.S.C. 802(45), 21 CFR 1300.02. This applies to non-prescription drug products only, not prescription drug products. Retail sales of SLCPs are excluded from the definition of a "regulated transaction" and from the registration requirement under 21 U.S.C. 823, but are subject to a separate system of retail sales controls under 21 U.S.C. 830. 21 U.S.C. 802(39)(A)(v).

Other requirements of the CMEA include:

1. Requirement of regulated sellers to place the products behind the counter or in locked cabinets. 21 CFR 1314.25(b).

2. Requirement of regulated sellers to check the identity of purchasers and maintain a log of each sale that includes the purchaser's name and address, signature of the purchaser, product sold, quantity sold, date, and time. 21 CFR 1314.30(a), (b).

3. Requirement of regulated sellers to maintain the logbook for at least two years. 21 CFR 1314.30(e).

4. Requirement of regulated sellers to train employees in the requirements of the law and certify to DEA that the training has occurred. 21 CFR 1314.35(a).

5. Places a quantity limit of each of the chemicals that may be sold to an individual in a day to 3.6 grams of the chemical (base) without regard to the number of transactions. 21 CFR 1314.20(a).

6. For non-liquids, product packaging is limited to blister packs containing no more than 2 dosage units per blister. Where blister packs are not technically feasible, the product must be packaged in unit dose packets or pouches. 21 CFR 1314.05.

7. For individuals, purchases in a 30-day period are limited to 9 grams, of which not more than 7.5 grams may be imported by means of a private or commercial carrier or the U.S. Postal Service. 21 U.S.C. 844(a).

While many states have enacted their own legislation regarding the regulation of these products, federal law also requires regulated sellers to complete a self-certification process with DEA that includes training their employees on the new regulations and procedures. 21 U.S.C. 830(e)(1)(B). The self-certification process must be completed online at www.DEAdiversion.usdoj.gov. 21 CFR 1314.35, 1314.40. If state law differs from federal law regarding the regulation of these products, retail outlets are to adhere to the stricter provisions of both. 21 CFR 1307.02.

Copies of the Interim Final Rule are available at www.DEAdiversion.usdoj.gov (click on the *Combat Methamphetamine Epidemic Act of 2005*, then *Interim Final Rule - Retail Sales of Scheduled Listed Chemical Products)*. 71 FR 56008 (Sept. 26, 2006). Details on specific provisions of the CMEA that may impact a pharmacy that engages in retail sales of SLCPs are outlined below.

Recordkeeping Requirements

Under 21 CFR 1314.30(a), regulated sellers are required to maintain a written (bound logbook) or electronic list of sales that identifies the transactions with the following information:

1. The name of the purchaser;

2. The address of the purchaser;

3. The date and time of the sale;

4. The name and amount of product sold.

The logbook requirement does not apply to any purchase by an individual of a single sales package that contains not more than 60 milligrams of pseudoephedrine. 21 CFR 1314.30(a).

Concurrently, purchasers, under 21 CFR 1314.30(b)(1) and (2), are required to:

1. Present a photo identification issued by a state or the Federal Government, or other forms of identification deemed acceptable under 8 CFR 274a.2(b)(1)(v)(A)-(B). (See Proof of Identity Requirements below for a complete list of acceptable forms of identification.)

2. Sign a *written* logbook pursuant to 21 CFR 1314.30(b)(2)(i), and enter his or her name, address, date, and time of sale.

   OR

3. Sign an *electronic* logbook pursuant to 21 CFR 1314.30(b)(2)(ii).

Once identification of the purchaser is presented to the seller, the seller, under 21 CFR 1314.30(b)(2)(ii)(C)-(3), 1314.30(c)(1) and (2), is required to:

1. Determine that the name in the logbook corresponds to the name on the identification and that the date and time are correct.

2. Enter into the logbook the name of the product and the quantity sold.

The logbook must include a notice to purchasers that entering false statements or misrepresentations in the logbook may subject purchasers to criminal penalties under 18 U.S.C.1001. 21 CFR 1314.30(d). Sellers must maintain each entry in the logbook for not fewer than two years after the date on which the entry is made. 21 CFR 1314.30(e).

Loss or Theft of Scheduled Listed Chemical Products

A report should be made orally to the local DEA Diversion Field Office (Appendix K) in the area where the pharmacy is located at the earliest practicable opportunity after becoming aware of the circumstances involved. 21 CFR 1314.15(b). Per 21 CFR 1314.15(c), a written report of losses must be filed within 15 days after the pharmacist becomes aware of the loss or theft. A written report should include the DEA registration number (if applicable), name, business address, date of loss, type of loss, and a description of the circumstances of the loss (e.g., in-transit, theft from premises). 21 CFR 1314.15(e). The written report must be filed using a DEA From 107 (Report of Theft or Loss of Listed Chemicals). DEA amended 21 CFR 1310.05 to require reports of unusual or excessive loss or disappearance of a listed chemical to be filed through the

DEA Diversion control Division secure network application. Data will be entered through a secure connection to the online application system. If you have questions regarding the electronic submission, please call the DEA Call Center at 1-800-882-9539.

Proof of Identity Requirements

The CMEA requires an individual to present an unexpired identification card that includes a photograph and is issued by a state or the Federal Government or a document considered acceptable under 8 CFR 274a.2(b)(1)(v)(A) and (B). Those documents currently include the following:

1. United States passport;

2. Alien Registration Receipt Card or Permanent Resident Card, Form I-551;

3. A foreign passport that contains a temporary I-551 stamp, or temporary I-551 printed notation on a machine-readable immigrant visa;

4. An Employment Authorization Document which contains a photograph (Form I-766);

5. In the case of an individual who is employment-authorized incident to status or parole with a specific employer, a foreign passport with an Arrival/Departure Record, Form I-94 (as defined in 8 CFR 1.4), or Form I-94A, bearing the same name as the passport and containing an endorsement by DHS indicating such employment-authorized status or parole, as long as the period of endorsement has not yet expired and the employment is not in conflict with the individual's employment-authorized status or parole;

6. A passport from the Federated States of Micronesia (FSM) or the Republic of the Marshall Islands (RMI) with Form I-94 or Form I-94A indicating non-immigrant admission under the Compact of Free Association Between the United States and the FSM or RMI;

7. In the case of an individual lawfully enlisted for military service in the Armed Forces under 10 U.S.C. 504, a military identification card issued to such individual may be accepted only by the Armed Forces.

For individuals 16 years of age or older:

1. A driver's license or identification card containing a photograph, issued by a state or an outlying possession of the United States. If the driver's license or identification card does not contain a photograph, identifying information shall

be included such as: name, date of birth, sex, height, color of eyes, and address;

2. School identification card with a photograph;

3. Voter's registration card;

4. U.S. military card or draft record;

5. Identification card issued by federal, state, or local government agencies or entities. If the identification card does not contain a photograph, identifying information shall be included such as: name, date of birth, sex, height, color of eyes, and address;

6. Military dependent's identification card;

7. Native American tribal documents;

8. United States Coast Guard Merchant Mariner Card;

9. Driver's license issued by a Canadian government authority.

For individuals under age 18 who are unable to produce a document from the list above, the following documents are acceptable to establish identity:

1. School record or report card;

2. Clinic doctor or hospital record;

3. Daycare or nursery school record.

NOTE: The list of acceptable forms of identification, as cited in the CMEA, may change ("in effect on or after the date of enactment"). DEA has no discretion to alter the list.

Product Placement

SLCPs must be stored behind the counter or, if in an area where the public has access, in a locked cabinet. 21 U.S.C. 830(e)(1)(A). Although DEA does not include cabinet specifications in the rule, a locked cabinet should be substantial enough that it cannot be easily picked up and removed. In a store setting, the cabinet should be similar to those used to store items, such as cigarettes, that can be accessed only by sales staff. 21 CFR 1314.25(b).

Self-Certification

As part of the requirements of CMEA, an annual self-certification is required for all regulated sellers of SLCPs. 21 CFR 1314.40(b). A regulated seller must not sell SLCPs unless it has self-certified with DEA. 21 CFR 1314.40(a). In self-certifying, the regulated seller is confirming:

1. The employees who will be engaged in the sale of SLCPs have undergone training regarding provisions of CMEA. 21 U.S.C. 830(e)(1)(A)(vii).

2. Records of the training are maintained. 21 U.S.C. 830(e)(1)(A)(viii).

3. Sales to individuals do not exceed 3.6 grams of ephedrine, pseudoephedrine, or phenylpropanolamine per day. 21 U.S.C. 830(d)(1).

4. Non-liquid forms are packaged as required. 21 U.S.C. 830(d)(2).

5. SLCPs are stored behind the counter or in a locked cabinet. 21 U.S.C. 830(e)(1)(A)(i).

6. A written or electronic logbook containing the required information on sales of these products is properly maintained. 21 U.S.C. 830(e)(1)(A)(iii)-(iv).

7. The logbook information will be disclosed only to federal, state, or local law enforcement and only to ensure compliance with Title 21 of the United States Code or to facilitate a product recall. 21 U.S.C. 830(c).

Regulated sellers of SLCPs self-certify through DEA's Diversion website at www.DEAdiversion.usdoj.gov. Self-certification can be accomplished on any computer (e.g., at the store, at home, at the library, or at any other location).

A certificate will be generated by DEA upon receipt of the self-certification application. The regulated seller may print this certificate, or if the regulated seller is unable to print it, DEA will print and mail the certificate to the regulated seller. Chain stores wishing to file self-certifications for more than 10 locations should print or copy the form electronically and submit the information to DEA by mail. DEA will work with these persons to facilitate this process. Persons interested in this self-certification option should contact DEA for assistance at 1-800-882-9539. For current DEA registrants, the system will pre-populate the form with basic information if the registrant enters his or her DEA registration number in the field provided.

The regulated seller must self-certify to DEA as described above on an **annual basis**. 21 CFR 1314.40(b). It is the responsibility of the regulated seller to ensure that all employees have been trained prior to self-certifying each time. 21 CFR 1314.35(a).

It is the regulated seller's responsibility to annually renew before the certificate expires if the regulated seller intends to continue selling SLCPs at retail. 21 CFR 1314.40(b). The certificate contains a self-certification number in the upper right corner. The expiration date of the certificate is listed under the self-certification number. Regulated sellers may verify the expiration date of their certificate at www.DEAdiversion.usdoj.gov.

The self-certification requirement is subject to the provisions of 18 U.S.C. 1001. A regulated seller who knowingly or willfully certifies to facts that are not true is subject to fines and imprisonment.

Required Training

Training materials designed by DEA may be used, although a regulated seller may include information in addition to that provided by DEA. DEA training materials may be found at www.DEAdiversion.usdoj.gov.

Training Records

Each employee of a regulated seller who is responsible for delivering SLCPs to purchasers or who deals directly with purchasers by obtaining payment for the SLCPs must undergo training. The regulated seller must maintain a copy of all records demonstrating that such employees have undergone training. 21 CFR 1314.35(a) & (b).

Self-Certification Fee

On December 29, 2008, DEA published a Final Rule in the Federal Register entitled *Combat Methamphetamine Epidemic Act of 2005: Fee for Self-Certification for Regulated Sellers of Scheduled Listed Chemical Products*. 73 FR 79318. (Dec. 29, 2008). The rule established a self-certification fee for regulated sellers of SLCPs that are not DEA pharmacy registrants. 21 CFR 1314.42.

SECTION XIV – Ryan Haight Online Pharmacy Consumer Protection Act of 2008

Summary of the Ryan Haight Act's Major Provisions

On October 15, 2008, the President signed into law the *Ryan Haight Online Pharmacy Consumer Protection Act of 2008*, often referred to as the *Ryan Haight Act*. This law amends the CSA by adding a series of new regulatory requirements and criminal provisions designed to combat the proliferation of "rogue Internet sites" that unlawfully dispense controlled substances by means of the Internet. The *Ryan Haight Act* applies to all controlled substances in all schedules.

This law became effective April 13, 2009. As of that date, it is illegal under federal law to deliver, distribute, or dispense a controlled substance by means of the Internet unless the online pharmacy holds a modification of DEA registration authorizing it to operate as an online pharmacy. 21 U.S.C. 822(b), 823(f), and 21 CFR 1306.09(b). Thus, a pharmacy which knowingly or intentionally dispenses a controlled substance by means of the Internet that does not have a modification of the DEA registration allowing such activity is in violation of 21 U.S.C. 841(h)(1) and subject to potential criminal prosecution and (in the case of DEA registrants) loss of DEA registration. 21 U.S.C. 841(h)(1) & (2)(A).

Definition of an Online Pharmacy

An online pharmacy is a person, entity, or Internet site, whether in the United States or abroad, that knowingly or intentionally delivers, distributes, or dispenses, or offers or attempts to deliver, distribute, or dispense, a controlled substance by means of the Internet. 21 U.S.C. 802(52)(A) and (B), 21 CFR 1300.04(h). Examples of an online pharmacy may include (but are not limited to) the following:

1. Any website that sells, or offers to sell, any controlled substance or a prescription therefor to a person in the United States.

2. Any person who operates such a website.

3. Any person who pays a practitioner to issue prescriptions for controlled substances for customers of such a website.

4. Any person who pays a pharmacy to fill prescriptions for controlled substances that were issued to customers of such a website.

5. Any pharmacy that knowingly or intentionally fills prescriptions for controlled substances that were issued to customers of such a website.

6. Any person who sends an e-mail that:

   a. Offers to sell a controlled substance or a prescription for a controlled substance in a manner not authorized by the Act;

   b. Directs buyers to a website operating in violation of the Act;

   c. Or otherwise causes or facilitates the delivery, distribution, or dispensing of a controlled substance in a manner not authorized by the Act.

Online Pharmacy Registration Exemptions

The following are exempt from the Ryan Haight Act's definition of an "online pharmacy" so long as their activities are limited solely to the exemptions provided:

1. Manufacturers or distributors registered under 21 U.S.C. 823(a),(b),(d), or (e) who do not dispense controlled substances to non-registrants. 21 U.S.C. 802(52)(B)(i) and 21 CFR 1300.04(h)(1).

2. Non-pharmacy practitioners who are registered under 21 U.S.C. 823(f) and whose activities are authorized by that registration, provided that any website operated by such non-pharmacy practitioners complies with 21 CFR 1304.50, which requires the website to post in a visible and clear manner on its homepage, or on a page directly linked thereto in which the hyperlink is also visible and clear on the homepage, a list of the DEA registered non-pharmacy practitioners who are affiliated with the website. 21 U.S.C. 802(52)(B)(ii) and 21 CFR 1300.04(h)(2).

3. Any hospital or other medical facility registered under 21 U.S.C. 823(f) that is operated by an agency of the United States (including the Armed Forces). 21 U.S.C. 802(52)(B)(iii) and 21 CFR 1300.04(h)(3).

4. A health care facility owned or operated by an Indian tribe or tribal organization carrying out a contract or compact under the Indian Self-Determination and Education Assistance Act. 21 U.S.C. 802(52)(B)(iv) and 21 CFR 1300.04(h)(4).

5. Any agent or employee of any hospital or facility that is operated by an agency of the United States, provided that hospital or other facility is registered under 21 U.S.C. 823(f), and any agent or employee of any hospital or facility owned or operated by an Indian tribe or tribal organization carrying out a contract or compact under the Indian Self-Determination and Education Assistance Act, provided such agent or employee is lawfully acting in the

usual course of business or employment, and within the scope of the official duties of such agent or employee, with such hospital or facility, and, with respect to agents or employees of such health care facilities only to the extent such individuals are furnishing services pursuant to those contracts or compacts. 21 U.S.C. 802(52)(B)(v) and 21 CFR 1300.04(h)(5).

6. Mere advertisements that do not attempt to facilitate an actual transaction involving a controlled substance. 21 U.S.C. 802(52)(B)(vi) and 21 CFR 1300.04(h)(6).

7. A person, entity, or Internet site that is not in the United States and does not facilitate the delivery, distribution, or dispensing of a controlled substance by means of the Internet to any person in the United States. 21 U.S.C. 802(52)(B)(vii) and 21 CFR 1300.04(h)(7).

8. A pharmacy registered under 21 U.S.C. 823(f) whose dispensing of controlled substances via the Internet consists solely of "refilling prescriptions for controlled substances in schedule III, IV, or V," as that term is defined in 21 U.S.C. 802(55) and 21 CFR 1300.04(k). (This definition is set forth at the end of Section XIV). 21 U.S.C. 802(52)(B)(viii)(I). 21 CFR 1300.04(h)(8)(i).

9. A pharmacy registered under 21 U.S.C. 823(f) whose dispensing of controlled substances via the Internet consists solely of "filling new prescriptions for controlled substances in schedule III, IV, or V," as that term is defined in 21 CFR 1300.04(d). (This definition is set forth at the end of Section XIV.) 21 U.S.C. 802(52)(B)(viii)(II) and 21 CFR 1300.04(h)(8)(ii).

10. Any registered pharmacy whose delivery, distribution, or dispensing of controlled substances by means of the Internet consists solely of filling prescriptions that were electronically prescribed in a manner authorized by the CSA, and if, in view of all of its activities other than those referred to in this paragraph, it would fall outside the definition of online pharmacy. 21 U.S.C. 802(52)(B)(ix) and 21 CFR 1300.04(h)(9).

11. Any registered pharmacy whose delivery, distribution, or dispensing of controlled substances by means of the Internet consists solely of the transmission of prescription information between a pharmacy and an automated dispensing system located in an LTCF when the registration of the automated dispensing system is held by that pharmacy as described in 21 CFR 1301.17, 1301.27 and the pharmacy is otherwise complying with DEA regulations. 21 U.S.C. 802(52) and 21 CFR 300.04(h)(10).

Notification Requirements

Thirty days prior to offering a controlled substance for sale, delivery, distribution, or dispensing by means of the Internet, the online pharmacy must notify DEA and the state boards of pharmacy in any states in which the online pharmacy offers to sell, deliver, distribute, or dispense controlled substances. 21 CFR 1304.40(a)(1). Completion of the *Application for Modification of Registration for Online Pharmacies* serves as the notification requirement to DEA.

The online pharmacy must make a separate thirty-day advance notice to the state boards of pharmacy in each state in which it intends to offer to sell, deliver, distribute, or dispense controlled substances. Online pharmacies that apply for the modification of registration are required to certify that the applicable state boards of pharmacy have been notified. 21 CFR 1304.40(a)(2).

How to Register as an Online Pharmacy

To operate legally as an online pharmacy, the online pharmacy must first be registered with DEA as a pharmacy under 21 CFR 1301.13. Once registered with DEA as a pharmacy, the pharmacy may apply for a modification of registration to operate as an online pharmacy. 21 CFR 1301.19. To apply for a modification of registration, complete the *Application for Modification of Registration for Online Pharmacies* online at:

https://apps.DEAdiversion.usdoj.gov/webforms/jsp/regapps/ipharms/ipharmsLogin.jsp

There is no fee to apply to modify a DEA registration to an online pharmacy. 21 CFR 1301.51(c).

If the modification of registration is approved, the pharmacy will be issued a modified DEA Certificate of Registration with the new business activity listed as online pharmacy. 21 CFR 1301.51(c). The registrant will keep the same DEA registration number. A pharmacy may perform the activities of a retail pharmacy and an online pharmacy at the same time.

State Licensure Requirements

An online pharmacy must comply with the requirements of all applicable state laws concerning the licensure of pharmacies in each state from which it, and in each state to which it delivers, distributes, or dispenses, or offers to deliver, distribute, or dispense, controlled substances by means of the Internet. 21 U.S.C. 831(b) and 21 CFR 1301.19(b). In addition, online pharmacies must certify they are in compliance with these requirements when completing the *Application for Modification of Registration for Online Pharmacies*. 21 CFR 1304.40(a).

The requirement that an online pharmacy list the states in which it is licensed to dispense controlled substances is designed to ensure that an online pharmacy only dispenses controlled substances to patients in states in which it is authorized to practice pharmacy. (See 21 CFR 1304.45(b)(4)). Dispensing beyond the scope of state licensure is one of the recurring transgressions of some rogue online pharmacies and generally violates state law. A state may bring civil action in federal court to enjoin any violation of the Ryan Haight Act—not merely those violations of state law—and to obtain other appropriate legal or equitable relief. 21 U.S.C. 882(c).

Online Pharmacy Website Requirements

When a pharmacy applies for a modification of registration to become an online pharmacy, it must display on its homepage a declaration that it has done so. Under 21 CFR 1304.40(d), this declaration must state the following:

> *"In accordance with the Controlled Substances Act and the DEA regulations, this online pharmacy has made the notifications to the DEA Administrator required by 21 U.S.C. 831 and 21 CFR 1304.40."*

Once approved to operate as an online pharmacy, the online pharmacy must display at all times on the homepage of its Internet site a declaration of compliance with the requirements of 21 U.S.C. 831 with respect to the delivery or sale or offer for sale of controlled substances. 21 CFR 1304.45(a). This statement must include the name of the pharmacy as it appears on the DEA Certificate of Registration. 21 CFR 1304.45(a).

An online pharmacy is required to post Internet Pharmacy Site Disclosure Information on the homepage of each Internet site it operates. 21 U.S.C 831(c) and 21 CFR 1304.45(b). Pursuant to 21 U.S.C. 831(c)(1-7) and 21 CFR 1304.45(b)(1-7), it must be posted in a visible and clear manner and contain the following information:

1. The name and address of the pharmacy as it appears on the pharmacy's DEA Certificate of Registration.

2. The pharmacy's telephone number and e-mail address.

3. Name of pharmacist-in-charge, professional degree, states of licensure, and telephone number.

4. List of state(s) in which the pharmacy is licensed to dispense controlled substances.

5. Certification that the pharmacy is registered to deliver, distribute, or dispense controlled substances by means of the Internet.

6. The name, address, telephone number, professional degree, and states of licensure of any practitioner who has a contractual relationship to provide medical evaluations or issue prescriptions for controlled substances, through referrals from the website or at the request of the owner or operator of the website, or any employee or agent thereof.

7. The following statement must be visible on the website:

   "*This online pharmacy is obligated to comply fully with the Controlled Substances Act and DEA regulations. As part of this obligation, this online pharmacy has obtained a modified DEA registration authorizing it to operate as an online pharmacy. In addition, this online pharmacy will only dispense a controlled substance to a person who has a valid prescription issued for a legitimate medical purpose based upon a medical relationship with a prescribing practitioner. This includes at least one prior in-person medical evaluation in accordance with section 309 of the Controlled Substances Act (21 U.S.C. 829), or a medical evaluation via telemedicine in accordance with section 102(54) of the Controlled Substances Act (21 U.S.C. 802(54)).*"

If at any time an online pharmacy should change its Internet site web address, the online pharmacy must notify DEA at least thirty days in advance of this change. 21 CFR 1304.40(b)(3).

Reporting Requirements

Each online pharmacy must submit a monthly report to DEA of the total quantity of each controlled substance that the online pharmacy has dispensed the previous calendar month. 21 CFR 1304.55(a). The report is required for every month in which the total amount of dispensing of controlled substances by the pharmacy is either (i) 100 or more prescriptions filled or (ii) 5,000 or more dosage units dispensed of all controlled substances combined. 21 CFR 1304.55(a). Should an online pharmacy's total quantity of dispensed controlled substances fall below both of the thresholds listed above, a report is still required that indicates a negative response for that given month. 21 CFR 1304.55(b).

The report must include the total amount of such dispensing by any means including all controlled substances dispensed via Internet transactions, mail-order transactions, face-to-face transactions, or any other means. It is not required that the online pharmacy identify the means of the dispensing in its report. 21 CFR 1304.55(a). Reporting shall be by National Drug Code (NDC) numbers. 21 CFR 1304.55(f). Report the total number of dosage units dispensed for each NDC number. 21 CFR 1304.55(f).

This report is due on or before the 15th day of the following month. 21 CFR 1304.55(e). For example, an online pharmacy would submit its report for the month of January no later than February 15th. Reports must be submitted electronically via online reporting, electronic upload, or other means as approved by DEA. 21 CFR 1304.55(d). All reports must be kept for at least two years and be readily retrievable for inspection. 21 CFR 1304.55(g).

The reporting requirements apply to every pharmacy that, at any time during a calendar month, holds a modified registration authorizing it to operate as an online pharmacy, regardless of whether it dispenses any controlled substances by means of the Internet during the month. 21 CFR 1304.55(c).

Prescription Requirements

In order for a prescription to be valid, it must be issued for a legitimate medical purpose in the usual course of professional practice by a practitioner who has conducted at least one in-person medical evaluation of the patient or by a covering practitioner. 21 U.S.C. 829(e)(2)(A), and 21 CFR 1300.04(l)(1). An in-person medical evaluation is a medical evaluation that is conducted with the patient in the physical presence of the practitioner, without regard to whether portions of the evaluation are conducted by other health professionals. 21 U.S.C. 829(e)(2)(B)(i) and 21 CFR 1300.04(f).

Definition of Prescription Terms

A pharmacy website is exempted from the Ryan Haight Act's definition of an "online pharmacy" if its Internet-facilitated activity relating to controlled substances is limited to filling new and/or refilling prescriptions for controlled substances in schedules III, IV, or V. 21 U.S.C. 802(52)(B)(viii). If the pharmacy is so exempted from the definition of an "online pharmacy," it is not required under the Act to obtain a modification of its DEA registration authorizing it to operate as an online pharmacy. 21 U.S.C. 802(52)(B)(viii). Thus, it is important to understand precisely the definitions of the following terms.

Filling New Prescriptions for Controlled Substances in Schedules III-V

As stated in 21 U.S.C. 802(56) and 21 CFR 1300.04(d), the term "filling new prescriptions for controlled substances in schedule III, IV, or V" means filling a prescription for an individual for a controlled substance in schedule III, IV, or V, if:

1. The pharmacy dispensing that prescription has previously dispensed to the patient a controlled substance other than by means of the Internet and pursuant to the valid prescription of a practitioner that meets the applicable requirements of subsections (b) and (c) of section 309 of the Act (21 U.S.C. 829) and 21 CFR 1306.21, 1306.22 (for purposes of this definition, such a prescription shall be referred to as the "original prescription");

2. The pharmacy contacts the practitioner who issued the original prescription at the request of that individual to determine whether the practitioner will authorize the issuance of a new prescription for that individual for the controlled substance described in paragraph (1) above (i.e., the same controlled substance as described in paragraph (1)); and

3. The practitioner, acting in the usual course of professional practice, determines there is a legitimate medical purpose for the issuance of the new prescription.

Refilling Prescriptions for Controlled Substances in Schedules III-V

As stated in 21 U.S.C. 802(55) and 21 CFR 1300.04(k), the term "**refilling prescriptions for controlled substances in schedule III, IV, or V":**

1. Means the dispensing of a controlled substance in schedule III, IV, or V in accordance with refill instructions issued by a practitioner as part of a valid prescription that meets the requirements of 21 U.S.C. 829 and 21 CFR 1306.21,1306.22, as appropriate; and

2. Does not include the issuance of a new prescription to an individual for a controlled substance that individual was previously prescribed.

APPENDICES

APPENDIX A

This summary is provided as a quick reference to the provisions of the Controlled Substances Act. It is not intended to replace any statutory or regulatory requirement thereof. For complete guidance as to the provisions of each area indicated below, please check the appropriate section of this Pharmacist's Manual.

Summary of Controlled Substances Act Requirements

	Schedule II	Schedules III & IV	Schedule V
Registration	Required	Required	Required
Receiving Records	DEA Form 222	Invoices, readily retrievable	Invoices, readily retrievable
Prescriptions	Written[1] prescriptions (oral prescriptions only allowed in emergency situations)[2]	Written, oral, or fax	Written, oral, or fax
Refills	No	No more than 5 within 6 months	As authorized when prescription is issued or if renewed by a practitioner
Maintenance of Prescriptions [3]	Separate file	Separate file or readily retrievable	Separate file or readily retrievable
Distribution Between Registrants	DEA Form 222	Invoices	Invoices
Security	Locked cabinet or dispersed among non-controlled pharmaceuticals	Locked cabinet or dispersed among non-controlled pharmaceuticals	Locked cabinet or dispersed among non-controlled pharmaceuticals
Theft or Significant Loss	Report to DEA and complete DEA Form 106	Report to DEA and complete DEA Form 106	Report to DEA and complete DEA Form 106

NOTE: ***All records*** must be maintained for 2 years, unless state law requires a longer period. 21 U.S.C. 827(b).

---

[1] Written prescriptions include paper prescriptions and electronic prescriptions that meet DEA's requirements for such prescriptions.

[2] Emergency oral prescriptions are allowable under schedule II and require a signed follow-up prescription within seven days. 21 CFR 1306.11(d)(4).

Exceptions: A facsimile prescription for a schedule II controlled substance serves as the original prescription when issued to a resident of an LTCF. 21 CFR 1306.11(f). A facsimile prescription for a schedule II narcotic substance serves as the original prescription when issued to hospice patients, or patients with a diagnosed terminal illness, or for direct administration by parenteral, intravenous, intramuscular, subcutaneous, or intraspinal infusion. 21 CFR 1306.11(e), (f) and (g).

[3] The record of dispensing can also be a bound record book, if the controlled substance is not a prescription drug as determined under the Federal Food, Drug, and Cosmetic Act. 21 CFR 1306.26(e).

APPENDIX B

Definitions Based on the Controlled Substances Act and the Code of Federal Regulations

The following definitions may be found in 21 CFR Part 1300 and/or 21 U.S.C. Parts 802 and 823.

Administer
The direct application of a controlled substance to the body of a patient or research subject by 1) a practitioner or (in their presence) by their authorized agent, or 2) the patient or research subject at the direction and in the presence of the practitioner, whether such application is by injection, inhalation, ingestion, or any other means.

Collector
A hospital/clinic with an on-site pharmacy, or retail pharmacy that is authorized under the CSA and DEA regulations to receive a controlled substance for the purpose of destruction from an ultimate user, a person lawfully entitled to dispose of an ultimate user decedent's property, or an LTCF on behalf of an ultimate user who resides or has resided at that facility.

Central Fill Pharmacy
A pharmacy which is permitted by the state in which it is located to prepare controlled substance orders for dispensing pursuant to a valid prescription transmitted to it by a registered retail pharmacy and to return the labeled and filled prescriptions to the retail pharmacy for delivery to the ultimate user. Such central fill pharmacy shall be deemed "authorized" to fill prescriptions on behalf of a retail pharmacy only if the retail pharmacy and central fill pharmacy have a contractual relationship providing for such activities or share a common owner.

Chemicals
Please see the definitions for List I Chemical, Retail Distributor, and Scheduled Listed Chemical Product.

Dispense
To deliver a controlled substance to an ultimate user or research subject by, or pursuant to the lawful order of, a practitioner, including the prescribing and administering of a controlled substance and the packaging, labeling, or compounding necessary to prepare the substance for such delivery.

Distribute
To deliver (other than by administering or dispensing) a controlled substance or a listed chemical. The term "distributor" means a person who so delivers a controlled substance or a listed chemical.

Individual Practitioner
A physician, dentist, veterinarian, or other individual licensed, registered or otherwise permitted, by the United States or the jurisdiction in which they practice, to dispense a controlled substance in the course of professional practice, but does not include a pharmacist, a pharmacy, or an institutional practitioner.

Institutional Practitioner
A hospital or other person (other than an individual) licensed, registered or otherwise permitted, by the United States or the jurisdiction in which it practices, to dispense a controlled substance in the course of professional practice, but does not include a pharmacy.

Inventory
All factory and branch stocks in finished form of a basic class of controlled substance manufactured or otherwise acquired by a registrant, whether in bulk, commercial containers, or contained in pharmaceutical preparations in the possession of the registrant (including stocks held by the registrant under separate registration as a manufacturer, importer, exporter, or distributor).

List I Chemical
A chemical specifically designated by the DEA Administrator in 21 CFR 1310.02(a) that, in addition to legitimate uses, is used in manufacturing a controlled substance in violation of the Controlled Substances Act and is important to the manufacture of a controlled substance.

Long-Term Care Facility
A nursing home, retirement care, mental care, or other facility or institution that provides extended health care to resident patients.

Mid-level Practitioner (MLP)
An individual practitioner, other than a physician, dentist, veterinarian, or podiatrist, who is licensed, registered or otherwise permitted by the United States or the jurisdiction in which he or she practices, to dispense a controlled substance in the course of professional practice. Examples of MLPs include, but are not limited to, nurse practitioners, nurse midwives, nurse anesthetists, clinical nurse specialists, and physician assistants who are authorized to dispense controlled substances by the state in which they practice. Because this authority varies greatly by state, check with the state licensing authority to determine which MLP disciplines are authorized to dispense controlled substances in a particular state or visit www.DEAdiversion.usdoj.gov. (Click on *Registration Support*, then *Resources*, then *Mid-level Practitioners Authorization by State*.)

Online Pharmacy
An online pharmacy is a person, entity, or Internet site, whether in the United States or abroad, that knowingly or intentionally delivers, distributes, or dispenses, or offers or attempts to deliver, distribute, or dispense, a controlled substance by means of the Internet.

On-Site
Located on or at the physical premises of the registrant's registered location.

Pharmacist
Any pharmacist licensed by a state to dispense controlled substances, and shall include any other person (e.g., pharmacist intern) authorized by a state to dispense controlled substances under the supervision of a pharmacist licensed by such state.

Practitioner
A physician, dentist, veterinarian, scientific investigator, pharmacy, hospital, or other person licensed, registered, or otherwise permitted, by the United States or the jurisdiction in which they practices or does research, to distribute, dispense, conduct research with respect to, administer, or use in teaching or chemical analysis, a controlled substance in the course of professional practice or research.

Prescription
An order for medication which is dispensed to or for an ultimate user but does not include an order for medication which is dispensed for immediate administration to the ultimate user (e.g., an order to dispense a drug to a bed patient for immediate administration in a hospital is not a prescription).

Qualifying Practitioner
A physician who is licensed under state law, who is registered with DEA to dispense controlled substances, and who is qualified through at least eight (8) hours of specialized training and/or certification to dispense, including prescribing, narcotics in schedule III-V, or a combination of such drugs, approved by the FDA specifically for use in narcotic maintenance or detoxification treatment.

Qualifying Other Practitioner
A nurse practitioner, clinical nurse specialist, certified registered nurse anesthetist, certified nurse midwife, or physician assistant who satisfies each of the following: (1) "is licensed under state law to prescribe schedule III, IV, or V medications for the treatment of pain"; (2) "has completed not fewer than 24 hours of initial training addressing each of the topics listed in [21 U.S.C. 823(g)(2)(G)(ii)(IV)] … or has such other training or experience as the Secretary of HHS determines will demonstrate the ability of the nurse practitioner or physician assistant to treat and manage opiate-dependent patients"; and (3) "[t]he nurse practitioner or physician assistant is supervised by, or works in collaboration with, a qualifying physician, if the nurse practitioner or physician assistant

is required by state law to prescribe medications for the treatment of opioid use disorder in collaboration with or under the supervision of a physician."

Readily Retrievable

Certain records which are kept by automatic data processing systems or other electronic or mechanized recordkeeping systems in such a manner that they can be separated out from all other records in a reasonable time and/or records kept in such a manner that certain items are asterisked, redlined, or in some other manner visually identifiable apart from other items appearing on the records.

Regulated Seller

A retail distributor (including a pharmacy or a mobile retail vendor), except that the term does not include an employee or agent of the distributor.

Retail Distributor

A grocery store, general merchandise store, drug store, or other entity or person whose activities as a distributor relating to drug products containing ephedrine, pseudoephedrine, or phenylpropanolamine are limited almost exclusively to sales for personal use, both in number of sales and volume of sales, either directly to walk-in customers or in face-to-face transactions by direct sales.

Reverse Distributor

A registrant who receives controlled substances acquired from another DEA registrant or law enforcement for the purpose of returning unwanted, unusable, or outdated controlled substances to the manufacturer or another registrant authorized by the manufacturer to accept returns on the manufacturer's behalf, or where necessary, processing such substances or arranging for processing such substances for disposal.

Scheduled Listed Chemical Product (SLCP)

A product that contains ephedrine, pseudoephedrine, or phenylpropanolamine which may be marketed or distributed lawfully in the United States under the Federal, Food, Drug, and Cosmetic Act as a non-prescription drug. Ephedrine, pseudoephedrine, and phenylpropanolamine include their salts, optical isomers, and salts of optical isomers.

Ultimate User

A person who has lawfully obtained, and who possesses, a controlled substance for his or her own use or for the use of a member of his or her household or for an animal owned by him or her or by a member of his or her household.

APPENDIX C

Definitions of Abbreviations

CARA	Comprehensive Addiction and Recovery Act of 2016
CFR.	Code of Federal Regulations
CMEA	Combat Methamphetamine Epidemic Act of 2005
CSA	Controlled Substances Act
CSAT	Center for Substance Abuse Treatment
CSOS	Controlled Substance Ordering System
CSRPA	Controlled Substance Registrant Protection Act of 1984
DATA	Drug Addiction Treatment Act of 2000
DEA	Drug Enforcement Administration
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
LTCF	Long-Term Care Facility
NATA	Narcotic Addiction Treatment Act of 1974
SAMHSA	Substance Abuse and Mental Health Services Administration
UIN	Unique Identification Number
U.S.	United States
U.S.C.	United States Code

APPENDIX D

Pharmacist's Guide to Prescription Fraud and Identifying Out of Scope Prescriptions

The purpose of this guide is to ensure that controlled substances continue to be available for legitimate medical and scientific purposes while preventing diversion into the illicit market. It is not the intent of this publication to discourage or prohibit the use of controlled substances where medically indicated. However, nothing in this guide should be construed as authorizing or permitting any person to conduct any act that is not authorized or permitted under federal or state laws.

Pharmacist's Responsibilities

The abuse of prescription drugs—especially controlled substances—is a serious social and health problem in the United States today. As healthcare professionals, pharmacists share responsibility for preventing prescription drug abuse and diversion.

1. Pharmacists have a personal responsibility to protect their practice from becoming an easy target for drug diversion. They need to know of the potential situations where drug diversion can occur, and establish safeguards to prevent drug diversion.

2. The dispensing pharmacist must maintain constant vigilance against forged or altered prescriptions. 21 CFR 1301.71(a) 1306.04(a). The CSA holds the pharmacist responsible for knowingly dispensing a prescription that was not issued in the usual course of professional treatment. 21 CFR 1306.04(a).

Types of Fraudulent Prescriptions

Pharmacists should be aware of the various kinds of forged prescriptions that may be presented for dispensing. Some patients, in an effort to obtain additional amounts of legitimately prescribed drugs, alter the practitioner's prescription. They may have prescription pads printed using a legitimate doctor's name, but with a different call back number that is answered by an accomplice to verify the prescription. Drug seeking individuals may also call in their own prescriptions and give their own telephone number as a call-back for confirmation. Drug abusers sometimes steal legitimate prescription pads from practitioner's offices and/or hospitals and prescriptions are written using fictitious patient names and addresses.

In addition, individuals may go to emergency rooms complaining of pain in the hopes of receiving a controlled substance prescription. The prescription can then be altered or copied to be used again. Computers are often used to create prescriptions for non-existent doctors or to copy legitimate doctors' prescriptions. The quantity of drugs prescribed and frequency of prescriptions filled are not lone indications of fraud or

improper prescribing, especially if a patient is being treated with opioids for pain management. Pharmacists should also recognize that drug tolerance and physical dependence may develop as a consequence of a patient's sustained use of opioid analgesics for the legitimate treatment of chronic pain.

Identifing Out of Scope Prescriptions

The following criteria may indicate that a prescription was not issued for a legitimate medical purpose:

- The prescriber writes significantly more prescriptions (or in larger quantities) compared to other practitioners in the same specialty in the area.
- The patient appears to be returning too frequently. A prescription which should last for a month in legitimate use is being refilled on a biweekly, weekly, or even a daily basis.
- The prescriber writes prescriptions for antagonistic drugs, such as depressants and stimulants, at the same time. Drug abusers often request prescriptions for "uppers and downers" at the same time.
- The patient presents prescriptions written in the names of other people.
- A number of people appear simultaneously, or within a short time, all bearing similar prescriptions from the same physician.
- People who are not regular patrons or residents of the community show up with prescriptions from the same physician.

Identifying Fraudulent Prescriptions

The following criteria may indicate a forged prescription:

- Prescription looks "too good." The prescriber's handwriting is too legible.
- Quantities, directions, or dosages differ from usual medical usage.
- Prescription does not comply with the acceptable standard abbreviations or appears to be textbook presentations.
- Prescription appears to be photocopied.
- Directions are written in full with no abbreviations.

- Prescription is written in different color inks or written in different handwriting.

Prevention Techniques:

- Know the prescriber and his or her signature.
- Know the prescriber's DEA registration number.
- Know the prescriber's authorized agents and request a copy of any written agreement between prescriber and their agent.
- Know the patient.
- Check the date on the prescription order to determine if it has been presented in a reasonable length of time since being issued by the prescriber.

When there is a question about any aspect of the prescription order, the pharmacist should contact the prescriber for verification or clarification.

If at any time a pharmacist is in doubt, they should require proper identification. Although this procedure is not foolproof (identification papers can also be stolen/forged), it does increase the drug abuser's risk. If a pharmacist believes the prescription is forged or altered, they should not dispense it and should call the local police. If a pharmacist believes they have discovered a pattern of prescription abuse, they should contact the state Board of Pharmacy or the local DEA Diversion Field Office (Appendix K). Both DEA and state authorities consider retail-level diversion a priority issue.

Proper Controls

Dispensing procedures without control and professional caution are an invitation to the drug abuser. Proper controls can be accomplished by following common sense, sound professional practice, and proper dispensing procedures. In addition, pharmacy staff should have knowledge of these safeguards, as it will help prevent and protect the pharmacy from becoming a source of diversion.

Most drug abusers seek out areas where communication and cooperation between health care professionals are minimal because it makes the drug abuser's work easier. Thus, a pharmacist should encourage other local pharmacists and physicians to develop a working relationship which will promote teamwork and camaraderie. In addition, the pharmacist should become familiar with those controlled substances that are popular for abuse and resale on the streets in the area and should discuss those findings with other pharmacists and practitioners in the community.

APPENDIX E

Affidavit for a New Pharmacy[1]

I, _____, the _____ (Title of officer, official, partner, or other position) of _____ (Corporation, partnership, or sole proprietor), doing business as _____ (Store name) at _____ (Number and Street), _____ (City) _____ (State) _____ (Zip Code), hereby certify that said store was issued a pharmacy permit No. _____ by the _____ (Board of Pharmacy or Licensing Agency) of the State of _____ on _____ (Date).

This statement is submitted in order to obtain a Drug Enforcement Administration registration number. I understand that if any information is false, the Administration may immediately suspend the registration for this store and commence proceedings to revoke under 21 U.S.C. 824(a) because of the danger to public health and safety. I further understand that any false information contained in this affidavit may subject me personally and the above-named corporation/partnership/business to prosecution under Title 18, United States Code (18 U.S.C.).

_____

Signature (Person who signs Application for Registration)

State of _____ County of _____ Subscribed to and sworn before me this _____ day of _____, 20_____.

_____

Notary Public

[1] 21 CFR 1301.17(a).

APPENDIX F

Affidavit for Transfer of a Pharmacy[1]

I, _____, the _____ (Title of officer, official, partner, or other position) of _____ (Corporation, partnership, or sole proprietor), doing business as _____ (Store name) hereby certify:

(1) That said company was issued a pharmacy permit No. _____ by the _____ (Board of Pharmacy or Licensing Agency) of the State of _____ and a DEA Registration Number _____ for a pharmacy located at _____ (Number and Street), _____(City) _____ (State) _____ (Zip Code); and

(2) That said company is acquiring the pharmacy business of _____ (Name of Seller) doing business as _____ with DEA Registration Number _____ on or about _____ (Date of Transfer) and that said company has applied (or will apply on _____ (Date)) for a pharmacy permit from the Board of Pharmacy (or Licensing Agency) of the State of _____ to do business as _____ (Store name) at _____ (Number and Street) _____ (City) _____ (State) _____ (Zip Code).

This statement is submitted in order to obtain a Drug Enforcement Administration registration number.

I understand that if a DEA registration number is issued, the pharmacy may acquire controlled substances but may not dispense them until a pharmacy permit or license is issued by the state board of pharmacy or licensing agency.

I understand that if any information is false, the Administration may immediately suspend the registration for this store and commence proceedings to revoke under 21 U.S.C. 824(a) because of the danger to public health and safety. I further understand that any false information contained in this affidavit may subject me personally and the above-named corporation/partnership/business to prosecution under Title 18, United States Code (18 U.S.C.).

_____
Signature (Person who signs Application for Registration)

State of _____ County of _____ Subscribed to and sworn before me this _____ day of _____, 20_____.

_____
Notary Public

---

[1] 21 CFR 1301.17(b).

APPENDIX G

Equivalency Tables for Ephedrine, Pseudoephedrine, and Phenylpropanolamine Under the Combat Methamphetamine Epidemic Act of 2005

RETAIL DAILY SALE LIMITS ARE NOT TO EXCEED THE FOLLOWING AMOUNTS PER PURCHASER	
Ingredient	Number of Tablets = 3.6 grams
25 mg Ephedrine HCl	175
25 mg Ephedrine Sulfate	186
30 mg Pseudoephedrine HCl	146
60 mg Pseudoephedrine HCl	73
120 mg Pseudoephedrine HCl	36
30 mg Pseudoephedrine Sulfate	155
60 mg Pseudoephedrine Sulfate	77
120 mg Pseudoephedrine Sulfate	38
Phenylpropanolamine (PPA)	The Food and Drug Administration issued a voluntary recall of this ingredient as being unsafe for human consumption. Veterinary use is by prescription only.

30-DAY SALE LIMITS ARE NOT TO EXCEED THE FOLLOWING AMOUNTS PER PURCHASER		
Ingredient	Number of tablets at retail = 9 grams	Number of tablets for mail orders = 7.5 grams
25 mg Ephedrine HCl	439	366
25 mg Ephedrine Sulfate	466	389
30 mg Pseudoephedrine HCl	366	305
60 mg Pseudoephedrine HCl	183	152
120 mg Pseudoephedrine HCl	91	76
30 mg Pseudoephedrine Sulfate	389	324
60 mg Pseudoephedrine Sulfate	194	162
120 mg Pseudoephedrine Sulfate	97	81

Phenylpropanolamine (PPA)	The Food and Drug Administration issued a voluntary recall of this ingredient as being unsafe for human consumption. Veterinary use is by prescription only.

APPENDIX H

Guidelines for Emergency Kits in Long-Term Care Facilities

A pharmacy may place an emergency kit with controlled substances in a non-DEA registered LTCF if the appropriate state agency or regulatory authority specifically approves the placement and promulgates procedures that delineate:

1. The source from which the LTCF may obtain controlled substances for emergency kits and that the source of supply is a DEA registered hospital/clinic, pharmacy, or practitioner.

2. The security safeguards for each emergency kit stored at the LTCF, including who may have access to the emergency kit, and specific limitation of the type and quantity of controlled substances permitted in the kit.

3. The responsibility for proper control and accountability of the emergency kit within the LTCF, including the requirement that the LTCF and the supplying registrant maintain complete and accurate records of the controlled substances placed in the emergency kit, the disposition of the controlled substances, and the requirement to take and maintain periodic physical inventories.

4. The emergency medical conditions under which the controlled substances may be administered to LTCF patients, including the requirement that controlled substances be administered by authorized personnel only as expressly authorized by an individual practitioner and in compliance with the provisions of 21 CFR 1306.11 and 1306.21.

5. The prohibited activities that if violated could result in state revocation, denial, or suspension of the privilege to supply or possess emergency kits containing controlled substances.

The requirements for emergency kits in LTCFs were published in a Federal Register notice on April 9, 1980. 45 FR 24128. Pharmacies and LTCFs may wish to consult the notice to ensure compliance with the requirements.

APPENDIX I

Guidelines for Completing the DEA Form 106 (Theft or Loss of Controlled Substances) or the DEA Form 107 (Theft or Loss of Listed Chemicals)

Instructions for completing the DEA Form 106 are provided when filling out either the paper or electronic version of the form. Instructions are provided when filling out the electronic form of the DEA Form 107. Listed below are additional guidelines:

1. Do not use a DEA Form 106 to report an accidental spillage. Save the broken bottles, salvage the product if possible, and contact the local DEA Diversion Field Office (Appendix K) for additional instructions. This type of a loss, if considered significant, should be reported on a DEA Form 41, Registrants Inventory of Drugs Surrendered. 21 CFR 1304.21(e).

2. If thefts have occurred due to employee pilferage over a period of time, document on the DEA Form 106 or DEA Form 107 the date of discovery in block 4. Provide estimated beginning and ending dates of the thefts in box 17 with an explanation.

3. If there are multiple thefts or losses on the same day (e.g., mail-order pharmacy), report each theft or loss on a separate DEA Form 106 or DEA Form 107.

4. Miscounts or adjustments to inventory involving clerical errors on the part of the pharmacy should not be reported on a DEA Form 106 or DEA Form 107.

5. In block 9, enter the number of thefts or losses experienced in the last 24 months, but do not include the current theft or loss being reported. If the current theft or loss was the only theft or loss in the last 24 months, enter 0 (zero).

6. In block 12, enter the amount the pharmacy paid for the controlled substances or listed chemical products, not the retail value.

7. In blocks 14 b & c, if the customer accepted the controlled substances or listed chemical products before discovering a loss in transit, identify the supplier and its DEA registration number.

8. In block 14 f, when explaining how many losses occurred from the same carrier, do not include the current loss.

9. The date next to the signature and title on page 2 should be the date the form was completed, signed, and sent to the local DEA Diversion Field Office (Appendix K).

10. Document the National Drug Code (NDC) number of the controlled substance, and if the loss was a partial container, document the actual amount of theft or loss within the container.

11. For the DEA Form 106, If the controlled substance contains hydrocodone, oxycodone or a similar controlled substance and contains acetaminophen, aspirin, or ibuprofen, indicate the strength of the non-controlled substance as well as the strength of the controlled substance contained in the product.

12. If amending a paper version of a prior DEA Form 106, print **Amended** in the upper front page margin, with the date of the theft.

APPENDIX J

DEA Policy Statement on Role of Authorized Agents

On October 6, 2010, DEA published in the Federal Register a statement of policy to provide guidance under existing law regarding the proper role of a duly authorized agent of a DEA registered individual practitioner in connection with the communication of a controlled substance prescription to a pharmacy.

Please refer to DEA's Diversion website, www.DEAdiversion.usdoj.gov, to see the complete policy statement on the *Role of Authorized Agents in Communicating Controlled Substance Prescriptions to Pharmacies* 75 FR 61613 (Oct. 6, 2010).

APPENDIX K

DEA Registration Program Specialists in Field Divisions

Registration Program Specialists are available during normal business hours to provide information about new applications, renewals, order forms, or changes to a DEA registration. Addresses and telephone numbers are subject to change. The most current listing of Registration Program Specialists is located on DEA's Diversion website, www.DEAdiversion.usdoj.gov. Click on "Registration" and then look for the "Registration Support" subheading near the end of the page, wherein you will find a link to help you locate your local field office registration program specialist.

APPENDIX L

Drug Enforcement Administration
Diversion Field Office Locations

Visit www.DEAdiversion.usdoj.gov for current addresses and telephone numbers.

APPENDIX M

Internet Resources

DEA's Diversion Control Division Website
www.DEAdiversion.usdoj.gov

DEA Homepage
www.dea.gov

U.S. Government Publishing Office
https://www.govinfo.gov

Provides access to the CFR, Parts 1300 to End, primary source for the Pharmacist's Manual, and the Federal Register which contains proposed and finalized amendments to the CFR.

Office of National Drug Control Policy (ONDCP)
www.whitehouse.gov/ondcp

Food and Drug Administration
www.FDA.gov

SAMHSA
www.samhsa.gov

CSAT
https://www.samhsa.gov/about-us/who-we-are/offices-centers/csat

Federation of State Medical Boards
www.FSMB.org

National Association of Boards of Pharmacy
https://nabp.pharmacy

National Association of State Controlled Substances Authorities
www.nascsa.org

APPENDIX N

Small Business and Agriculture Regulatory Enforcement Ombudsman

The Small Business and Agriculture Regulatory Enforcement Ombudsman and 10 Regional Fairness Boards were established to receive comments from small businesses about federal agency enforcement actions. The Ombudsman will annually evaluate the enforcement activities and rate each agency's responsiveness to small business. If you wish to comment on DEA enforcement actions, you may contact the Ombudsman at 1-888-REG-FAIR (1-888-734-3247).

APPENDIX O

Additional Assistance

This publication is intended to provide guidance and information on the requirements of the CSA and its implementing regulations. If you require additional clarification or assistance, or wish to comment on any matter regarding DEA's requirements or regulatory activities, please contact your local DEA Diversion Field Office (Appendix K). Every effort will be made to respond promptly to your inquiry.

Plain Language

The Drug Enforcement Administration has made every effort to write this Pharmacist's Manual in clear, plain language. If you have suggestions as to how to improve the clarity of this Pharmacist's Manual, please contact us at:

Drug Enforcement Administration
Diversion Control Division
Attn: Policy Section/DPY
8701 Morrissette Drive
Springfield, VA 22152

Chapter Phar 8

REQUIREMENTS FOR CONTROLLED SUBSTANCES

Phar 8.01 Scope. Procedures governing the manufacture, distribution and dispensing of controlled substances pursuant to ch. 961, Stats., are set forth generally by that chapter and specifically by sections of this chapter and chs. Phar 12 and 13.

History: Cr. Register, January, 1983, No. 325, eff. 2–1–83; am. Register, August, 1991, No. 428, eff. 9–1–91; am. Register, December, 1998, No. 516, eff. 1–1–99.

Phar 8.02 Records. (1) Any pharmacy, practitioner, or other federal drug enforcement administration registrant, as referenced in ch. 961, Stats., shall maintain complete and accurate records of each controlled substance received, manufactured, distributed, dispensed or disposed of in any other manner.

(2) Records required by the federal controlled substances act and ch. 961, Stats., shall be maintained at the location where the drug is received, manufactured, distributed or dispensed, and be available for inspection by authorized persons for at least 5 years from the date of such record. Financial and shipping records such as invoices and packing slips, but not executed order forms, may be kept at a central location. A complete and accurate biennial physical inventory of all schedule II, III, IV and V controlled substances pursuant to ss. 961.16, 961.18, 961.20 and 961.22, Stats., and ch. CSB 2 on hand shall be made in conformance with all applicable federal and state laws.

(2m) Records required under s. 450.11 (1b) (bm), Stats., shall be maintained for at least 5 years from the date the drug was dispensed, or, for a record that is subject to s. 961.385, Stats., until the name of a person to whom a drug is dispensed is delivered to the controlled substances board under s. 961.385, Stats., whichever is sooner.

(3) Required records shall be maintained as follows:

(a) Records of schedule II controlled substances, other than prescription orders, shall be maintained separately from all other records.

(b) Records of schedule III, IV and V controlled substances shall be maintained either separately or in such form that the information required is readily retrievable from the registrant's ordinary records.

(c) The official drug enforcement administration order forms, DEA form 222, used in the procurement and distribution of schedule II substances shall be maintained at the locations from which the drug was distributed and where it is received.

(d) Any person authorized to manufacture, distribute or dispense controlled substances shall maintain complete and accurate records with the following information:

1. The name of the substance.

2. The dosage form, strength and quantity of the substance.

3. The quantity and date of distribution as well as the name, address and DEA registration number of the person to whom distributed.

4. The number of units and date of receipt as well as the name, address and DEA registration number of the person from whom received.

5. The name and address of the person for whom dispensed, date of dispensing, quantity dispensed and name or initials of the individual who dispensed the substance.

(e) Records for dispensed schedule V substances shall be maintained as follows:

1. If a schedule V drug is dispensed pursuant to the prescription order of a practitioner, the prescription shall be labeled properly and the order filed in accordance with the requirements for schedule III and IV orders.

2. If a schedule V drug is dispensed other than pursuant to a prescription order, the dispenser shall make the record required by s. 961.23, Stats., in a bound controlled substance V register at the time of the transaction.

(f) In any instance that a pharmacy, practitioner or other DEA registrant authorized to possess controlled substances is required to file with the DEA a report of theft or loss of controlled substances, the pharmacy, practitioner or other DEA registrant shall also send a copy to the board within 2 weeks of filing with the DEA.

Note: The Drug Enforcement Administration regional office is at 1800 Dirksen Federal Building, 219 S. Dearborn, Chicago, Illinois 60604.

History: Cr. Register, January, 1983, No. 325, eff. 2–1–83; am. (3) (f), r. (4) (a) and (b), Register, August, 1991, No. 428, eff. 9–1–91; am. (1), (2) and (3) (e) 2., Register, December, 1998, No. 516, eff. 1–1–99; CR 06–052: am. (3) (f) Register October 2006 No. 610, eff. 11–1–06; **CR 16–018: cr. (2m) Register September 2016 No. 729, eff. 10–1–16; correction in (2m) made under s. 35.17, Stats., Register September 2016 No. 729.**

Phar 8.03 Filing prescription orders. (1) All controlled substance prescription orders shall be maintained on file, in chronological order, for a period of at least 5 years. The orders shall be readily accessible to enforcement personnel authorized by s. 961.51, Stats.

(2) Schedule II prescription orders may be filed separately from all other orders or they may be filed with those for schedule III, IV and V drugs provided all orders in the file for schedule III, IV and V drugs are stamped in red ink with the letter "C" one inch in height, in the lower right hand corner of the order. Under no circumstances may schedule II orders be filed together with those for non–controlled drugs.

(3) Schedule III, IV and V prescription orders may be filed with those for non–controlled drugs provided that orders for schedule III, IV and V drugs are stamped in red ink with the letter "C" one inch in height in the lower right hand corner of the order or orders for schedule III, IV and V substances may be filed separately. However, if a pharmacy employs an automated data processing system or other electronic recordkeeping system for prescription orders which permits identification by prescription order number and retrieval of original documents by prescriber's name, patient's name, drug dispensed, and date filled, then the requirement to mark the hard copy prescription order with a red "C" is waived.

History: Cr. Register, January, 1983, No. 325, eff. 2–1–83; am. (2) and (3), Register, August, 1991, No. 428, eff. 9–1–91; am. (1) and (3), Register, December, 1998, No. 516, eff. 1–1–99.

Phar 8.04 Purpose of issue of prescription order. **(1)** Prescription orders for controlled substances shall be issued for a legitimate medical purpose by individual practitioners acting in the usual course of professional practice. Responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who dispenses the prescription. An order purporting to be a prescription order not issued in the usual course of professional treatment or in legitimate and authorized research is not a prescription order within the meaning and intent of ss. 450.01 (21) and 961.38, Stats. The person knowingly dispensing pursuant to such a purported order, as well as the person issuing it, shall be subject to the penalties provided for violation of the provision of law relating to controlled substances.

(2) A prescription order issued by a practitioner to obtain controlled substances for the purpose of general dispensing or administration to patients by the practitioner is not valid.

History: Cr. Register, January, 1983, No. 325, eff. 2–1–83; am. Register, August, 1991, No. 428, eff. 9–1–91; am. (1), Register, December, 1998, No. 516, eff. 1–1–99.

Phar 8.05 Dispensing. **(1)** All controlled substance prescription orders shall be dated as of, and signed on, the day issued and shall contain the full name and address of the patient, the drug name, strength, dosage form, quantity prescribed, directions for use and the name, address and registration number of the practitioner. Prescription orders shall be written with ink or indelible pencil or be typewritten and shall be signed by the practitioner. Orders for controlled substances may be issued only by individual practitioners who are authorized to prescribe controlled substances by the jurisdiction in which he or she is licensed to practice and registered or exempt from registration under the federal controlled substances act.

(2) A pharmacist may dispense a controlled substance listed in schedule II, III or IV only pursuant to a prescription order issued by an individual practitioner. The order shall be initialed and dated by the dispensing pharmacist as of the date the prescription is dispensed. If the person accepting the medication pursuant to any prescription order for a schedule II controlled substance, specified in s. 961.16, Stats., is not personally known to the pharmacist, there shall be written in ink, on the reverse side, the printed name, signature and address of the person.

(3) An individual practitioner may dispense directly a controlled substance listed in schedule II, III or IV provided that the prescription container is labeled and records are maintained in accordance with the requirements of this code.

(4) A prescription containing a controlled substance listed in schedule II may be dispensed only pursuant to a written hard copy or electronic order signed by the prescribing individual practitioner, except in emergency situations. A prescription for a controlled substance listed in schedule II may not be dispensed more than 60 days after the date of issue on the prescription order.

(7) A prescription order for a controlled substance may not be dispensed unless the prescription order contains all of the information required in sub. (1). For any controlled substance prescription order, a pharmacist may not add, modify or clarify the patient's name, the controlled substance prescribed, except for generic substitution as permitted by law, and the prescribing practitioner's signature. After consultation with the prescribing practitioner, a pharmacist may add, modify or clarify the strength, dosage form, quantity prescribed, date of issuance and directions for use for a schedule II controlled substance prescription order. For a schedule II controlled substance prescription order, a pharmacist may add, modify or clarify the registration number of the practitioner, and the address of the practitioner and the patient if that information is verifiable and retrievable from information maintained by the pharmacist or is obtained through consultation with the practitioner. A pharmacist may add, modify or clarify any information allowed in this subsection missing from a prescription order for a schedule III, IV or V controlled substance that is verifiable and retrievable from information maintained by the pharmacist or that is obtained through consultation with a practitioner. A patient may only provide information to a pharmacist to add, modify or clarify the patient's address. The prescription order shall be initialed and dated by the pharmacist and shall indicate the addition, modification or clarification of information and the manner by which the pharmacist obtained that information.

History: Cr. Register, January, 1983, No. 325, eff. 2–1–83; am. (1), (2), (3) and (5), cr. (6), Register, August, 1991, No. 428, eff. 9–1–91; cr. (7), Register, January, 1996, No. 481, eff. 2–1–96; am. (4), Register, February, 1996, No. 482, eff. 3–1–96; am. (2), Register, December, 1998, No. 516, eff. 1–1–99; am. (1) and (7), r. (6), Register, February, 2001, No. 542, eff. 3–1–01; CR 01–154: am. (4), r. (5), Register 2002 No. 559, eff. 8–1–02; CR 13–075: am. (4) Register August 2014 No. 704, eff. 9–1–14.

Phar 8.06 Renewing prescriptions. **(1)** No prescription containing a schedule II substance may be renewed.

(2) The prescribing practitioner may authorize renewals of schedule III or IV controlled substances on the original prescription order or through an electronic or oral renewal authorization transmitted to the pharmacist. The following conditions must be met:

(a) The pharmacist obtaining the electronic or oral authorization shall note on the prescription order, medication profile record or readily retrievable and uniformly maintained document the following information:

1. Date authorization is received.
2. Quantity of drug authorized.
3. Number of renewals.
4. Identification of practitioner authorizing the renewals if different from the original prescriber.
5. Identification of the pharmacist who received the authorization.

(b) The quantity of each renewal authorized is equal to or less than the quantity authorized for the initial dispensing of the original prescription.

(3) No prescription containing a controlled substance listed in schedule III or IV may be dispensed or renewed more than 6 months after the date on which the prescription order was issued and no prescription authorized to be renewed may be renewed more than 5 times.

(4) A prescription containing a drug listed in schedule V may be renewed only as expressly authorized by the practitioner.

History: Cr. Register, January, 1983, No. 325, eff. 2–1–83; renum. (2) and (3) to be (3) and (4) and am. (3), cr. (2), Register, August, 1991, No. 428, eff. 9–1–91; am. (2) (intro.) and (a) (intro.), Register, November, 1999, No. 527, eff. 12–1–99.

Phar 8.07 Partial dispensing. **(1)** A pharmacist may partially dispense a prescription containing a controlled substance listed in schedule III, IV and V.

(2) The partial dispensing of a prescription containing a controlled substance listed in schedule II is permissible, if the pharmacist is unable to supply the full quantity called for in a written, electronic, or emergency oral prescription order, and the pharmacist makes a notation of the quantity supplied on the face of the written hard copy prescription order or written record of the electronic or emergency oral prescription order. The remaining portion of the prescription may be dispensed within 72 hours of the first partial dispensing. If the remaining portion is not dispensed within the 72 hour period, the pharmacist shall so notify the prescribing individual practitioner. No further quantity may be supplied beyond the 72 hours without a new prescription order.

(3) Prescription orders for schedule II controlled substances written for patients in long term care facilities (LTCF) or for patients with a medical diagnosis documenting a terminal illness may be dispensed in partial quantities to include individual dosage units. The prescribing practitioner may document a terminal illness by writing upon the face of the prescription order the phrase "terminal illness" or words of similar meaning. If there is any question whether a patient may be classified as having a terminal illness, the pharmacist shall contact the prescribing practitioner

prior to partially dispensing the prescription. Documentation of a terminal illness, whether substantiated by the presence of an appropriate phrase written upon the face of the prescription order or through pharmacist contact with the prescribing practitioner, shall be placed within the individual medication profile record maintained under s. Phar 7.07. The pharmacist shall record on the prescription order whether the patient is"terminally ill" or an "LTCF patient." A prescription order that is partially dispensed and does not contain the notation "terminally ill" or"LTCF patient" shall be deemed to have been dispensed in violation of this section. For each partial dispensing, the dispensing pharmacist shall record on the back of the prescription order or on another appropriate record, uniformly maintained and readily retrievable, the date of the partial dispensing, quantity dispensed, remaining quantity authorized to be dispensed and the identification of the dispensing pharmacist. Subsequent partial dispensing is not permitted under this section if the patient becomes deceased, or is no longer diagnosed as terminally ill, or no longer resides within an LTCF. The total quantity of a schedule II controlled substance dispensed by partial dispensing may not exceed the total quantity prescribed. Prescription orders for schedule II controlled substances for patients in an LTCF or patients with a medical diagnosis documenting a terminal illness shall be valid for a period not to exceed 60 days from the issue date unless terminated earlier by the discontinuance of medication.

(4) Information pertaining to current prescription orders for schedule II controlled substances for patients in an LTCF or for patients with a medical diagnosis documenting a terminal illness may be maintained in a computerized system if the system has the capability to permit:

(a) Display or printout of: the original prescription order designation; date of issue; identification of prescribing practitioner; identification of patient; name and address of the LTCF or name and address of the hospital or residence of the patient; identification of medication authorized, including dosage form, strength and quantity; listing of partial quantities that have been dispensed under each prescription order and the information required in sub. (3).

(b) Immediate (real time) updating of the prescription order record each time there is partial dispensing of the prescription.

(c) Retrieval of partially dispensed schedule II prescription information identical to that required by s. Phar 7.05 (2) for all prescription renewal information.

History: Cr. Register, January, 1983, No. 325, eff. 2–1–83; r. and recr. Register, August, 1991, No. 428, eff. 9–1–91; am. (3), (4) (intro.) and (a), r. (5), Register, September, 1994, No. 465, eff. 10–1–94; am. (2), Register, November, 1999, No. 527, eff. 12–1–99; CR 13–075: am. (2) Register August 2014 No. 704, eff. 9–1–14; **CR 15–064: am. (2) Register September 2016 No. 729, eff. 10–1–16.**

Phar 8.08 Labeling prescriptions. (1) The pharmacist dispensing a prescription containing a controlled substance shall affix to the immediate container a label showing the date of dispensing; the pharmacy name and address; serial number of the prescription; full name of the patient; name of the prescribing practitioner; directions for use; and cautionary statements, contained in the prescription order or required by law.

(2) Practitioners who personally dispense any controlled substance to patients in the course of their professional practice other than by prescribing or administering shall conform to ch. Med 17, standards for dispensing drugs.

History: Cr. Register, January, 1983, No. 325, eff. 2–1–83; am. Register, August, 1991, No. 428, eff. 9–1–91.

Phar 8.09 Emergency dispensing. (1) For the purpose of authorizing an oral prescription order for a schedule II controlled substance, the term "emergency" means those situations in which the prescribing practitioner determines that:

(a) Immediate administration of the controlled substance is necessary for proper treatment of the patient.

(b) No appropriate alternative treatment is available, including the administration of a drug which is not a schedule II controlled substance.

(c) It is not reasonably possible for the prescribing practitioner to provide a written prescription order to be presented to the pharmacist prior to dispensing.

(2) In an emergency a pharmacist may dispense a controlled substance listed in schedule II upon receiving oral authorization of a practitioner if:

(a) The quantity prescribed and dispensed is limited to the amount adequate to treat the patient during the emergency period.

(b) The prescription order is immediately reduced to writing by the pharmacist and contains all information required in s. Phar 8.05, except for the signature of the practitioner.

(3) If the practitioner is not known to the pharmacist, the pharmacist shall make a reasonable effort to determine that the oral authorization came from an authorized practitioner, which may include a call back to the prescribing practitioner using good faith efforts to insure the practitioner's identity.

(4) Within 7 days after authorizing an emergency oral prescription order, the practitioner shall cause a written or electronic order for the emergency quantity prescribed to be delivered to the dispensing pharmacist. In addition to conforming to the requirements of s. Phar 8.05, the order shall contain on its face "authorization for emergency dispensing" and the date of the oral order. The written or electronic order may be delivered to the pharmacist in person or by mail or electronically, but if delivered by mail it shall be postmarked within the 7 day period. Upon receipt, the dispensing pharmacist shall attach this prescription order to the oral emergency order reduced to writing under sub. (2) (b). The pharmacist shall notify the board or department of safety and professional services if the practitioner fails to deliver the written or electronic order. Failure of the pharmacist to provide notification shall void the authority conferred by this section to dispense without a written or electronic order of a practitioner.

History: Cr. Register, January, 1983, No. 325, eff. 2–1–83; am. Register, August, 1991, No. 428, eff. 9–1–91; am. (4), Register, December, 1998, No. 516, eff. 1–1–99; am. (1) (intro.), (2) (intro.), (3) and (4), Register, November, 1999, No. 527, eff. 12–1–99; correction in (4) made under s. 13.92 (4) (b) 6., Stats., Register February 2012 No. 674; CR 13–075: am. (1) (intro.), (2) (intro.), (3), (4) Register August 2014 No. 704, eff. 9–1–14.

Phar 8.10 Disclosure of suspicious orders of controlled substances. Manufacturers and distributors of controlled substances shall disclose suspicious orders of controlled substances. Suspicious orders include, without limitation because of enumeration, orders of unusual size, orders deviating substantially from a normal pattern and orders of unusual frequency. The licensee shall notify the regional office of the DEA and the board of all suspicious orders.

History: Cr. Register, August, 1991, No. 428, eff. 9–1–91.

Phar 8.11 Controlled substances in emergency kits for long term care facilities. Long term care facilities which are not registered with the DEA shall meet all of the following requirements regarding emergency kits containing controlled substances:

(1) The source of supply must be a DEA registered hospital, pharmacy or practitioner.

(2) The pharmaceutical services committee of the facility shall establish security safeguards for each emergency kit stored in the LTCF which shall include the designation of individuals who may have access to the emergency kits and a specific limitation of the type and quantity of controlled substances permitted to be placed in each emergency kit.

(3) A pharmacist shall be responsible for proper control and accountability for such emergency kits within the LTCF which includes the requirement that the LTCF and the providing DEA registered hospital, pharmacy or practitioner maintain complete and accurate records of the controlled substances placed in the

emergency kits, the disposition of those controlled substances, plus the requirement to take at least monthly physical inventories.

(4) The pharmaceutical services committee will establish the emergency medical conditions under which the controlled substances may be administered to patients in the LTCF which shall include the requirement that medication be administered by authorized personnel only as expressly authorized by an individual DEA registered practitioner and in compliance with all applicable federal and state laws.

(5) Noncompliance with this rule may result in revocation, denial or suspension of the privilege of having or placing emergency kits, containing controlled substances, in LTCF.

History: Cr. Register, August, 1991, No. 428, eff. 9–1–91.

Phar 8.12 Prescription orders transmitted by facsimile machine. (1) PRESCRIPTION DRUGS OTHER THAN SCHEDULE II CONTROLLED SUBSTANCES. A pharmacist may dispense a prescription drug, other than a schedule II controlled substance, pursuant to a prescription order transmitted by a facsimile machine from the practitioner or the practitioner's agent to the dispensing pharmacy if all of the following conditions are met:

(a) The transmitted facsimile prescription order shall contain all of the information required for a valid written prescription order. The order shall also contain the time and date of the transmission, as well as the telephone number and name of the transmitter.

(b) Unless the facsimile paper is non–fading, the facsimile prescription order received shall be duplicated by copy machine or other similar device and the copy must be physically attached to the order received.

(2) SCHEDULE II CONTROLLED SUBSTANCES. A pharmacist may not dispense a schedule II controlled substance pursuant to a prescription order transmitted by a facsimile machine unless all of the conditions stated in sub. (1) are satisfied, and any of the following conditions are met:

(a) The prescription order is written for a schedule II controlled substance to be compounded for the direct administration to a patient by parenteral, intravenous, intramuscular, subcutaneous or intraspinal infusion, and is transmitted by the practitioner or the practitioner's agent to the dispensing pharmacy by facsimile.

(b) The prescription order is written for a schedule II controlled substance for a patient who resides in a long term care facility, or who meets the eligibility requirements for placement in a long term care facility but elects to reside at home, and is transmitted by the practitioner or the practitioner's agent to the dispensing pharmacy by facsimile.

(c) The prescription order is written for a schedule II controlled substance for a patient enrolled in a hospice certified by medicare under Title XVIII or licensed by this state, and is transmitted by the practitioner or the practitioner's agent to the dispensing pharmacy by facsimile.

(3) PRESCRIPTION ORDERS TRANSMITTED BY FACSIMILE CONSIDERED WRITTEN ORDERS. For all purposes under chs. 450 and 961, Stats., and the rules of the board, a prescription order transmitted by facsimile machine shall be considered the original written prescription order.

History: Cr. Register, December, 1998, No. 516, eff. 1–1–99; CR 09–098: am. (2) (b) Register May 2010 No. 653, eff. 6–1–10.

Phar 8.13 Identification card exception for a health care facility. In s. 450.11 (1b) (e) 3., Stats., "health care facility" means a facility, as defined in s. 647.01 (4), Stats.; any hospital, nursing home, community–based residential facility, county home, county infirmary, county hospital, county mental health complex, or other place licensed or approved by the department of health services under s. 49.70, 49.71, 49.72, 50.03, 50.032, 50.033, 50.034, 50.35, 51.08, or 51.09, Stats.; a facility under s. 45.50, 51.05, 51.06, 233.40, 233.41, 233.42, or 252.10, Stats.; and a hospice facility under s. 50.90 (1) (c), Stats.

History: CR 16–018: cr. Register September 2016 No. 729, eff. 10–1–16; correction made under s. 35.17, Stats., Register September 2016 No. 729.

Review of Pharmacy Examining Board Phar 8

https://docs.legis.wisconsin.gov/code/admin_code/phar/8

and

Federal 2020 DOJ/DEA Pharmacy Manual guidance

https://www.deadiversion.usdoj.gov/pubs/manuals /

1/28/2021

Some Differences between State and Federal

1. *Record Retention*: State 5 year, Fed 2 year
2. State Prescription *Renewal* vs. **Federal** *Refill*: Different terms to mean same thing.
3. *Physical inventory* every 2 years. Rules Committee indicated it may prefer annual. Authority?
4. *Schedule V, terms*: state, register vs. **Fed** logbook.
5. *Recordkeeping*: Wisconsin – to DEA and Pharmacy Board within 2 weeks of filing to DEA. **Fed** – Report to DEA and complete form 106 found online. Within one day.
6. *Dispensing controlled substances* without a prescription: much more specific in **federal**
7. *Reporting theft or loss*: Wisconsin – to DEA and Pharmacy Board within 2 weeks of filing to DEA. **Fed** – Report to DEA and complete form 106 found online. Within one day.
8. Federal outlines specifics for *direct dispensing*. Phar 8 does not.
9. Wisconsin –Discusses term *"emergency*". Requires notification to Pharmacy Board if no written prescription. **Fed** – Discusses term "emergency situation." Pharmacist to notify DEA as a requirement, not included in state requirements.
10. *Label requirements*: Wisconsin –requirements same as federal; No Central fill requirements, No Caution phrase requirement. Fed- requirements for Central fill pharmacies. Includes Caution phrase, not required under Phar 8
11. **Feds** permit 90-day supply with conditions. State does not indicate in Phar 8.

Issue	Phar 8	Federal	Comparison
Recordkeeping – Inventory, record retention	Phar 8.02 (2) 5-year record retention policy	If a prescription is created, signed, transmitted, and received electronically, all records related to that prescription must be retained electronically. 21 CFR 1311.305(a). Electronic records must be maintained electronically for two years from the date of their creation or receipt. 21 CFR 1311.305(b). Records regarding controlled substances must be readily retrievable from all other records. Electronic records must be easily readable or easily rendered into a format that a person can read. 21 CFR 1311.305(c).	Wis – 5 year Fed – 2 year States are authorized to have longer record retention policy.
Recordkeeping – Inventory	Phar 8.02(2) A complete and accurate **biennial physical inventory** of all schedule II, III, IV and V controlled substances pursuant to s. 961.16, 961.18, 961.20 and 961.22, Stats., and ch. CSB 2 on hand shall be made in conformance with all applicable federal and state laws.	After the initial inventory, the registrant is required to take a new inventory **at least every two years**, which requires the same information as the initial inventory of all controlled substances on hand. 21 CFR 1304.11(c). There is no requirement to submit a copy of the inventory to DEA. Under 21 CFR 1304.11(a), (b) and (e)(6), the inventory shall include: 1. The date of the inventory, 2. Whether the inventory was taken at the beginning or close of business, 3. The name of each controlled substance inventoried, 4. The finished form of each of the substances (e.g., 10 milligram tablet), 5. The number of dosage units or volume of each finished form in the commercial container (e.g., 100 tablet bottle or 3 milliliter vial),	Same Wis and Fed - 2 year physical inventory

		6. The number of commercial containers of each finished form (e.g., four 100 tablet bottles), and 7. The total count of the substance.	
Issue	**Phar 8**	**Federal**	**Comparison**
Recordkeeping – Inventory, identification card	s. 450.11 (1b)(bm), Stats. A pharmacist or other person dispensing or delivering a drug shall legibly record the name on each identification card presented under par (b) to the pharmacist or other person, and the name of each person to whom a drug is dispensed or delivered subject to par (e)2., and shall maintain that record for a time established by the board by rule or, for a record that is subject to s. 961.385, until the name is delivered to the controlled substances board under s. 961.385, whichever is sooner. Phar 8.02 (3) (d) Any person authorized to manufacture, distribute or dispense controlled substances shall maintain complete and accurate records with the following information: **1.** The name of the substance. **2.** The dosage form, strength and quantity of the substance. **3.** The quantity and date of distribution as well as the name, address and DEA registration number of the person to whom distributed. **4.** The number of units and date of receipt as well as the name, address and DEA registration number of the person from whom received. **5.** The name and address of the person for whom dispensed, date of dispensing, quantity dispensed and name or initials of the individual who dispensed the substance.	The CMEA requires an individual to present an unexpired identification card that includes a photograph and is issued by a state or the Federal Government or a document considered acceptable under 8 CFR 274a.2(b)(1)(v)(A) and (B). Pursuant to 21 CFR 1304, the records which must be maintained by a pharmacy are: Executed official order forms (DEA Form 222) or the electronic equivalent. Power of Attorney authorization to sign order forms. 21 CFR 1305.05(a). Receipts and/or invoices for schedules III, IV, and V controlled substances. All inventory records of controlled substances, including the initial and biennial inventories, dated as of beginning or close of business. Records of controlled substances distributed (i.e., sales to other registrants, returns to vendors, distributions to reverse distributors Records of controlled substances dispensed, to include prescriptions or a logbook of controlled substances which may be lawfully dispensed without a prescription. **Schedule III-IV.** The electronic system must provide online retrieval of original prescription information for those prescriptions which are currently authorized for refill. The information	Wis – requires reporting of name to CSB. List of required data Fed – lists required data virtually same as state however refills are permitted

		must include, but is not limited to: the original prescription number; date of issuance; full name and address of the patient; the prescriber's name, address, and DEA registration number; the name, drug strength, dosage form and quantity of the controlled substance prescribed (and quantity dispensed if different from the quantity prescribed); and the total number of refills authorized by the prescriber. 21 CFR 1306.22(f)(1).	
Issue	**Phar 8**	**Federal**	**Comparison**
Recordkeeping – Inventory Schedule II, III, IV, V	Phar 8.02 (3) Required records shall be maintained as follows: (a) Records of schedule II controlled substances, other than prescription orders, shall be maintained separately from all other records. (b) Records of schedule III, IV and V controlled substances shall be maintained either separately or in such form that the information required is readily retrievable from the registrant's ordinary records. (c) The official drug enforcement administration order forms, DEA form 222, used in the procurement and distribution of schedule II substances shall be maintained at the locations from which the drug was distributed and where it is received.	Separate filing for schedule II. Prescriptions for schedules III, IV, and V controlled substances shall be maintained at the registered location either in a separate prescription file for schedules III, IV, and V, or in such form that they are readily retrievable from the other prescription records of the pharmacy. 21 CFR 1304.04(h)(4). Required submission of DEA form 222 for Schedule II drug orders. Readily retrievable invoices for schedule III, IV, V. A pharmacy's electronic system must have the capability of printing out any refill data which the pharmacy must maintain under the CSA. a. Prescribing practitioner's name b. Patient's name and address c. Quantity and date dispensed on each refill d. Name or identification code of the dispensing pharmacist e. Original prescription number	Virtually the same provisions.

		In any electronic system employed by a user pharmacy, the central recordkeeping location must be capable of providing a printout to a requesting pharmacy of the above information within 48 hours. 21 CFR 1306.22(f)(4).	
Recordkeeping - Schedule V	Phar 8.02 (3) (e) Records for dispensed schedule V substances shall be maintained as follows: 1. If a schedule V drug is dispensed pursuant to the prescription order of a practitioner, the prescription shall be labeled properly and the order filed in accordance with the requirements for schedule III and IV orders. 2. If a schedule V drug is dispensed other than pursuant to a prescription order, the dispenser shall make the record required by s. 961.23, Stats., in a bound controlled substance V register at the time of the transaction.	Records of controlled substances dispensed, to include prescriptions or a logbook of controlled substances which may be lawfully dispensed without a prescription.	State – Outlined in statutes in s. 961.23 "record required in a bound controlled subs V register. Fed - logbook

Recordkeeping – Theft or loss reporting to DEA and board	Phar 8.02 (f) In any instance that a pharmacy, practitioner or other DEA registrant authorized to possess controlled substances is required to file with the DEA a report of theft or loss of controlled substances, the pharmacy, practitioner or other DEA registrant shall also send a copy to the board within 2 weeks of filing with the DEA.	Under 21 CFR 1301.76(b), should a theft or significant loss of any controlled substance occur at a pharmacy, the following procedures must be implemented within one business day of the discovery of the theft or loss. A. Notify DEA and Local Police The theft of controlled substances from a registrant is a criminal act and a source of diversion that requires notification to DEA. A pharmacy must notify in writing the local DEA Diversion Field Office within one business day of discovery of a theft or significant loss of a controlled substance. 21 CFR 1301.76(b). Although not specifically required by federal law or regulations, the registrant should also notify local law enforcement and state regulatory agencies. DEA must be notified directly. 21 CFR 1301.76(b). This requirement is not satisfied by reporting the theft or significant loss in any other manner. A pharmacy must complete a DEA Form 106 (Report of Theft or Loss of Controlled Substances) (21 CFR 1301.76(b))	Wisconsin – to DEA and Pharmacy Board within 2 weeks of filing to DEA. Fed – Report to DEA and complete form 106 found online. Within one day.
Filling Orders – Recordkeeping	Phar 8.03 (1) All controlled substance prescription orders shall be maintained on file, in chronological order, for a period of at least 5 years. The orders shall be readily accessible to enforcement personnel authorized by s. 961.51, Stats.	Electronic records must be maintained electronically for two years from the date of their creation or receipt. 21 CFR 1311.305(b). Records regarding controlled substances must be readily retrievable from all other records. Electronic records must be easily readable or easily rendered into a format that a person can read. 21 CFR 1311.305(c).	State – five years Fed – two years

Issue	Phar 8	Federal	Comparison
Filling Orders – Schedule II	Phar 8.03 (2) Schedule II prescription orders may be filed separately from all other orders or they may be filed with those for schedule III, IV and V drugs provided all orders in the file for schedule III, IV and V drugs are stamped in red ink with the letter "C" one inch in height, in the lower right hand corner of the order. Under no circumstances may schedule II orders be filed together with those for non-controlled drugs. Phar 8.05(4) A prescription containing a controlled substance listed in schedule II may be dispensed only pursuant to a written hard copy or electronic order signed by the prescribing individual practitioner, except in emergency situations. A prescription for a controlled substance listed in schedule II may not be dispensed more than 60 days after the date of issue on the prescription order	Only schedule I and II controlled substances are ordered with an official paper order form, DEA Form 222, or the electronic equivalent (See below, Controlled Substance Ordering System (CSOS) – Electronic Order Forms.) DEA Forms 222 must be maintained separately from all other records of the registrant. 21 CFR 1305.17(c). DEA Forms 222 are required to be kept available for inspection for a period of two years. 21 CFR 1305.17(c). Paper prescriptions for schedule II controlled substances shall be maintained at the registered location in a separate prescription file. 21 CFR Part 1306 - the pharmacist is to make notation on the prescription if the prescription were a paper prescription, the pharmacist must make the same notation electronically when filling an electronic prescription and retain the annotation electronically in the prescription record or linked files.	Virtually the same Specifically noted a "C" for state Feds are "make notation"
Filling Orders - Identification of III, IV and V orders – hard copy vs electronic	Phar 8.03 (3) Schedule III, IV and V prescription orders may be filed with those for non-controlled drugs provided that orders for schedule III, IV and V drugs are stamped in red ink with the letter "C" one inch in height in the lower right hand corner of the order or orders for schedule III, IV and V substances may be filed separately. However, if a pharmacy employs an automated data processing system or other electronic recordkeeping system for prescription orders which permits identification by prescription order number and retrieval of original documents by prescriber's name, patient's name, drug dispensed, and date filled, then the requirement to mark the hard copy prescription order with a red ``C" is waived.	21 CFR 1304.04(h)(2). Prescriptions for schedules III, IV, and V controlled substances shall be maintained at the registered location either in a separate prescription file for schedules III, IV, and V, or in such form that they are readily retrievable from the other prescription records of the pharmacy. 21 CFR 1304.04(h)(4). 21 CFR Part 1306 - the pharmacist is to make notation on the prescription if the prescription were a paper prescription, the pharmacist must make the same notation electronically when filling an electronic prescription and retain the annotation electronically in the prescription record or linked files.	Waiver of "C" if digital system is used.

Purpose of Order Legitimate medical purpose and corresponding responsibility.	Phar 8.04 (1) Prescription orders for controlled substances shall be issued for a legitimate medical purpose by individual practitioners acting in the usual course of professional practice. Responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who dispenses the prescription. An order purporting to be a prescription order not issued in the usual course of professional treatment or in legitimate and authorized research is not a prescription order within the meaning and intent of ss. 450.01 (21) and 961.38, Stats. The person knowingly dispensing pursuant to such a purported order, as well as the person issuing it, shall be subject to the penalties provided for violation of the provision of law relating to controlled substances.	An order purporting to be a prescription that is not issued for a legitimate medical purpose in the usual course of professional treatment or in legitimate and authorized research is not a prescription within the meaning and intent of 21 U.S.C. 829. The person knowingly filling such a purported prescription, as well as the person issuing it, shall be subject to the penalties provided for violations of the provisions of law relating to controlled substances. 21 U.S.C. 841(a)(1) and 21 CFR 1306.04(a). A pharmacist has a corresponding responsibility for the proper dispensing of controlled substances. An order purporting to be a prescription that is not issued for a legitimate medical purpose in the usual course of professional treatment or in legitimate and authorized research is an invalid prescription within the meaning and intent of the CSA. The person knowingly filling such a purported prescription, as well as the person issuing it, shall be subject to the penalties provided for violations of the provisions of law relating to controlled substances. 21 U.S.C. 841(a)(1), 21 U.S.C. 842(a)(1), and 21 CFR 1306.04(a).	Virtually same provision
Issue	**Phar 8**	**Federal**	**Comparison**
Dispensing Requirements of prescription orders (info on written orders) Issuance by authorized practitioners-registered or exempted under	Phar 8.05 (1) All controlled substance prescription orders shall be dated as of, and signed on, the day issued and shall contain the full name and address of the patient, the drug name, strength, dosage form, quantity prescribed, directions for use and the name, address and registration number of the practitioner. Prescription orders shall be written with ink or indelible pencil or be typewritten and shall be signed by the practitioner. Orders for	A prescription for a controlled substance must be dated and signed on the date when issued. The prescription must include the patient's full name and address, and the practitioner's full name, address, and DEA registration number. 21 CFR 1306.05(a). Under 21 CFR 1306.05(a), 1306.22(b), the prescription must also include: Drug name, Drug strength, Dosage form, Quantity	Federal includes number of refills authorized, to be included on the prescription.

federal controlled substance act.	controlled substances may be issued only by individual practitioners who are authorized to prescribe controlled substances by the jurisdiction in which he or she is licensed to practice and registered or exempt from registration under the federal controlled substances act.	prescribed, Directions for use, Number of refills authorized (if any) A paper prescription must be written in ink or indelible pencil or typewritten, or printed on a computer printer, and must be manually signed by the practitioner on the date when issued.	
Dispensing Schedule II, III, IV dispensing, dating, personal knowledge of person for schedule II, no personal knowledge then name/address and signature of person on back.	Phar 8.05 (2) A pharmacist may dispense a controlled substance listed in schedule II, III or IV only pursuant to a prescription order issued by an individual practitioner. The order shall be initialed and dated by the dispensing pharmacist as of the date the prescription is dispensed. If the person accepting the medication pursuant to any prescription order for a schedule II controlled substance, specified in s. 961.16, Stats., is not personally known to the pharmacist, there shall be written in ink, on the reverse side, the printed name, signature and address of the person.	The pharmacist dispensing a prescription for a controlled substance listed in schedules II, III, IV, or V must affix to the package a label showing date of filling, the pharmacy name and address, the serial (prescription) number, the name of the patient, the name of the prescribing practitioner, and directions for use and cautionary statements, if any, contained in such prescription as required by law. 21 CFR 1306.14(a), 1306.24(a).	Differences noted.
Dispensing Schedule II, III, IV dispensing- labels, records	Phar 8.05 (3) An individual practitioner may dispense directly a controlled substance listed in schedule II, III or IV provided that the prescription container is labeled and records are maintained in accordance with the requirements of this code.	Dispensing a controlled substance without a prescription is governed by 21 CFR 1306.26. The regulation states that a controlled substance listed in schedules II, III, IV, or V which is not a prescription drug as determined under the Federal Food, Drug, and Cosmetic Act, may be dispensed by a pharmacist without a prescription to a purchaser at retail, provided that: 1. Such dispensing is made only by a pharmacist and not by a non-pharmacist employee even if under the supervision of a pharmacist 21 CFR 1306.26(a). 2. Not more than 240 cc. (8 ounces) of any such controlled substance containing opium, nor more than 120 cc. (4 ounces) of any other such controlled substance, nor more than 48 dosage units of any such controlled substance containing opium, nor more than 24 dosage units of any other	Specifics of criteria for direct dispensing are outlined in federal.

		such controlled substance, may be dispensed at retail to the same purchaser in any given 48-hour period. 21 CFR 1306.26(b). 3. The purchaser is at least 18 years of age. 21 CFR 1306.26(c). 4. The pharmacist requires every purchaser of a controlled substance not known to him to furnish suitable identification (including proof of age where appropriate). 21 CFR 1306.26(d). 5. A bound record book must be maintained in accordance with the recordkeeping requirement of 21 CFR 1304.04. (See Section VI – Recordkeeping Requirements.) It is maintained by the pharmacist, and contains the name and address of the purchaser, the name and quantity of the controlled substance purchased, the date of each purchase, and the name or initials of the pharmacist who dispensed the substance to the purchaser. 21 CFR 1306.26(e). 6. A prescription is not required for distribution or dispensing of the substance pursuant to any other federal, state or local law. 21 CFR 1306.26(f).	
Dispensing Schedule II dispensing, 60 day limit	Phar 8.05 (4) A prescription containing a controlled substance listed in schedule II may be dispensed only pursuant to a written hard copy or electronic order signed by the prescribing individual practitioner, except in emergency situations. A prescription for a controlled substance listed in schedule II may not be dispensed more than 60 days after the date of issue on the prescription order.	Schedule II controlled substances require a written prescription which must be manually signed by the practitioner or an electronic prescription that meets all DEA requirements for electronic prescriptions for controlled substances. 21 CFR 1306.11(a), 1306.08, 1311.100(b). There is no federal time limit within which a schedule II prescription must be filled after being signed by the practitioner. However, the pharmacist must determine that the prescription is still needed by the patient, and the amount dispensed must be consistent with the requirement that a prescription for a	State- 60 day time limit for dispensing Federal – no time limit, LTCF does have 60 day limit for Schedule II prescriptions.

		controlled substance be issued only for a legitimate medical purpose. 21 CFR 1306.04(a). For a schedule II controlled substance, an oral order is only permitted in an emergency situation. 21 CFR 1306.11(d).	
Issue	**Phar 8**	**Federal**	**Comparison**
Dispensing Required info, allowable modifications. Changes with consultation	Phar 8.05 (7) A prescription order for a controlled substance may not be dispensed unless the prescription order contains all of the information required in sub. (1). For any controlled substance prescription order, a pharmacist may not add, modify or clarify the patient's name, the controlled substance prescribed, except for generic substitution as permitted by law, and the prescribing practitioner's signature. After consultation with the prescribing practitioner, a pharmacist may add, modify or clarify the strength, dosage form, quantity prescribed, date of issuance and directions for use for a schedule II controlled substance prescription order. For a schedule II controlled substance prescription order, a pharmacist may add, modify or clarify the registration number of the practitioner, and the address of the practitioner and the patient if that information is verifiable and retrievable from information maintained by the pharmacist or is obtained through consultation with the practitioner. A pharmacist may add, modify or clarify any information allowed in this subsection missing from a prescription order for a schedule III, IV or V controlled substance that is verifiable and retrievable from information maintained by the pharmacist or that is obtained through consultation with a practitioner. A patient may only provide information to a pharmacist to add, modify or clarify the patient's address. The prescription order shall be initialed and dated by the pharmacist and shall indicate the addition,	A pharmacist may dispense a schedule II controlled substance, which is a prescription drug as determined under the Federal Food, Drug, and Cosmetic Act, only pursuant to a written prescription signed by the practitioner, except in an emergency situation as defined in the FDA regulations, and as described below. 21 CFR 1306.11(a).	Wisconsin - allows consultation for schedule II to change the prescription. See green. Fed – it is not clear that this is allowable. Word 'consultation' is not found in manual.

	modification or clarification of information and the manner by which the pharmacist obtained that information.		
Issue	**Phar 8**	**Federal**	**Comparison**
Dispensing – practitioners of a hospital or institution	N/A	21 CFR 1301.22(c), practitioners who are agents or employees of a hospital or other institution, may, when acting in the usual course of business or employment, administer, dispense, or prescribe controlled substances under the registration of the hospital or other institution in which he or she is employed, in lieu of individual registration, provided that: 1. The dispensing, administering, or prescribing is in the usual course of professional practice. 2. The practitioner is authorized to do so by the state in which he or she is practicing. 3. The hospital or institution has verified that the practitioner is permitted to administer, dispense, or prescribe controlled substances within the state. 4. The practitioner acts only within the scope of employment in the hospital or institution. 5. The hospital or institution authorizes the practitioner to administer, dispense, or prescribe under its registration and assigns a specific internal code number for each practitioner.	State does not include requirements for agents or employees of a hospital related to registration at DEA.
Renewals	Phar 8.06 (1) No prescription containing a schedule II substance may be renewed. (2) The prescribing practitioner may authorize renewals of schedule III or IV controlled substances on the original prescription order or through an electronic or oral renewal authorization transmitted to the pharmacist. The following conditions must be met:	The refilling of a prescription for a controlled substance listed in schedule II is prohibited. 21 U.S.C. 829(a). Schedules III and IV controlled substances may be refilled if authorized on the prescription. However, the prescription may only be refilled	Virtually Same Provisions on "Renewals" or "Refills" Wisconsin uses term renewal, renewed, etc. Fed uses term refill, refilling, refilled.

	(a) The pharmacist obtaining the electronic or oral authorization shall note on the prescription order, medication profile record or readily retrievable and uniformly maintained document the following information: 1. Date authorization is received. 2. Quantity of drug authorized. 3. Number of renewals. 4. Identification of practitioner authorizing the renewals if different from the original prescriber. 5. Identification of the pharmacist who received the authorization. (b) The quantity of each renewal authorized is equal to or less than the quantity authorized for the initial dispensing of the original prescription. **(3)** No prescription containing a controlled substance listed in schedule III or IV may be dispensed or renewed more than 6 months after the date on which the prescription order was issued and no prescription authorized to be renewed may be renewed more than 5 times. **(4)** A prescription containing a drug listed in schedule V may be renewed only as expressly authorized by the practitioner.	up to five times within six months after the date of issue. Schedule V Refills as authorized when prescription is issued or if renewed by a practitioner	
Issue	**Phar 8**	**Federal**	**Comparison**
Partial Dispensing	Phar 8.07 (1) A pharmacist may partially dispense a prescription containing a controlled substance listed in schedule III, IV and V. **(2)** The partial dispensing of a prescription containing a controlled substance listed in schedule II is permissible, if the pharmacist is unable to supply the full quantity called for in a written, electronic, or emergency oral prescription order, and the pharmacist makes a notation of the quantity supplied on the face of the written hard copy prescription order or written record of the electronic or emergency oral prescription order. The remaining portion of the prescription may be dispensed within 72	A prescription for a schedule II controlled substance may be partially dispensed if the pharmacist is unable to supply the full quantity of a written or emergency oral (telephone) prescription, provided the pharmacist notes the quantity supplied on the front of the written prescription, on a written record of the emergency oral prescription, or in the electronic prescription record. The remaining portion may be dispensed within 72 hours of the first partial dispensing. However, if the remaining portion is not or cannot be filled within the 72 hour period, the pharmacist must notify the prescribing practitioner. No further	Virtually the Same Wisconsin – prescription order Federal – prescription. An order implies the ordering of Controlled substances schedule I or II that requires DEA form 222 be filled out for the order.

	hours of the first partial dispensing. If the remaining portion is not dispensed within the 72 hour period, the pharmacist shall so notify the prescribing individual practitioner. No further quantity may be supplied beyond the 72 hours without a new prescription order.	quantity may be supplied beyond 72 hours without a new prescription. 21 CFR 1306.13(a).	
Partial Dispensing – LTCF/Terminal illness	Phar 8.07(3) Prescription orders for schedule II-controlled substances written for patients in long term care facilities (LTCF) or for patients with a medical diagnosis documenting a terminal illness may be dispensed in partial quantities to include individual dosage units. The prescribing practitioner may document a terminal illness by writing upon the face of the prescription order the phrase "terminal illness" or words of similar meaning. If there is any question whether a patient may be classified as having a terminal illness, the pharmacist shall contact the prescribing practitioner prior to partially dispensing the prescription. Documentation of a terminal illness, whether substantiated by the presence of an appropriate phrase written upon the face of the prescription order or through pharmacist contact with the prescribing practitioner, shall be placed within the individual medication profile record maintained under s. Phar 7.07. The pharmacist shall record on the prescription order whether the patient is "terminally ill" or an "LTCF patient." A prescription order that is partially dispensed and does not contain the notation "terminally ill" or "LTCF patient" shall be deemed to have been dispensed in violation of this section. For each partial dispensing, the dispensing pharmacist shall record on the back of the prescription order or on another appropriate record, uniformly maintained and readily retrievable, the date of the partial dispensing, quantity dispensed, remaining quantity authorized to be dispensed and the identification of the dispensing	A prescription for a schedule II controlled substance written for a patient in an LTCF or for a patient with a medical diagnosis documenting a terminal illness, may be filled in partial quantities to include individual dosage units. 21 CFR 1306.13(b). If there is any question whether a patient may be classified as having a terminal illness, the pharmacist must contact the practitioner prior to partially filling the prescription. 21 CFR 1306.13(b). Both the pharmacist and the prescribing practitioner have a corresponding responsibility to assure that the controlled substance is for a terminally ill patient. 21 CFR 1306.13(b). The pharmacist must record on the prescription whether the patient is "terminally ill" or an "LTCF patient." 21 CFR 1306.13(b). A prescription that is partially filled and does not contain the notation "terminally ill" or "LTCF patient" must be deemed to have been filled in violation of the CSA. 21 CFR 1306.13(b). For each partial filling, the dispensing pharmacist must record on the back of the prescription (or on another appropriate record, uniformly maintained, and readily retrievable) the date of the partial filling, quantity dispensed, remaining quantity authorized to be dispensed, and the identification of the dispensing pharmacist. 21 CFR 1306.13(b). The total quantity of schedule II controlled substances dispensed in all partial fillings must not exceed the total quantity prescribed. 21 CFR 1306.13(b). Schedule II prescriptions for patients in an LTCF or terminally ill patients are valid for a period not	Section is substantially the same between Wisconsin and Federal. Issues: No longer required to have medication profile record from previous Phar 7.07. – now medication profile record system under Phar 7.11(3) Notation is required under fed CSA, not clear what violations exist from Wisconsin. Prescription order vs. Prescription

	pharmacist. Subsequent partial dispensing is not permitted under this section if the patient becomes deceased, or is no longer diagnosed as terminally ill, or no longer resides within an LTCF. The total quantity of a schedule II controlled substance dispensed by partial dispensing may not exceed the total quantity prescribed. Prescription orders for schedule II controlled substances for patients in an LTCF or patients with a medical diagnosis documenting a terminal illness shall be valid for a period not to exceed 60 days from the issue date unless terminated earlier by the discontinuance of medication.	to exceed 60 days from the issue date unless sooner terminated by the discontinuance of medication. 21 CFR 1306.13(b).	
Issue	**Phar 8**	**Federal**	**Comparison**
Partial Dispensing Schedule II LTCF/terminal illness, computerized system and retrieval of information.	Phar 8.07 (4) Information pertaining to current prescription orders for schedule II controlled substances for patients in an LTCF or for patients with a medical diagnosis documenting a terminal illness may be maintained in a computerized system if the system has the capability to permit: (a) Display or printout of: the original prescription order designation; date of issue; identification of prescribing practitioner; identification of patient; name and address of the LTCF or name and address of the hospital or residence of the patient; identification of medication authorized, including dosage form, strength and quantity; listing of partial quantities that have been dispensed under each prescription order and the information required in sub. (3). (b) Immediate (real time) updating of the prescription order record each time there is partial dispensing of the prescription. (c) Retrieval of partially dispensed schedule II prescription information identical to that required by s. Phar 7.05 (2) for all prescription renewal information.	Not identified in federal specific to LTCF– application to general electronic filing for recordkeeping applies. General provisions for types of drugs applies.	Wisconsin/federal provisions provide the same intent, as all prescriptions require recordkeeping. The difference is identification of terminal illness. Medication profile system outlined in Phar 7.11(3).

Issue	Phar 8	Federal	Comparison
Labeling prescriptions	Phar 8.08 Labeling prescriptions. (1) The pharmacist dispensing a prescription containing a controlled substance shall affix to the immediate container a label showing the date of dispensing; the pharmacy name and address; serial number of the prescription; full name of the patient; name of the prescribing practitioner; directions for use; and cautionary statements, contained in the prescription order or required by law. (2) Practitioners who personally dispense any controlled substance to patients in the course of their professional practice other than by prescribing or administering shall conform to ch. Med 17, standards for dispensing drugs.	The pharmacist dispensing a prescription for a controlled substance listed in schedules II, III, IV, or V must affix to the package a label showing date of filling, the pharmacy name and address, the serial (prescription) number, the name of the patient, the name of the prescribing practitioner, and directions for use and cautionary statements, if any, contained in such prescription as required by law. 21 CFR 1306.14(a), 1306.24(a). In addition to this information, if a prescription is filled at a central fill pharmacy, the central fill pharmacy must affix to the package a label showing the retail pharmacy name and address and a unique identifier (i.e., the central fill pharmacy's DEA registration number) indicating that the prescription was filled at the central fill pharmacy. 21 CFR 1306.14(b), 1306.24(b). Federal Food and Drug Administration (FDA) regulations found in 21 CFR 290.5 require that the label of any drug listed as a "controlled substance" in schedules II, III, or IV of the CSA must, when dispensed to or for a patient, contain the following warning: "CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed." In addition, a pharmacist who receives a prescription for a controlled substance must dispense that prescription to the patient or a member of the patient's household. 21 U.S.C. 802(10) and (27).	Wisconsin – label requirements same as federal No Central fill requirements No Caution phrase requirement Federal – laws for Central fill pharmacies. Includes Caution phrase, not required under Phar 8
Emergency Dispensing	Phar 8.09 Emergency dispensing. (1) For the purpose of authorizing an oral prescription order for a schedule II controlled substance, the term "emergency" means those situations in which the prescribing practitioner determines that:	Under FDA and DEA regulations, an "emergency situation" in this context means that the prescribing practitioner has determined that immediate administration of the drug is necessary for proper treatment of the intended ultimate user, that no appropriate alternative	Wisconsin –Discusses term "emergency". Requires notification to Pharmacy Board if no written prescription.

	Phar 8.09(1)(a) (a) Immediate administration of the controlled substance is necessary for proper treatment of the patient. (b) No appropriate alternative treatment is available, including the administration of a drug which is not a schedule II controlled substance. (c) It is not reasonably possible for the prescribing practitioner to provide a written prescription order to be presented to the pharmacist prior to dispensing. (2) In an emergency a pharmacist may dispense a controlled substance listed in schedule II upon receiving oral authorization of a practitioner if: (a) The quantity prescribed and dispensed is limited to the amount adequate to treat the patient during the emergency period. (b) The prescription order is immediately reduced to writing by the pharmacist and contains all information required in s. Phar 8.05, except for the signature of the practitioner. (3) If the practitioner is not known to the pharmacist, the pharmacist shall make a reasonable effort to determine that the oral authorization came from an authorized practitioner, which may include a call back to the prescribing practitioner using good faith efforts to insure the practitioner's identity. (4) Within 7 days after authorizing an emergency oral prescription order, the practitioner shall cause a written or electronic order for the emergency quantity prescribed to be delivered to the dispensing pharmacist. In addition to conforming to the requirements of s. Phar 8.05, the order shall contain on its face "authorization for emergency dispensing" and the date of the oral order. The written or electronic order may be delivered to the pharmacist in person or by mail or electronically, but if delivered by mail it shall be postmarked within the 7 day period. Upon receipt, the	treatment is available (including a drug which is not a schedule II controlled substance), and it is not reasonably possible for the prescribing practitioner to provide a written prescription for the drug at that time. 21 CFR 1306.11(d) and 21 CFR 290.10. A practitioner may telephone a schedule II prescription to the pharmacist who may then dispense the prescription. Under 21 CFR 1306.11(d), the prescribing practitioner must provide a written and signed prescription to the pharmacy within seven days and meet the below requirements: 1.The drug prescribed and dispensed must be limited to the amount needed to treat the patient during the emergency period. Prescribing or dispensing beyond the emergency period must be pursuant to a paper or electronic prescription signed by the prescribing individual practitioner. 21 CFR 1306.11(d)(1). 2. The prescription order must be immediately reduced to writing by the pharmacist and must contain all required information, except for the prescribing practitioner's signature. 21 CFR 1306.11(d)(2). 3. If the prescribing individual practitioner is not known to the pharmacist, he or she must make a reasonable effort to determine that the oral authorization came from a registered individual practitioner, which may include a call back to the prescribing individual practitioner using his or her telephone number as listed in the telephone directory and/or other good faith efforts to insure his or her identity. 21 CFR 1306.11(d)(3). 4. Within seven days after authorizing an emergency oral prescription, the prescribing practitioner must furnish the pharmacist a written, signed prescription for the emergency	Fed – Discusses term "emergency situation." Pharmacist to notify DEA as a requirement, not included in state requirements. These not consistent. Fed - Electronic Prescription requirements Wisconsin – No requirements on electronic prescriptions (Phar 8.)

	dispensing pharmacist shall attach this prescription order to the oral emergency order reduced to writing under sub. (2) (b). The pharmacist shall notify the board or department of safety and professional services if the practitioner fails to deliver the written or electronic order. Failure of the pharmacist to provide notification shall void the authority conferred by this section to dispense without a written or electronic order of a practitioner.	quantity of the controlled substance prescribed. 21 CFR 1306.11(d)(4). The prescription must have written on its face "Authorization for Emergency Dispensing" and the date of the oral order. 21 CFR 1306.11(d)(4). The written prescription may be delivered to the pharmacist in person or by mail, but if delivered by mail, it must be postmarked within the seven day period. 21 CFR 1306.11(d)(4). 5. Upon receipt, the dispensing pharmacist must attach this written prescription to the oral emergency prescription which had earlier been reduced to writing by the pharmacist. 21 CFR 1306.11(d)(4). 6. By regulation, the pharmacist must notify the local DEA Diversion Field Office (Appendix K) if the prescriber fails to provide a written prescription within seven days. 21 CFR 1306.11(d)(4). Failure of the pharmacist to do so will void the authority conferred on the pharmacy to dispense the controlled substance without a written prescription of a prescribing practitioner. 7. For electronic prescriptions, the pharmacist must annotate the record of the electronic prescription with the original authorization and date of the oral order. 21 CFR 1306.11(d)(4).	
Suspicious orders – Disclosure to DEA	Phar 8.10 Disclosure of suspicious orders of controlled substances. Manufacturers and distributors of controlled substances shall disclose suspicious orders of controlled substances. Suspicious orders include, without limitation because of enumeration, orders of unusual size, orders deviating substantially from a normal pattern and orders of unusual frequency. The licensee shall notify the regional office of the DEA and the board of all suspicious orders.	…pharmacies must have a system to identify any suspicious orders, which when identified must be reported online to SORS. The Suspicious Orders Report System (SORS) should be accessed on-line and only be used by DEA registrants that distribute controlled substances to other DEA registrants. Reporting a suspicious order to SORS Online constitutes compliance with the reporting requirement under 21 U.S.C. 832. The SUPPORT Act requires that ALL DEA registrants that distribute	Wis – Notify regional office of DEA. Pharmacy Board. Fed – Notify online to SORS Differences noted.

		controlled substances report suspicious orders to DEA.	
Issue	**Phar 8**	**Federal**	**Comparison**
LTCF Emergency Kits	Phar 8.11 Controlled substances in emergency kits for long term care facilities. Long term care facilities which are not registered with the DEA shall meet all of the following requirements regarding emergency kits containing controlled substances: (1) The source of supply must be a DEA registered hospital, pharmacy or practitioner. (2) The pharmaceutical services committee of the facility shall establish security safeguards for each emergency kit stored in the LTCF which shall include the designation of individuals who may have access to the emergency kits and a specific limitation of the type and quantity of controlled substances permitted to be placed in each emergency kit. (3) A pharmacist shall be responsible for proper control and accountability for such emergency kits within the LTCF which includes the requirement that the LTCF and the providing DEA registered hospital, pharmacy or practitioner maintain complete and accurate records of the controlled substances placed in the emergency kits, the disposition of those controlled substances, plus the requirement to take at least monthly physical inventories. (4) The pharmaceutical services committee will establish the emergency medical conditions under which the controlled substances may be administered to patients in the LTCF which shall include the requirement that medication be administered by authorized personnel only as expressly authorized by an individual DEA registered practitioner and in compliance with all applicable federal and state laws.	…an emergency kit is for use in emergencies as defined by the state… in accordance with the CSA and DEA regulations, a controlled substance may only be dispensed for emergency purposes (or otherwise) pursuant to a valid prescription or medical order. 21 U.S.C. 841(a)(1), 21 CFR 1306.04(a), 21 CFR 1300.01(b) ("prescriptions"). Thus, where the kit is maintained at the LTCF by a pharmacy, controlled substances may not be dispensed from the kit for emergencies prior to receipt by the pharmacist of a valid prescription in accordance with the requirements of 21 CFR 1306.11, 1306.21. No changes since 1980 on these fed provisions.	State and Federal generally have similar provisions. Wisconsin – What is a pharmaceutical services committee and where is it defined? Federal – No such committee. State - Monthly inventory required Fed – periodic inventory required.

	(5) Noncompliance with this rule may result in revocation, denial or suspension of the privilege of having or placing emergency kits, containing controlled substances, in LTCF.		
Issue	**Phar 8**	**Federal**	**Comparison**
Prescription Orders by Fax machine Schedule II and others	Phar 8.12 Prescription orders transmitted by facsimile machine. Phar 8.12(1)(1) Prescription drugs other than schedule II controlled substances. A pharmacist may dispense a prescription drug, other than a schedule II controlled substance, pursuant to a prescription order transmitted by a facsimile machine from the practitioner or the practitioner's agent to the dispensing pharmacy if all of the following conditions are met: (a) The transmitted facsimile prescription order shall contain all of the information required for a valid written prescription order. The order shall also contain the time and date of the transmission, as well as the telephone number and name of the transmitter. (b) Unless the facsimile paper is non-fading, the facsimile prescription order received shall be duplicated by copy machine or other similar device and the copy must be physically attached to the order received. (2) Schedule II controlled substances. A pharmacist may not dispense a schedule II controlled substance pursuant to a prescription order transmitted by a facsimile machine unless all of the conditions stated in sub. (1) are satisfied, and any of the following conditions are met: (a) The prescription order is written for a schedule II controlled substance to be compounded for the direct administration to a patient by parenteral, intravenous, intramuscular, subcutaneous or intraspinal infusion, and is transmitted by the practitioner or	The original schedule II prescription must be presented to the pharmacist and verified against the facsimile prior to the actual dispensing of the controlled substance. 21 CFR 1306.11(a). The pharmacist must make sure the original document is properly annotated and filed with the records that are required to be kept. 21 CFR 1306.11(a), 1304.04(h). Three exceptions to the facsimile prescription requirements for schedule II controlled substances. The facsimile of a schedule II prescription may serve as the original prescription if: 1. A practitioner prescribing a schedule II narcotic controlled substance to be compounded for the direct administration to a patient by parenteral, intravenous, intramuscular, subcutaneous or intraspinal infusion may transmit the prescription by facsimile. The facsimile serves as the original written prescription and no further documentation is required. All normal requirements of a legal prescription must be followed. 21 CFR 1306.11(e). 2. Practitioners prescribing schedule II controlled substances for residents of Long-Term Care Facilities may transmit, or direct their authorized agent to transmit, a prescription to the dispensing pharmacy by facsimile. The facsimile prescription serves as the original written prescription for the pharmacy. No further documentation is required. 21 CFR 1306.11(f).	

	the practitioner's agent to the dispensing pharmacy by facsimile. (b) The prescription order is written for a schedule II controlled substance for a patient who resides in a long term care facility, or who meets the eligibility requirements for placement in a long term care facility but elects to reside at home, and is transmitted by the practitioner or the practitioner's agent to the dispensing pharmacy by facsimile. (c) The prescription order is written for a schedule II controlled substance for a patient enrolled in a hospice certified by medicare under Title XVIII or licensed by this state, and is transmitted by the practitioner or the practitioner's agent to the dispensing pharmacy by facsimile. (3) Prescription orders transmitted by facsimile considered written orders. For all purposes under chs. 450 and 961, Stats., and the rules of the board, a prescription order transmitted by facsimile machine shall be considered the original written prescription order.	3. A practitioner prescribing a schedule II narcotic controlled substance for a patient enrolled in a hospice care program certified and/or paid for by Medicare under Title XVIII or a hospice program which is licensed by the state, may transmit, or direct his or her authorized agent to transmit, a prescription to the dispensing pharmacy by facsimile. The practitioner will note on the prescription that it is for a hospice patient. The facsimile serves as the original written prescription. No further documentation is required. 21 CFR 1306.11(g). A pharmacist may dispense directly a controlled substance listed in schedule III, IV, or V only pursuant to either a paper prescription signed by a practitioner, a facsimile of a signed paper prescription transmitted by the practitioner or the practitioner's agent to the pharmacy, an electronic prescription that meets DEA's requirements for such prescriptions, or a call-in prescription which is promptly reduced to writing by the pharmacist. 21 CFR 1306.21(a).	
ID Card Exception for Health Care Facility	Phar 8.13 Identification card exception for a health care facility. In s. 450.11 (1b) (e) 3., Stats., "health care facility" means a facility, as defined in s. 647.01 (4), Stats.; any hospital, nursing home, community-based residential facility, county home, county infirmary, county hospital, county mental health complex, or other place licensed or approved by the department of health services under s. 49.70, 49.71, 49.72, 50.03, 50.032, 50.033, 50.034, 50.35, 51.08, or 51.09, Stats.; a facility under s. 45.50, 51.05, 51.06, 233.40, 233.41, 233.42, or 252.10, Stats.; and a hospice facility under s. 50.90 (1) (c), Stats.	N/A	State ID requirement for health facilities is an exception noted.

90 Day Supply-multiple prescriptions for schedule II drugs	N/A	Under 21 CFR 1306.12(b)(1), an individual practitioner may issue multiple prescriptions authorizing the patient to receive a total of up to a 90-day supply of a schedule II controlled substance provided the following conditions are met: 1. Each separate prescription must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of professional practice. 21 CFR 1306.12(b)(1)(i). 2. The individual practitioner must provide written instructions on each prescription (other than the first prescription, if the prescribing practitioner intends for that prescription to be filled immediately) indicating the earliest date on which a pharmacy may fill each prescription. 21 CFR 1306.12(b)(1)(ii). 3. The individual practitioner concludes that providing the patient with multiple prescriptions in this manner does not create an undue risk of diversion or abuse. 21 CFR 1306.12(b)(1)(iii). 4. The issuance of multiple prescriptions is permissible under applicable state laws. 21 CFR 1306.12(b)(1)(iv). 5. The individual practitioner complies fully with all other applicable requirements under the CSA and CFR, as well as any additional requirements under state law. 21 CFR 1306.12(b)(1)(v).	Feds permit 90 day supply with conditions.

Summary of Controlled Substances Act Requirements

	Schedule II	Schedules III & IV	Schedule V
Registration	Required	Required	Required
Receiving Records	DEA Form 222	Invoices, readily retrievable	Invoices, readily retrievable
Prescriptions	Written[1] prescriptions (oral prescriptions only allowed in emergency situations)[2]	Written, oral, or fax	Written, oral, or fax
Refills	No	No more than 5 within 6 months	As authorized when prescription is issued or if renewed by a practitioner
Maintenance of Prescriptions[3]	Separate file	Separate file or readily retrievable	Separate file or readily retrievable
Distribution Between Registrants	DEA Form 222	Invoices	Invoices
Security	Locked cabinet or dispersed among non-controlled pharmaceuticals	Locked cabinet or dispersed among non-controlled pharmaceuticals	Locked cabinet or dispersed among non-controlled pharmaceuticals
Theft or Significant Loss	Report to DEA and complete DEA Form 106	Report to DEA and complete DEA Form 106	Report to DEA and complete DEA Form 106

NOTE: ***All records*** must be maintained for 2 years, unless state law requires a longer period. 21 U.S.C. 827(b).

[1] Written prescriptions include paper prescriptions and electronic prescriptions that meet DEA's requirements for such prescriptions.

[2] Emergency oral prescriptions are allowable under schedule II and require a signed follow-up prescription within seven days. 21 CFR 1306.11(d)(4). Exceptions: A facsimile prescription for a schedule II controlled substance serves as the original prescription when issued to a resident of an LTCF. 21 CFR 1306.11(f). A facsimile prescription for a schedule II narcotic substance serves as the original prescription when issued to hospice patients, or patients with a diagnosed terminal illness, or for direct administration by parenteral, intravenous, intramuscular, subcutaneous, or intraspinal infusion. 21 CFR 1306.11(e), (f) and (g).

[3] The record of dispensing can also be a bound record book, if the controlled substance is not a prescription drug as determined under the Federal Food, Drug, and Cosmetic Act. 21 CFR 1306.26(e). 2020

STATEMENT OF SCOPE

PHARMACY EXAMINING BOARD

Rule No.: Phar 15

Relating to: Compounding Pharmaceuticals

Rule Type: Permanent

1. Finding/nature of emergency (Emergency Rule only): N/A

2. Detailed description of the objective of the proposed rule:

The objective of the rule is to review the updated United States Pharmaceopeia (USP) 797 standards, which have an intended publication date of June 1, 2019 with an anticipated official date of December 1, 2019, and amend Phar 15 to align with the USP 795 and 797 chapters without creating an unnecessary burden on Wisconsin pharmacies.

3. Description of the existing policies relevant to the rule, new policies proposed to be included in the rule, and an analysis of policy alternatives:

The Pharmacy Examining Board recently completed a major revision to Phar 15 which became effective on November 1, 2018. During the legislative review period, the Pharmacy Examining Board represented to the Joint Committee on Review of Administrative Rules and stakeholder associations that when the new USP 797 chapter is published the Pharmacy Examining Board would monitor relevant USP compounding chapters and update Phar 15 so that it remains aligned with USP standards.

This proposed rule would review chapter Phar 15 with the USP compounding chapters and make necessary updates to chapter Phar 15.

4. Detailed explanation of statutory authority for the rule (including the statutory citation and language):

15.08 (5) (b) The Board shall promulgate rules for its own guidance and for the guidance of the trade or profession to which it pertains, and define and enforce professional conduct and unethical practices not inconsistent with the law relating to the particular trade or profession.

450.02 (3) (e) The board may promulgate rules establishing minimum standards for the practice of pharmacy.

5. Estimate of amount of time that state employees will spend developing the rule and of other resources necessary to develop the rule:

200 hours

6. List with description of all entities that may be affected by the proposed rule:

Pharmacies, including pharmacies located within hospitals, and pharmacists.

7. Summary and preliminary comparison with any existing or proposed federal regulation that is intended to address the activities to be regulated by the proposed rule:

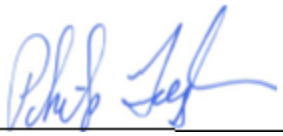
The states are primarily responsible for the oversight of compounding in pharmacies. Pursuant to the Drug Quality and Security Act, the federal government is responsible for outsourcing facilities, which by definition are not pharmacies, and are subject to current good manufacturing practice requirements, labeling requirements and may distribute compunded drugs in response to an order that is not patient specific.

The Food, Drug and Cosmetic Act requires drugs to be prepared, packed or held under sanitary conditions.

8. Anticipated economic impact of implementing the rule (note if the rule is likely to have a significant economic impact on small businesses):

Moderate economic impact. It may have an economic impact on small businesses.

Contact Person: Sharon Henes, Administrative Rules Coordinator, (608) 261-2377



Authorized Signature

February 27, 2019
Date Submitted

Chapter Phar 15

COMPOUNDING PHARMACEUTICALS

Note: Chapter Phar 15 is shown as repealed and recreated by CR 16−085, effective November 1, 2018, Register April 2018 No. 748.

Phar 15.01 Intent. The intent of this chapter is to create a state regulatory standard that aligns with compounding standards found in the United States Pharmaceopeia (USP) general chapters lower than the number 1000.

History: CR 16−085: cr. Register April 2018 No. 748 eff. 11−1−18.

Phar 15.015 Definitions. In this chapter:

(1) "Active pharmaceutical ingredient" or "API" means any substance or mixture of substances intended to be used in the compounding of a drug preparation and that, when used in the compounding of a drug preparation, becomes an active ingredient in the preparation intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and animals or affecting the structure and function of the body.

(2) "Added substances" means ingredients that are necessary to compound a drug preparation that are not intended or expected to cause a pharmacologic response if administered alone in the amount or concentration contained in a single dose of the compounded preparation.

(3) "Adverse drug event" means an injury resulting from the use of a drug.

(4) "Beyond use date" or "BUD" means one of the following:

(a) The date after which a non−sterile compounded preparation shall not be used.

(b) The date and time after which a sterile compounded preparation shall not be used.

(5) "Certificate of analysis" means a report from the supplier of a component, container, or closure that accompanies the component, container, or closure and contains the specifications and results of all analyses and a description.

(6) "Chemical stability" means each active pharmaceutical ingredient retains its chemical integrity and labeled potency, within specified limits.

(7) "Classified area" means a space that maintains an air cleanliness classification based on the International Organization for Standardization (ISO).

(8) "Component" means any active pharmaceutical ingredient, or added substances used in the compounding of a drug preparation.

(9) "Compounding" means the preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug delivery device, or a device in accordance with a prescription, or medication order. Compounding does not include repackaging. Compounding includes any of the following:

(a) Preparation of drug dosage forms for both human and animal patients.

(b) Preparation of drugs or devices in anticipation of prescription drug orders based on routine, regularly observed prescribing patterns.

(c) Reconstitution or manipulation of commercial products that may require the addition of one or more ingredients. Notwithstanding this paragraph, the reconstituting, mixing, or storage and beyond use dating that is performed for non−sterile preparations in accordance with the directions contained in approved labeling provided by the manufacturer is not compounding.

(d) Preparation of drugs or devices for the purposes of, or as an incident to, research, teaching, or chemical analysis.

(10) "Container−closure system" means the sum of packaging components that together contain and protect a dosage form, including primary packaging components and secondary packaging components.

(11) "Controlled room temperature" means a temperature maintained thermostatically that encompasses the usual and customary working environment of 68 degrees to 77 degrees Fahrenheit.

(12) "FDA" means the United States food and drug administration.

(13) "Freezer" means a place in which a the temperature is maintained between −13 degrees and 14 degrees Fahrenheit.

(14) "Microbiological stability" means sterility or resistance to microbial growth is retained according to specified requirements and antimicrobial agents that are present retain effectiveness within specified limits.

(15) "NF" means the National Formulary.

(16) "Physical stability" means the original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability, are retained.

(17) "Refrigerator" means a cold place in which the temperature is maintained between 36 degrees and 46 degrees Fahrenheit.

(18) "Stability" means the extent to which a compounded preparation retains, within specified limits and through its beyond use date, the same properties and characteristics that it possessed at the time of compounding.

(19) "Therapeutic stability" means the therapeutic effect remains unchanged.

(20) "Toxicological stability" means no significant increase in toxicity occurs.

(21) "USP" means the United States Pharmacopeia.

History: CR 16−085: cr. Register April 2018 No. 748 eff. 11−1−18.

Subchapter I – General

Phar 15.10 Facilities. A pharmacist engaged in compounding shall ensure all of the following:

(1) An area designated for compounding.

(2) Orderly placement of compounding equipment, materials, and components in order to minimize the potential for compounding errors.

(3) The compounding area is maintained in a clean and sanitary condition.

(4) The compounding area is easily accessible to all of the following:

(a) Hot and cold running water, exclusive of the bathroom sink.

(b) Soap or detergent.

(c) Single–use towels.

(5) All compounding equipment, materials, and components shall be stored off the floor and in a manner to prevent contamination and permit inspection and cleaning of the compounding and storage areas.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18.

Phar 15.11 Equipment and Drug Preparation Containers. (1) A pharmacy shall possess equipment and drug preparation containers or packaging appropriate to the type of compounding performed at the pharmacy.

(2) Equipment and drug preparation containers or packaging used in compounding shall be of appropriate design and capacity, and shall be suitably stored in a manner to facilitate use, cleaning, maintenance, and protect it from contamination.

(3) Equipment and drug preparation containers or packaging used in compounding drug products shall be of suitable composition and may not be reactive, additive, adsorptive, or absorptive so as to alter the stability of the compounded preparation.

(4) Equipment used in compounding shall be thoroughly cleaned and sanitized after each use, and when necessary, prior to use, according to written policies and procedures, in order to reduce bioburden and reduce the opportunity for cross–contamination.

(5) All equipment utilized in compounding preparations shall be inspected, maintained, calibrated, and validated at appropriate intervals, consistent with manufacturer's recommendations, to ensure the accuracy and reliability of equipment performance. Records shall be kept indicating the equipment was inspected, maintained, calibrated, and validated.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18.

Phar 15.12 Records of compounding. The managing pharmacist shall ensure written or electronic compounding documentation to systematically trace, evaluate, and replicate the compounding steps throughout the process of a preparation. The compounding documentation shall be maintained for a period of 5 years after the date of the last refill. The compounding documentation shall include all of the following:

(1) Official or assigned name, strength, and dosage form of the preparation.

(2) List of all APIs and added substances and their quantities.

(3) Vendor or manufacturer, lot number and expiration date of each APIs and added substances.

(4) Equipment and supplies needed to prepare the preparation.

(5) Mixing instructions pertinent to the replication of the preparation as compounded.

(6) Compatibility and stability information, including references or laboratory testing.

(7) Container or container–closure system used in dispensing.

(8) Packaging and storage requirements.

(9) Quality control procedures.

(10) Sterilization method when using non–sterile ingredients to make a sterile preparation.

(11) Total quantity compounded.

(12) Name of the person who prepared the preparation.

(13) Name of the person who performed the quality control procedures.

(14) Name of the person who approved the preparation.

(15) Date of preparation.

(16) Assigned control or prescription number.

(17) Assigned BUD.

(18) Copy of the label to dispense final product.

(19) Documentation of any adverse reactions or preparation problems reported by the patient or caregiver.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18.

Phar 15.13 Quality control. (1) One or more pharmacists shall complete a verification of all the following before dispensing:

(a) Written procedures were followed in the compounding process.

(b) Preparation instructions were followed.

(c) Finished preparation appears as expected.

(d) Label includes all required elements.

(e) Quality control procedures were completed.

(f) Compounding records are complete.

(2) A pharmacist shall investigate any discrepancies found during any of verifications and take appropriate corrective action before dispensing.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18.

Phar 15.14 Training, Policies, and Procedures. (1) TRAINING. All personnel involved in the compounding, evaluation, packaging, and dispensing of compounded preparations shall be properly trained and competency is assessed for the type of compounding conducted. It is the responsibility of the managing pharmacist to ensure personnel training and competency assessments are completed and documented.

(2) POLICIES AND PROCEDURES. The pharmacy and managing pharmacist shall establish written policies and procedures governing all of the following:

(a) Personnel qualifications and training, responsibilities, and competencies.

(b) Personal hygiene, garb, garbing, and personal protective gear.

(c) Use and maintenance of compounding facilities and equipment, including applicable certifications.

(d) Environmental monitoring.

(e) Cleaning and disinfection of compounding area.

(f) Component selection.

(g) Sterilization and depyrogenation, if pharmacy does sterilization and depyrogenation.

(h) Documentation requirements.

(i) Establishing BUD.

(j) Reporting of adverse drug events.

(k) A risk management program, including documentation of incidents, adverse drug reactions and product contamination.

(L) A quality assurance program.

(m) Maintaining the integrity of any classified work areas.

(n) Handling small and large spills of antineoplastic agents and other hazardous substances.

(o) Notification to patients or practitioners of a preparation which is recalled when there is potential for patient harm.

(3) REVIEW OF POLICIES AND PROCEDURES. The policy and procedures shall be reviewed at least once every 36 months and shall be updated, on a continuous basis, to reflect current practice. Doc-

umentation of the review shall be made available to the board upon request.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18; correction in (2) (o) made under s. 35.17, Stats., Register April 2018 No. 748.

Phar 15.15 Labeling. The label of a compounded preparation shall include all of the following:

(1) Labeling requirements in s. Phar 7.02 and 8.08.

(2) Storage conditions if other than controlled room temperature.

(3) BUD.

(4) Special handling instructions, when applicable.

(5) Indication that the preparation is compounded unless administered by health care personnel.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18.

Phar 15.16 Component Selection. (1) Active pharmaceutical ingredients or added substances used in compounding shall be manufactured by an FDA registered facility or accompanied by a certificate of analysis.

(2) APIs and added substances shall meet USP or NF monograph specifications when monographs are available. A pharmacist shall use professional judgement in selection of APIs if USP or NF grade is not available.

(3) All components shall be stored and handled consistent with the manufacturer's labeling or USP or NF monographs and in a manner that prevents contamination and deterioration.

(4) A pharmacist compounding for human use may not use components that have been withdrawn or removed from the market for safety or efficacy reasons by the FDA. A pharmacist compounding for food producing animal use may not use components prohibited for use in food producing animals.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18.

Phar 15.17 Non–patient specific compounding. Compounded preparations dispensed or distributed to a practitioner pursuant to a non–patient specific order to be administered by a practitioner or practitioner's agent shall meet all of the following:

(1) The order shall include the name and address of the practitioner, drug, strength, quantity, and the purpose of the compounded preparation.

(2) The label shall include the practitioner's name in place of the patient's name and state "For Practitioner Administration Only — Not for Dispensing or Distribution." If the sterility or integrity of the compounded preparation is not maintained after the initial opening of the container, the label shall state "Single–Dose Only."

(3) The pharmacist shall record the name and address of the location the compounded preparation was dispensed or distributed, and the lot number and BUD of all preparations dispensed or distributed to the practitioner.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18.

Subchapter II – Non–sterile Compounding

Phar 15.20 Component Selection. (1) Components with an expiration date from the manufacturer or distributor may be used before the expiration date provided all of the following:

(a) The component is stored in its original container under conditions to avoid decomposition.

(b) There is minimal exposure of the remaining component each time component is withdrawn from the container.

(2) Components without an expiration date assigned by the manufacturer or supplier shall be labeled with the date of receipt and assigned a conservative expiration date, not to exceed three years after receipt, based upon the nature of the component and its degradation mechanism, the container in which it is packaged and the storage conditions.

(3) Components transferred to another container which shall provide integrity that is minimally equivalent to the original container and shall be identified with all of the following:

(a) Component name.

(b) Original supplier.

(c) Lot or control number.

(d) Transfer date.

(e) Expiration date.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18.

Phar 15.21 Assigning BUD. (1) The BUD shall not be later than the expiration date on the container of any component.

(2) Only in the absence of stability information that is applicable to a specific drug product and preparation, the maximum BUD for a non–sterile compounded drug preparation that is packaged in a tight, light–resistant container is as follows:

(a) For nonaqueous formulations stored at controlled room temperature, the BUD shall not be later than the time remaining until the earliest expiration date of any active pharmaceutical ingredient or 6 months, whichever is earlier.

(b) For water–containing oral formulations, the BUD shall not be later than 14 days when stored in a refrigerator.

(c) For water–containing semisolid mucosal liquid, topical, or dermal formulations, stored at controlled room temperature, the BUD shall not be later than 30 days.

(3) Assignment of BUD shall include an assessment of the need for antimicrobial agents or storage in a refrigerator to protect against bacteria, yeast, and mold contamination introduced during or after the compounding process.

Subchapter III – Sterile Compounding

Phar 15.30 Definitions. In this subchapter:

(1) "Ante area" means an ISO Class 8 or better area where personnel hand hygiene and garbing procedures, staging of components, order entry, labeling and other high particulate generating activities are performed. The ante–area is the transition area between the unclassified area of the facility and the buffer area.

(2) "Buffer area" means an ISO Class 7 or ISO Class 8 if using an isolator or cleaner area where the primary engineering control that generates and maintains an ISO Class 5 environment is physically located.

(3) "Category 1" means a compounded sterile preparation compounded with a primary engineering control in a segregated compounding area.

(4) "Category 2" means a compounded sterile preparation compounded with a primary engineering control in a classified area.

(5) "Clean" means to physically remove debris, dirt, dust, and other impurities from surfaces or objects using a cleaning agent with a detergent.

(6) "Compounded sterile preparation" means a compounded final preparation intended to be sterile through the BUD.

(7) "Compounded stock solution" means a compounded solution to be used in the preparation of multiple units of a finished compounded sterile preparation.

(8) "Critical site" means a location that includes any component or fluid pathway surfaces or openings that are exposed and at risk of direct contact with air, moisture, or touch contamination.

(9) "Disinfect" means the killing of microorganisms when used according to the disinfectant's label.

(10) "HEPA" means high–efficiency particulate air.

(11) "ISO Class 5" means conditions in which the air particle count is no greater than a total of 3,520 particles of 0.5 micrometers and larger per cubic meter of air that is supplied by HEPA or HEPA–filtered air.

(12) "ISO Class 7" means conditions in which the air particle count is no greater than a total of 352,000 particles of 0.5 microm-

eters and larger per cubic meter of air that is supplied by HEPA or HEPA–filtered air.

(13) "ISO Class 8" means conditions in which the air particle count is no greater than a total of 3,520,000 particles of 0.5 micrometers and larger per cubic meter of air that is supplied by HEPA or HEPA–filtered air.

(14) "Isolator" means an enclosure that provides HEPA–filtered ISO Class 5 unidirectional air operated at a continuously higher pressure than its surrounding environment and is decontaminated using an automated system. An isolator uses only decontaminated interfaces or rapid transfer ports for materials transfer.

(15) "Primary engineering control" means a device or zone that provides an ISO Class 5 environment for sterile compounding.

(16) "Restricted access barrier system (RABS)" means an enclosure that provides HEPA–filtered ISO Class 5 unidirectional air that allows for the ingress or egress of materials through defined openings that have been designed and validated to preclude the transfer of contamination, and that generally are not to be opened during operations. RABS include compounding aseptic isolators and compounding aseptic containment isolators.

(17) "Sterility assurance level of 10^{-6}" means an equivalent to a probability that one unit in a million is nonsterile.

(18) "Segregated compounding area" means a designated, unclassified space, area, or room that contains a primary engineering control.

(19) "Urgent use compounded sterile preparation" means a preparation needed urgently for a single patient and preparation of the compounded sterile preparation under Category 1 or Category 2 requirements would subject the patient to additional risk due to delays.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18.

Phar 15.31 Facility design and environmental controls. (1) GENERAL. Facilities shall meet all of the following requirements:

(a) Be physically designed and environmentally controlled to minimize airborne contamination from contacting critical sites.

(b) Be accessible only to designated personnel.

(c) Have a heating, ventilation, and air conditioning system controlling the temperature and humidity.

(2) SEGREGATED COMPOUNDING AREA. A segregated compounding area shall meet all of the following requirements:

(a) Be located in an area away from unsealed windows and doors that connect to the outdoors, or significant traffic flow.

(b) Be located in an area which is not adjacent to construction sites, warehouses, and food preparation areas.

(c) Have a defined perimeter.

(d) Locate the primary engineering control at least one meter from any sink.

(3) CLASSIFIED AREA. A classified area shall meet all of the following:

(a) The surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets shall be smooth, impervious, free from cracks and crevices, and nonshedding.

(b) Work surfaces shall be constructed of smooth, impervious materials. All work surfaces shall be resistant to damage from cleaning and sanitizing agents.

(c) Junctures where ceilings meet walls shall be covered, caulked, or sealed to avoid cracks and crevices in which microorganisms and other contaminate can accumulate. All areas in ceilings and walls where the surface has been penetrated shall be sealed.

(d) Ceilings that consist of inlaid panels shall be impregnated with a polymer to render them impervious and hydrophobic and shall either be caulked or weighted and clipped.

(e) Walls shall be constructed of a durable material, panels locked together and sealed or of epoxy–coated gypsum board.

(f) Floors shall have a covering that shall be seamless or have heat–welded seams and coving to the sidewall. There shall be no floor drains.

(h) Ceiling lighting fixtures shall have exterior lens surfaces which are smooth, mounted flush, and sealed.

(i) Carts shall be constructed of stainless steel wire, nonporous plastic or sheet metal with cleanable casters.

(j) Tacky mats may not be used in a classified area.

(k) HEPA filters and unidirectional airflow shall be used to maintain the appropriate airborne particulate classification.

(L) The classified area shall measure not less than 30 air changes per hour of which at least half shall be HEPA–filtered fresh air.

(m) For classified areas physically separated through the use of walls, doors, and pass–throughs, a minimum differential positive pressure of 0.02–inch water column is required to separate each classified area. If a pass–through is used, only one door shall be opened at a time. A pressure gauge or velocity meter shall be used to monitor the pressure differential or airflow between classified areas with results documented at least daily.

(mm) For classified areas not physically separated, no sterile compounded preparation may be compounded using any ingredient that was at any time non–sterile in a classified area not physically separated and all of the following shall be met:

1. The buffer and ante areas shall be designated with a line of demarcation.

2. The principle of displacement airflow shall be used with an air velocity of 40 feet per minute or more from the buffer area across the entire plane of the line of demarcation.

(n) Devices and objects essential to compounding shall be located at an appropriate distance from the primary engineering control.

(p) The ante area shall meet all of the following requirements:

1. Be capable of maintaining an ISO Class 8 air or higher.

2. Have a sink with running hot and cold running water.

(q) The buffer area shall meet all of the following requirements:

1. Be capable of maintaining an ISO Class 7 air or better.

2. Only contain any of the following:

a. Items, including furniture, equipment, and supplies, that are required for the tasks to be performed in the buffer area.

b. Items that are smooth, impervious, free from cracks and crevices, nonshedding, and easily cleaned and disinfected.

c. Items that have been cleaned and disinfected immediately prior to their being placed in the buffer area.

3. Does not contain any sinks.

4. Does not contain any course cardboard, external shipping containers, and nonessential paper.

(4) PRIMARY ENGINEERING CONTROL. The primary engineering control shall be certified by an independent, qualified individual certified by the Controlled Environment Testing Association's National Board of Testing or another Board approved entity prior to initial use and then every six months. It shall also be certified when any of the following occurs:

(a) Redesign of the facility.

(b) Replacement of the primary engineering control.

(c) Relocation of the primary engineering control.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18.

Phar 15.32 Personnel hygiene, garbing and protective gear. (1) Personnel suffering from rashes, sunburn, oozing tattoos or sores, conjunctivitis, active respiratory infection, or other active communicable disease shall be excluded from working in compounding areas until the condition is resolved.

(2) All personnel who engage in compounding sterile preparations shall comply with all of the following requirements before entering the compounding area:

(a) Remove personal outer garments, all cosmetics, exposed jewelry and piercings, headphones, ear buds, and cell phones.

(b) Abstain from eating, chewing gum or drinking in the compounding area or bringing food, gum, or drink into the compounding area.

(c) Artificial nails, nail extenders or nail polish may not be worn while working in the compounding area. Nails shall be neat and trim.

(d) Don personnel protective equipment and perform hand hygiene in the following order:

1. Low–lint, disposable shoe covers.

2. Low–lint, disposable covers for head and facial hair that cover the ears and forehead and face masks.

3. Eye shields, if required due to working with irritants or hazardous drugs.

4. Wash hands and forearms up to the elbows with unscented soap and water for at least 30 seconds. Hands and forearms to the elbows shall be completely dried using either lint–free disposable towels or wipes.

5. Don low lint disposable gown or overalls.

6. Prior to donning sterile gloves, hand antisepsis shall be performed using an alcohol–based hand rub with sustained antimicrobial activity following the manufacturers labeled instructions and application times.

(3) Gloves on hands and gauntlet sleeves on RABS shall be routinely inspected for holes, punctures, or tears and shall be replaced immediately if any are detected. Sterile gloves shall be donned over the RABS gloves.

(4) Disinfection of contaminated gloved hands shall be accomplished by wiping or rubbing sterile 70% isopropyl alcohol on all contact surface areas of the gloves and letting the gloved hands dry thoroughly. Routine application of sterile 70% isopropyl alcohol shall occur throughout the compounding process and whenever non–sterile surfaces, including vials, counter tops, chairs, and carts, are touched.

(5) When compounding personnel exit the buffer or segregated compounding area, a gown may be removed and retained in the ante area or segregated compounding area if not visibly soiled, to be worn again during the same work shift. Coveralls, shoe covers, hair and facial hair covers, face masks, eye shields, and gloves shall be replaced with new ones before re–entering the compounding area.

(6) Garbing items, including gowns, shall be segregated and stored before use in an enclosure to prevent contamination.

(7) Visibly soiled gowns shall be changed immediately.

(8) Gloves shall be sterile and powder free and tested by the manufacturer for compatibility with alcohol disinfection.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18.

Phar 15.33 Cleaning and Disinfecting the Compounding Area and Supplies. (1) Compounding personnel are responsible determining the cleaning and disinfecting products to be used and for ensuring that the frequency of cleaning and disinfecting compounding area is done.

(2) Compounding personnel shall clean in accordance with the following:

(a) Primary engineering control work surfaces, counters, floors and work surfaces in the buffer zone area, ante room and segregated compounding areas daily.

(b) Walls, ceilings and storage shelving monthly.

(c) When a spill occurs or the surface is visibly soiled.

(d) Sporicidal agents shall be used at least weekly to clean compounding areas.

(3) Compounding personnel shall disinfect in accordance with the following:

(a) Primary engineering control work surfaces at the beginning and end of each compounding business day and before each batch, but not longer than 4 hours following the previous disinfection when ongoing compounding activities are occurring.

(b) When microbial contamination is known to have been or is suspected of having been introduced into the compounding area.

(4) All cleaning and disinfecting practices and policies for the compounding area shall be included in written standard operating procedures and shall be followed by all compounding and environmental services personnel.

(5) Cleaning, detergents and disinfection agents shall be selected and used with consideration of compatibilities, effectiveness, and inappropriate or toxic residues. The selection and use of disinfectants shall be guided by microbicidal activities, inactivation by organic matter, residue, and shelf life. Disinfectants shall have antifungal, antibacterial and antiviral activity. Sporicidal agents shall be used at least weekly to clean compounding areas.

(6) Storage sites for compounding ingredients and supplies shall remain free from dust and debris.

(7) Floors, walls, ceiling, and shelving in the classified and segregated compounding areas are cleaned when no aseptic operations are in progress. Cleaning shall be performed in the direction from cleanest to dirtiest areas.

(8) All cleaning tools and materials shall be low–lint and dedicated for use in the buffer room, ante room and segregated compounding areas. If cleaning tools and materials are reused, procedures shall be developed based on manufacturer recommendations that ensure that the effectiveness of the cleaning device is maintained and that repeated use does not add to the bioburden of the area being cleaned.

(9) Supplies and equipment removed from shipping cartons shall be wiped with a suitable disinfecting agent delivered from a spray bottle or other suitable delivery method. After the disinfectant is wiped on a surface to be disinfected, the disinfectant shall be allowed to dry, during which time the item shall not be used for compounding purposes.

(10) Entry points on bags and vials shall be wiped with small sterile 70% isopropyl alcohol swabs or comparable method for disinfecting, allowing the isopropyl alcohol to dry before piercing stoppers with sterile needles and breaking necks of ampuls. The surface of the sterile 70% isopropyl alcohol swabs used for disinfecting entry points of sterile package and devices may not contact any other object before contacting the surface of the entry point. Particle generating material may not be used to disinfect the sterile entry points of packages and devices.

(11) When sterile supplies are received in sealed pouches designed to keep them sterile until opening, the sterile supplies may be removed from the covering pouches as the supplies are introduced into the ISO Class 5 primary engineering control without the need to disinfect the individual sterile supply items.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18.

Phar 15.34 Urgent use compounded sterile preparations. (1) The compounding process shall be a continuous process that does not exceed one hour, unless required for the preparation.

(2) Administration shall begin within one hour of the completion of the preparation.

(3) Aseptic technique shall be followed during preparation, and procedures shall be used to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix–ups with other compounded sterile products.

(4) Unless immediately and completely administered by the person who prepared the compounded sterile preparation or immediate and complete administration is witnessed by the preparer, the compounded sterile preparation shall have a label listing patient identification information, the names and amounts of all ingredients, the name or initials of the person who prepared the compounded sterile preparation and the one hour BUD and time.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18.

Phar 15.35 Sterilization methods. (1) Sterilization methods employed shall sterilize while maintaining its physical and chemical stability and the packaging integrity of the compounding sterile preparations. The efficacy of sterilization and depyrogenation of container closure systems performed in the pharmacy shall be established, documented, and reproducible.

(2) Pre–sterilization requirements shall meet all of the following:

(a) During all compounding activities that precede terminal sterilization, including weighing and mixing, compounding personnel shall be garbed and gloved in the same manner as when performing compounding in an ISO Class 5 environment. All pre–sterilization procedures shall be completed in an ISO Class 8 or better environment.

(b) Immediately before use, all nonsterile measuring, mixing, and purifying devices used in the compounding process shall be thoroughly rinsed with sterile, pyrogen–free water and then thoroughly drained or dried.

(3) Sterilization shall be performed utilizing one of the following methods:

(a) *Sterilization by filtration.* Sterilization by filtration involves the passage of a fluid or solution through a sterilizing grade membrane to produce a sterile effluent. Filtration may not be used when compounding a suspension when the suspended particles are removed by the filter being used. This method shall meet all of the following:

1. Sterile filters used to sterile filter preparations shall meet all of the following requirements:

a. Be pyrogen–free and have a nominal pore size of 0.22 microns.

b. Be certified by the manufacturer to retain at least 10^7 microorganisms of a strain of Brevundimonas diminuta per square centimeter of upstream filter surface area under conditions similar to those in which the compounded sterile preparations will be filtered.

c. Be chemically and physically stable at the compounding pressure and temperature conditions.

d. Have sufficient capacity to filter the required volumes.

e. Yield a sterile filtrate while maintaining pre–filtration pharmaceutical quality, including strength of ingredients of the specific compounded sterile preparations.

2. The filter dimensions and liquid material to be sterile filtered shall permit the sterilization process to be completed rapidly without the replacement of the filter during the filtering process.

3. When compounded sterile preparations are known to contain excessive particulate matter, one of the following shall occur:

a. A pre–filtration step using a filter of larger nominal pore size.

b. A separate filter of larger nominal pore size placed upstream of the sterilizing filter to remove gross particulate contaminants before the compounding sterile compound is passed through the sterilizing grade filter.

4. Sterilization by filtration shall be performed entirely within an ISO Class 5 or better air quality environment.

5. Filter units used to sterilize compounded sterile preparations shall be subjected to the manufacturers' recommended post–use integrity test.

(b) *Sterilization by steam heat.* The process of thermal sterilization using saturated steam under pressure shall be the method for terminal sterilization of aqueous preparations in their final, sealed container closure system. The effectiveness of steam sterilization shall be established and verified with each sterilization run or load by using biological indicators, physicochemical indicators and integrators. This method shall meet all of the following:

1. All materials shall be directly exposed to steam under adequate pressure for the length of time necessary, as determined by use of appropriate biological indicators, to render the items sterile. The duration of the exposure period shall include sufficient time for the compounded sterile preparation to reach the sterilizing temperature.

2. The compounded sterile preparation and other items shall remain at the sterilizing temperature for the duration of the sterilization period. The sterilization cycle shall be designed to achieve a sterility assurance level of 10^{-6}.

3. Compounded sterile preparations shall be placed in trays which allow steam to reach the compounded sterile preparations without entrapment of air. Paper, glass, and metal devices or items shall be wrapped in low lint protective fabric, paper, or sealed in envelopes that will permit steam penetration and prevent post sterilization microbial contamination.

4. Immediately before filling ampules and vials, solutions shall be passed through a filter having a nominal pore size of not larger than 1.2 microns for removal of particulate matter.

5. Sealed containers shall be able to generate steam internally. Stoppered and crimped empty vials shall contain a small amount of moisture to generate steam. Deep containers, including beakers and graduated cylinders, shall be placed on their sides to prevent air entrapment or have a small amount of water placed in them.

6. Porous materials and items with occluded pathways shall only be sterilized by steam if the autoclave chamber has cycles for dry goods.

7. The steam supplied shall be free of contaminants and generated using clean water.

8. The seals on the doors of autoclave chambers shall be examined visually every day they are used for cracks or damage and the seal surfaces shall be kept clean.

9. A data recorder or chart shall be used to monitor each cycle and the data shall be reviewed to identify cycle irregularities in temperature or exposure time.

10. Materials in direct contact with the compounded sterile preparation shall undergo a depyrogenation process before being sterilized using steam heat unless the materials used are certified to be pyrogen–free.

(c) *Sterilization by dry heat.* Dry heat sterilization shall be used only for those materials that cannot be sterilized by steam or filtration. The effectiveness of dry heat sterilization shall be verified using appropriate biological indicators and temperature sensing devices. This method shall meet all of the following:

1. The duration of the exposure period shall include sufficient time for the compounding sterile preparation or items to reach the sterilizing temperature. The compounded sterile preparation and items shall remain at the sterilizing temperature for the duration of the sterilization period.

2. Heated air shall be evenly distributed throughout the chamber.

3. Sufficient space shall be left between materials to allow for good circulation of the hot air.

4. The oven shall be equipped with temperature controls and a timer.

5. A data recorder or chart shall be used to monitor each cycle and the data shall be reviewed to identify cycle irregularities in temperature or exposure time.

6. Materials shall first undergo a depyrogenation process before being sterilized using dry heat, unless the materials used are certified to be pyrogen–free.

(4) Dry heat depyrogenation shall be used to render glassware and other thermostable containers pyrogen free. The duration of the exposure period shall include sufficient time for the items to reach the depyrogenation temperature. The items shall remain at the depyrogenation temperature for the duration of the depyrogenation period. The effectiveness of the dry heat depyrogenation cycle shall be established and verified annually using endotoxin challenge vials to demonstrate that the cycle is capable of achieving at least a 3–log reduction in endotoxins.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18.

Phar 15.36 Inspection, sterility testing and antimicrobial effectiveness. (1) PHYSICAL INSPECTION. (a) At the completion of compounding, the compounded sterile preparation shall be inspected by performing all of the following:

1. Visually inspect the container closure for leakage, cracks in the container, or improper seals.

2. Visually check the compounded sterile preparation for phase separation.

3. Each individual injectable unit shall be inspected against a lighted white background and a black background for evidence of visible particulates or other foreign matter or discoloration.

(b) For compounded sterile preparations which will not be dispensed promptly after preparation, an inspection shall be conducted immediately before it is dispensed for any defects, including precipitation, cloudiness, or leakage, which may develop during storage.

(c) Compounded sterile preparations with any observed defects shall be immediately discarded or marked and segregated from acceptable units in a manner that prevents them from being dispensed.

(2) STERILITY TESTING. (a) The membrane filtration method shall be used for sterility testing unless it is not possible due to the compounded sterile preparation formulation. The direct inoculation of the culture method shall be used when the membrane filtration method is not possible.

(b) If a preparation may be needed before the results of sterility testing have been received, the pharmacy shall daily observe the incubating test specimens and immediately recall the dispensed preparations when there is any evidence of microbial growth in the test specimens. The patient and the prescriber to whom a potentially contaminated compounded sterile preparation was administered shall be notified immediately of the potential risk.

(c) Positive sterility test results shall prompt a rapid and systematic investigation into the causes of the sterility failure, including identification of the contaminating organism and any aspects of the facility, process or personnel that may have contributed to the sterility failure. The investigation and resulting corrective actions shall be documented.

(d) All Category 2 compounded sterile preparations made from one or more nonsterile ingredients, except those for inhalation and ophthalmic administration, shall be tested to ensure that they do not contain excessive bacterial endotoxins.

(e) Notwithstanding par. (d), a compounded sterile preparation does not need to be tested for bacterial endotoxins if the material is stored under cool and dry conditions and one of the following:

1. The certificate of analysis for the nonsterile ingredient lists the endotoxins burden, and that burden is found acceptable.

2. The pharmacy has predetermined the endotoxins burden of the nonsterile ingredient and that burden is found acceptable.

(3) ANTIMICROBIAL EFFECTIVENESS. Compounded sterile preparations containing a preservative added by the compounder shall pass an antimicrobial effectiveness testing with the results obtained on the specific formulation before any of the compounded sterile preparation is dispensed. The test may be conducted only once on each formulation in the particular container–closure system in which it will be stored or dispensed. The antimicrobial effectiveness test shall occur at one of the following times:

(a) At the completion of the sterility test.

(b) At the time of preparation for compounded sterile preparations which have not undergone a sterility testing.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18.

Phar 15.37 Beyond use dating. (1) Sterility and stability considerations shall be taken into account when establishing a BUD. The following dates and times for storage and initiation of administration of the compounded sterile preparations shall apply:

(a) For compounded sterile preparations including components from conventionally manufactured products, the BUD shall not exceed the shortest expiration of any of the starting components. If the compounded sterile preparation includes non–conventionally manufactured products, the BUD may not exceed the shortest BUD of any of the starting components.

(b) For Category 1 compounded sterile preparations, one of the following:

1. May not exceed 12 hours when the preparation is stored at controlled room temperature.

2. May not exceed 24 hours when the preparation is stored in a refrigerator.

(c) For aseptically prepared Category 2 compounded sterile preparations, one of the following:

1. Prepared with one or more nonsterile ingredients, which are sterilized with a validated sterilization procedure prior to compounding, no preservative added and no sterility testing performed, one of the following:

a. Within 4 days when the preparation is stored at controlled room temperature.

b. Within 7 days when the preparation is stored in a refrigerator.

c. Within 45 days when the preparation is stored in a freezer.

2. Prepared only with sterile ingredients, no preservative added and no sterility testing performed, one of the following:

a. Within 6 days when the preparation is stored at controlled room temperature.

b. Within 9 days when the preparation is stored in a refrigerator.

c. Within 45 days when the preparation is stored in a freezer.

3. Prepared only with sterile ingredients, preservative added and no sterility testing performed, one of the following:

a. Within 28 days when the preparation is stored at controlled room temperature.

b. Within 42 days when the preparation is stored in a refrigerator.

c. Within 45 days when the preparation is stored in a freezer.

4. Prepared only with sterile ingredients, no preservative added and sterility testing, one of the following:

a. Within 28 days when the preparation is stored at controlled room temperature.

b. Within 42 days when the preparation is stored in a refrigerator.

c. Within 45 days when the preparation is stored in a freezer.

5. Prepared with only sterile ingredients, preservative added and sterility testing, one of the following:

a. Within 42 days when the preparation is stored at controlled room temperature.

b. Within 42 days when the preparation is stored in a refrigerator.

c. Within 45 days when the preparation is stored in a freezer.

(d) For Category 2 compounded sterile preparations, terminally sterilized by a validated procedure, one of the following:

1. Prepared with no preservative added and no sterility testing performed, one of the following:

a. Within 14 days when the preparation is stored at controlled room temperature.

b. Within 28 days when the preparation is stored in a refrigerator.

c. Within 45 days when the preparation is stored in a freezer.

2. Prepared with no preservative added and sterility testing performed, one of the following:

a. Within 28 days when the preparation is stored at controlled room temperature.

b. Within 42 days when the preparation is stored in a refrigerator.

c. Within 45 days when the preparation is stored in a freezer.

3. Prepared with preservative added and no sterility testing performed, one of the following:

a. Within 28 days when the preparation is stored at controlled room temperature.

b. Within 42 days when the preparation is stored in a refrigerator.

c. Within 45 days when the preparation is stored in a freezer.

4. Prepared with preservative added and sterility testing performed, one of the following:

a. Within 42 days when the preparation is stored at controlled room temperature.

b. Within 42 days when the preparation is stored in a refrigerator.

c. Within 45 days when the preparation is stored in a freezer.

(2) The BUD established in sub. (1) may not be exceeded or extended for compounded sterile preparations without verifiable supporting valid scientific sterility and stability information that is directly applicable to the specific preparation or compound.

(3) For compounded sterile preparations which have been assigned a BUD based upon storage in a freezer, the integrity of the container–closure system with the specific compounded sterile preparation in it shall have been demonstrated for 45 days at frozen storage. The container–closure integrity test may be conducted only once on each formulation in the specific container closure–system in which it will be stored or dispensed.

(4) When a preservative is added, the compounded sterile formulation shall pass antimicrobial effectiveness testing that shall include inoculation of standardized microorganisms, incubation serial sampling, and calculation of the changes in colony forming unit concentrations in terms of log reduction. The results of antimicrobial effectiveness testing shall be obtained before any of the compounded sterile preparation is dispensed. Preservatives shall not be used as a substitute for good compounding practices.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18.

Phar 15.38 Training and evaluation. (1) GENERAL. The managing pharmacist, pharmacists, pharmacy technicians, pharmacy interns and pharmacy externs compounding sterile preparations shall successfully complete didactic or practical training. The didactic or practical training shall be done before any compounding personnel initially prepares compounded sterile preparations and annually thereafter and shall include all of the following:

(a) Hand hygiene and garbing.

(b) Cleaning and disinfection.

(c) Measuring and mixing.

(d) Aseptic manipulation.

(e) Cleanroom behavior.

(f) Sterilization and depyrogenation.

(g) Use of equipment.

(h) Documentation.

(i) Use of primary engineering controls.

(2) EVALUATION. Compounding personnel shall successfully complete an initial and annual evaluation which includes all of the following:

(a) Visual observation of hand hygiene and garbing.

(b) Visual observation of aseptic technique.

(c) Gloved fingertip and thumb sampling.

(d) Media–fill tests.

(3) GLOVED FINGERTIP. Successfully gloved and thumb sampling is measured by samplings resulting in zero colony–forming units no fewer than three times. Sampling shall be performed on sterile gloves inside of an ISO Class 5 primary engineering control. Gloved fingertip and thumb sampling in a RABS or an isolator shall be taken from the sterile gloves placed over the gauntlet gloves. When gloved fingertip sample results exceed action levels defined by the pharmacy, a review of hand hygiene and garbing procedures, glove and surface disinfection procedures and work practices shall be performed and documented.

(5) RECORDS. The pharmacy shall maintain written policies and procedures for the initial and ongoing training and evaluation of persons involved in compounding sterile preparations. Documentation of all training, assessments, gloved fingertip tests and media–fill simulations shall be maintained by the pharmacy for 5 years and made available to the Board upon request.

History: CR 16–085: cr. Register April 2018 No. 748 eff. 11–1–18.

2019

USP General Chapter <795> *Pharmaceutical Compounding – Nonsterile Preparations*

Reprinted from USP 42—NF 37

Links for Supplemental Resources

- Information on USP General Chapter <795>
- USP General Chapter Compounding FAQs
- USP General Chapter <795> Education Courses
- Sign up for USP Updates

This text is a courtesy copy of General Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations, intended to be used as an informational tool and resource only. Please refer to the current edition of the USP-NF for official text.

This chapter alone is not sufficient for a comprehensive approach to pharmaceutical compounding – nonsterile preparations. Additional chapters are required for complete implementation; see USP Compounding Compendium or USP-NF.

⟨795⟩ PHARMACEUTICAL COMPOUNDING—NONSTERILE PREPARATIONS

Change to read:

1. INTRODUCTION AND SCOPE

This chapter describes the minimum standards to be followed when preparing compounded nonsterile preparations (CNSPs) for humans and animals. For purposes of this chapter, nonsterile compounding is defined as combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering a drug or bulk drug substance to create a nonsterile medication.

The requirements in this chapter must be followed to minimize harm, including death, to human and animal patients that could result from 1) excessive microbial contamination, 2) variability from the intended strength of correct ingredients (e.g., ±10% of the labeled strength), 3) physical and chemical incompatibilities, 4) chemical and physical contaminants, and/or 5) use of ingredients of inappropriate quality.

Handling of nonsterile hazardous drugs (HDs) must additionally comply with *Hazardous Drugs—Handling in Healthcare Settings* ⟨800⟩.

1.1 Scope

CNSPS SUBJECT TO THE REQUIREMENTS IN THIS CHAPTER

CNSPs that must comply with this chapter include but are not limited to the following dosage forms:

- Solid oral preparations
- Liquid oral preparations
- Rectal preparations
- Vaginal preparations
- Topical preparations (i.e., creams, gels, ointments)
- Nasal and sinus preparations intended for local application (i.e., nasal sprays and nasal irrigation)
- Otic preparations

PRACTICES NOT SUBJECT TO THE REQUIREMENTS IN THIS CHAPTER

The following practices are not considered compounding and are not required to meet the requirements of this chapter:

Administration: Preparation of a single dose for a single patient when administration will begin within 4 hours of beginning the preparation is not required to meet the standards in this chapter.

Nonsterile radiopharmaceuticals: Compounding of nonsterile radiopharmaceuticals is not required to meet the standards in this chapter and is subject to the requirements in *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging* ⟨825⟩.

Reconstitution: Reconstitution of a conventionally manufactured nonsterile product in accordance with the directions contained in the manufacturer approved labeling is not required to meet the standards in this chapter.

Repackaging: Repackaging of conventionally manufactured drug products is not required to meet the standards in this chapter (see *Good Repackaging Practices* ⟨1178⟩).

Splitting tablets: Breaking or cutting a tablet into smaller portions is not required to meet the standards in this chapter.

PERSONNEL AND SETTINGS AFFECTED

This chapter applies to all persons who prepare CNSPs and all places where CNSPs are prepared. This includes but is not limited to pharmacists, technicians, nurses, physicians, veterinarians, dentists, naturopaths, and chiropractors, in all places including but not limited to pharmacies, hospitals and other healthcare institutions, patient treatment sites, and physicians' or veterinarians' practice sites.

The compounding facility's leadership and all personnel involved in preparing, storing, packaging, and transporting CNSPs are responsible for 1) ensuring that the applicable practices and quality standards in this chapter are continually and consistently applied to their operations, and 2) proactively identifying and remedying potential problems within their operations. Personnel engaged in the compounding of CNSPs must also comply with laws and regulations of the applicable regulatory jurisdiction.

The compounding facility must designate one or more individuals to be responsible and accountable for the performance and operation of the facility and personnel for the preparation of CNSPs. The responsibilities of the designated person(s) include but are not limited to:

- Overseeing a training program to ensure competency of personnel involved in compounding, handling, and preparing of CNSPs
- Selecting components
- Monitoring and observing compounding activities and taking immediate corrective action if deficient practices are observed
- Ensuring that standard operating procedures (SOPs) are fully implemented. The designated person(s) must ensure that follow-up is carried out if problems, deviations, or errors are identified
- Establishing, monitoring, and documenting procedures for the handling and storage of CNSPs and/or components of CNSPs

The designated person(s) must be identified in an SOP. If the compounding facility has only one person responsible for all of the compounding in the facility, then that person is the designated person.

2. PERSONNEL TRAINING AND EVALUATION

All personnel involved in the preparation and handling of CNSPs must be initially trained, must demonstrate competency, and must undergo refresher training every 12 months. Training and competency of personnel must be documented as described in *15. Documentation*.

A designated person must oversee a training program that describes the required training, the frequency of training, and the process for evaluating the competency of personnel involved in nonsterile compounding and handling of CNSPs. This program must equip personnel with knowledge and training in the required skills necessary to perform their assigned tasks.

Before beginning to prepare CNSPs independently, all compounding personnel must complete training and be able to demonstrate proficiency in the principles and hands-on skills of nonsterile manipulations for the type of compounding they will be performing. Proficiency must be demonstrated every 12 months in at least the following core competencies:

- Hand hygiene
- Garbing
- Cleaning and sanitizing
- Handling and transporting components and CNSPs
- Measuring and mixing
- Proper use of equipment and devices selected to compound CNSPs
- Documentation of the compounding process (e.g., Master Formulation Records and Compounding Records)

Steps in the training procedure must include the following:

- Read and understand this chapter, other applicable standards, and other relevant literature
- Understand and interpret Safety Data Sheets (SDSs) and, if applicable, Certificates of Analysis (COA)
- Read and understand procedures related to their compounding duties

A designated person must oversee the training of personnel. Training and observation may be performed by the designated person(s) or an assigned trainer. Personnel must be observed and guided throughout the training process. The personnel will then be expected to repeat the procedures independently, but under the direct supervision of the designated person(s) and/or trainer. Personnel will be permitted to perform the procedure without direct supervision only after independently demonstrating understanding and competency. Upon completion of the training program, the designated person(s) and/or trainer must document that the personnel has been trained and successfully completed competency assessments (see *15. Documentation*).

In addition to the initial and annual competency training and evaluation described in this section, a designated person should monitor and observe compounding activities and must take immediate corrective action if deficient practices are observed. SOPs must describe procedures for the monitoring and observing of compounding activities and personnel.

If the facility has only one person in the compounding operation, that person must document that they have obtained training and demonstrated competency, and they must comply with the other requirements of this chapter.

3. PERSONAL HYGIENE AND GARBING

Individuals entering the compounding area must maintain personal hygiene. Individuals must evaluate whether they have a personal risk of potentially contaminating the compounding environment and CNSP (e.g., personnel with rashes, recent tattoos or oozing sores, conjunctivitis, or active respiratory infection). Individuals must report these conditions to the designated person(s). The designated person(s) is responsible for evaluating whether these individuals should be excluded from working in compounding areas before their conditions have resolved because of the risk of contaminating the CNSP and the environment.

3.1 Personnel Preparation

Personnel engaged in compounding must maintain hand hygiene and maintain cleanliness required for the type of compounding performed.

Before entering the compounding area, compounding personnel must remove any items that are not easily cleanable and that might interfere with garbing. At a minimum, personnel must:

- Remove personal outer garments (e.g., bandanas, coats, hats, jackets)
- Remove all hand, wrist, and other exposed jewelry, including piercings that could interfere with the effectiveness of garbing or hand hygiene (e.g., watches, rings that may tear gloves)
- Remove earbuds or headphones

The designated person(s) may permit accommodations as long as the quality of the environment and CNSP will not be affected.

3.2 Hand Hygiene

Personnel must perform hand hygiene when entering the compounding area to compound as described in *Box 3-1*. Alcohol hand sanitizers alone are not sufficient.

Box 3-1. Hand Hygiene Procedures

- Wash hands and forearms up to the elbows with soap and water for at least 30 seconds.
- Dry hands and forearms to the elbows completely with disposable towels or wipers.
- Allow hands and forearms to dry thoroughly before donning gloves.

To minimize the risk of cross-contaminating other CNSPs and contaminating other objects (e.g., pens and keyboards), gloves should be wiped or replaced before beginning a CNSP with different components.

All gloves must be inspected for holes, punctures, or tears and must be replaced immediately if such defects are detected.

3.3 Garb and Glove Requirements

Gloves must be worn for all compounding activities. Other garb (e.g., shoe covers, head and facial hair covers, face masks, gowns) should be worn as needed for the protection of personnel from chemical exposures and for prevention of preparation contamination and must be appropriate for the type of compounding performed. The garbing requirements and frequency of changing the garb must be determined by the facility and documented in the facility's SOPs.

Garb must be stored in a manner that minimizes contamination (e.g., away from sinks to avoid splashing). Visibly soiled garb or garb with tears or punctures must be changed immediately.

If gowns are worn, they may be re-used if not soiled. If used, gloves, shoe covers, hair covers, facial hair covers, face masks, or head coverings may not be re-used and must be replaced with new ones. If used, non-disposable garb, such as goggles, should be cleaned and sanitized with 70% isopropyl alcohol before re-use.

4. BUILDINGS AND FACILITIES

4.1 Compounding Space

Space must be specifically designated for nonsterile compounding. The method of designation (e.g., visible perimeter) must be described in the facility's SOP. Other activities must not be occurring in the space at the same time as compounding. The compounding space must be well-lighted and must be maintained in a clean, orderly, and sanitary condition, and in a good state of repair. Carpet is not allowed in the compounding space. Surfaces should be resistant to damage by cleaning and sanitizing agents.

The space must provide for the orderly placement of equipment and materials to prevent mix-ups among components, containers, labels, in-process materials, and finished CNSPs. The space should be designed, arranged, and used in a way that minimizes cross-contamination from non-compounding areas.

4.2 Storage Area

Compounding personnel must monitor temperatures in storage area(s) either manually at least once daily on days that the facility is open or by a continuous temperature recording device to determine whether the temperature remains within the appropriate range for the CNSPs or components. The results of the temperature readings must be documented on a temperature log or stored in the continuous temperature recording device, and must be retrievable. All temperature monitoring equipment must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer.

The compounding facility must adhere to SOPs to detect and prevent temperature excursions within storage area(s). When it is known that a CNSP or component has been exposed to temperatures either below or above the storage temperature limits for the CNSP or component, personnel must determine whether the CNSP or component integrity or quality has been compromised and, if so, the CNSP or component must be discarded.

All CNSPs, components, equipment, and containers must be stored off the floor and in a manner that prevents contamination and permits inspection and cleaning of the storage area(s).

4.3 Water Sources

A source of hot and cold water and an easily accessible sink must be available for compounding. The sink must be emptied of all items unrelated to compounding and cleaned when visibly soiled before being used to clean any equipment used in nonsterile compounding. The plumbing system must be free of defects that may contribute to the contamination of any CNSP. *Purified Water* (see *Water for Pharmaceutical Purposes* ⟨1231⟩), distilled water, or reverse osmosis water should be used for rinsing equipment and utensils.

5. CLEANING AND SANITIZING

Cleaning and sanitizing of the surfaces in the nonsterile compounding area(s) must occur on a regular basis at the minimum frequencies specified in *Table 1* or, if compounding is not performed daily, cleaning and sanitizing must be completed before initiating compounding. Cleaning and sanitizing must be repeated when spills occur and when surfaces are visibly soiled.

Cleaning and sanitizing agents must be selected and used with consideration of compatibilities, effectiveness, and to minimize the potential to leave residues.

If cleaning and sanitizing are performed as separate steps, cleaning must be performed first.

Table 1. Minimum Frequency for Cleaning and Sanitizing Surfaces in Nonsterile Compounding Area(s)

Site	Minimum Frequency
Work surfaces	• At the beginning and end of each shift, after spills, and when surface contamination is known or suspected • Clean and sanitize the work surfaces between compounding CNSPs with different components
Floors	Daily, after spills, and when surface contamination (e.g., splashes) is known or suspected
Walls	Every 3 months, after spills, and when surface contamination (e.g., splashes) is known or suspected
Ceilings	When visibly soiled and when surface contamination is known or suspected
Storage shelving	Every 3 months, after spills, and when surface contamination (e.g., splashes) is known or suspected

6. EQUIPMENT AND COMPONENTS

6.1 Equipment

The equipment and supplies used for compounding a CNSP must be suitable for the specific compounding process. Equipment surfaces that contact components must not be reactive, additive, or sorptive, and must not alter the quality of the CNSPs. Disposable or dedicated equipment may be used to reduce the chance of bioburden and cross-contamination.

Equipment must be stored in a manner to minimize the risk of contamination and must be located to facilitate its use, maintenance, and cleaning. Equipment and devices used in the compounding or testing of compounded preparations must be inspected prior to use and, if appropriate, verified for accuracy as recommended by the manufacturer and at the frequency recommended by the manufacturer, or at least every 12 months, whichever is more frequent. After compounding, the equipment must be cleaned to prevent cross-contamination of the next preparation.

Weighing, measuring, or otherwise manipulating components that could generate airborne chemical particles [e.g., active pharmaceutical ingredients (APIs), added substances, conventionally manufactured products] must be assessed to determine if these activities must be performed in closed system processing device to reduce the potential exposure to personnel or contamination of the facility or CNSPs. Examples of closed system processing devices include containment ventilated enclosures (CVEs), biological safety cabinets (BSCs), or single-use containment glove bags. The process evaluation must be carried out in accordance with the facility SOP and the assessment must be documented.

If a BSC or CVE is used, it must be certified every 12 months according to requirements such as the current Controlled Environment Testing Association (CETA), NSF International, or American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE) guidelines, or other laws and regulations of the applicable regulatory jurisdiction.

If a CVE or other non-disposable device is used, it must be cleaned as described in *Table 2*.

Table 2. Minimum Frequency for Cleaning and Sanitizing Equipment in Nonsterile Compounding Area(s)

Site	Minimum Frequency
CVE	• At the beginning and end of each shift, after spills, and when surface contamination is known or suspected • Clean and sanitize the horizontal work surface of the CVE between compounding CNSPs with different components
Other devices and equipment used in compounding operations	• Before first use and thereafter in accordance with the manufacturer's recommendations • If no recommendation is available, after compounding CNSPs with different components

6.2 Components

The compounding facility must have written SOPs for the selection and inventory control of all components from receipt to use in a CNSP.

SDSs must be readily accessible to all personnel working with APIs and added substances located in the compounding facility. Personnel must be instructed on how to retrieve and interpret needed information.

COMPONENT SELECTION

A designated person must be responsible for selecting components to be used in compounding.

APIs:

- Must comply with the criteria in the *USP–NF* monograph, if one exists
- Must have a COA that includes the specifications and test results and shows that the API meets the specifications
- In the United States, must be obtained from an FDA-registered facility

- Outside of the United States, must comply with laws and regulations of the applicable regulatory jurisdiction

All components other than APIs:

- Should be accompanied by a COA that verifies that the component meets the criteria in the *USP–NF* monograph, if one exists, and any additional specifications for the component
- In the United States, should be obtained from an FDA-registered facility
    - If it cannot be obtained from an FDA-registered facility, the designated person(s) must select a component that is suitable for the intended use

- Outside of the United States, must comply with laws and regulations of the applicable regulatory jurisdiction

COMPONENT RECEIPT

Upon receipt of components other than conventionally manufactured products, the COA must be reviewed to ensure that the component has met the acceptance criteria in a *USP-NF* monograph, if one exists. For components other than conventionally manufactured products, information including the receipt date, quantity received, supplier name, lot number, expiration date, and results of any in-house or third-party testing performed must be documented.

The date of receipt by the compounding facility must be clearly and indelibly marked on each component package that lacks a vendor expiration date. Packages of components (i.e., API and added substances) that lack a vendor's expiration date must not be used by the compounding facility after 3 years from the date of receipt. A shorter expiration date must be assigned according to *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩, *9.3 Components, Component Receipt* if the same component container is also used in sterile compounding or if the ingredient is known to be susceptible to degradation.

For each use, the lot must be examined for evidence of deterioration and other aspects of unacceptable quality. Once removed from the original container, components not used in compounding (e.g., excess after weighing) should be discarded and not returned to the original container to minimize the risk of contaminating the original container.

Any component found to be of unacceptable quality must be promptly rejected, clearly labeled as rejected, and segregated from active stock to prevent use before appropriate disposal. Any other lots of that component from that vendor must be examined to determine whether the other lots have the same defect.

COMPONENT EVALUATION BEFORE USE

Before use, compounding personnel must visually re-inspect all components. Packages must be inspected to detect container breaks, looseness of the cap or closure, or deviation from the expected appearance or texture of the contents that might have occurred during storage.

Compounding personnel must ascertain before use that components are of the correct identity based on the labeling and have been stored under required conditions in the facility.

If the correct identity, strength, purity, and quality of components intended for preparation of CNSPs cannot be confirmed (e.g., containers with damaged or incomplete labeling), they must be immediately rejected. If they are not immediately discarded, they must be clearly labeled as rejected, and segregated to prevent their use before disposal.

COMPONENT HANDLING

All components must be handled in accordance with the manufacturer's instructions or per laws and regulations of the applicable regulatory jurisdiction. The handling must minimize the risk of contamination, mix-ups, and deterioration (e.g., loss of identity, strength, purity, and quality).

COMPONENT SPILL AND DISPOSAL

The facility must maintain chemical hazard and disposal information (e.g., SDSs) and must review and update its chemical hazard and disposal information every 12 months. The chemical hazard and disposal information (e.g., SDSs) must be made accessible to compounding personnel.

The facility must have an SOP for the management of nonhazardous component spills and disposal. If required by the SOP, these activities must be documented and corrective action taken.

The facility must have a readily accessible spill kit in the compounding area. The contents of the spill kit should be affixed to the packaging of the spill kit if not readily visible on the manufacturer's label.

All personnel who may be required to remediate a spill must receive training in spill management of chemicals used and stored at the compounding facility. Refresher training must be conducted every 12 months and documented for all personnel who may be required to clean up a spill.

Waste must be disposed of in accordance to laws and regulations of the applicable regulatory jurisdiction. The disposal of components must comply with laws and regulations of the applicable regulatory jurisdiction. For information on the handling of HDs, see ⟨800⟩.

7. MASTER FORMULATION AND COMPOUNDING RECORDS

7.1 Creating Master Formulation Records

A Master Formulation Record is a detailed record of procedures that describes how the CNSP is to be prepared. A Master Formulation Record must be created for each unique formulation of a CNSP. CNSPs are prepared according to the Master Formulation Record and the preparation information is documented on a Compounding Record (see *7.2 Creating Compounding Records*). Any changes or alterations to the Master Formulation Record must be approved and documented according to the facility's SOP. *Box 7-1* lists the information that must be included in a Master Formulation Record.

Box 7-1. Master Formulation Records

A Master Formulation Record must include at least the following information:

- Name, strength or activity, and dosage form of the CNSP
- Identities and amounts of all components
  - If applicable, relevant characteristics of components (e.g., particle size, salt form, purity grade, solubility)
- Container–closure system(s)
- Complete instructions for preparing the CNSP, including equipment, supplies, and a description of the compounding steps
- Physical description of the final CNSP
- Assigned beyond-use date (BUD) and storage requirements
- Reference source to support the assigned BUD and storage requirements
- If applicable, calculations to determine and verify quantities and/or concentrations of components and strength or activity of API
- Labeling requirements (e.g., shake well)
- Quality control (QC) procedures (e.g., pH testing, visual inspection) and expected results
- Other information needed to describe the compounding process and ensure repeatability (e.g., adjusting pH, temperature)

7.2 Creating Compounding Records

A Compounding Record documents the compounding of each CNSP. A Compounding Record must be created for all CNSPs. Each Compounding Record must be reviewed for completeness before the CNSP is released. The identifier of the person completing the review and the date of review must be documented on the Compounding Record. The Compounding Record must permit traceability of all components in the case of a recall or known quality issue. The Master Formulation Record can be used as the basis for preparing the Compounding Record. For example, a copy of the Master Formulation Record can be made that contains spaces to record the information needed to complete the Compounding Record. *Box 7-2* lists the information that must be included in a Compounding Record.

Box 7-2. Compounding Records

Compounding Records must include at least the following information:

- Name, strength or activity, and dosage form of the CNSP
- Date and time of preparation of the CNSP
- Assigned internal identification number (e.g., prescription, order, or lot number)
- A method to identify the individuals involved in the compounding process and verifying the final CNSP
- Name, vendor or manufacturer, lot number, and expiration date of each component
- Weight or measurement of each component
- Total quantity compounded
- Assigned BUD and storage requirements
- If applicable, calculations to determine and verify quantities and/or concentrations of components and strength or activity of API
- Physical description of the final CNSP
- Results of quality control procedures (e.g., pH testing, visual inspection)
- Master Formulation Record reference for the CNSP

8. RELEASE INSPECTIONS

At the completion of compounding and before release and dispensing, the CNSP must be visually inspected to determine whether the physical appearance is as expected. Inspections must also confirm that the CNSP and its labeling match the Compounding Record and the prescription or medication order. Some CNSPs, as noted in their Master Formulation Record, also must be visually checked for certain characteristics (e.g., emulsions must be checked for phase separation). All checks and inspections, and if required, any other tests necessary to ensure the quality of the CNSP must be detailed in the facility's Master Formulation Records. Checks and inspections must be documented. Additional quality assurance (QA) and quality control activities are described in *12. Quality Assurance and Quality Control*. Pre-release inspection also must include a visual inspection of container–closure integrity (e.g., checking for leakage, cracks in the container, or improper seals). CNSPs with observed defects must be immediately discarded, or marked and segregated from acceptable units in a manner that prevents them from being released or dispensed.

9. LABELING

The term labeling designates all labels and other written, printed, or graphic matter on the immediate container or on, or in, any package or wrapper in which the article is enclosed, except any outer shipping container. The term label designates the part of the labeling on the immediate container. See *Labeling* ⟨7⟩.

Every dispensed CNSP must be labeled with adequate, legible identifying information to prevent errors during storage, dispensing, and use. All labeling must be in compliance with laws and regulations of the applicable regulatory jurisdiction.

The label on each immediate container of the CNSP must, at a minimum, display the following information:

- Assigned internal identification number (e.g., barcode, prescription, order, or lot number)
- Active component(s), and amounts, activities, or concentrations
- Dosage form
- Amount or volume in each container
- Storage conditions if other than controlled room temperature
- BUD

The labeling on the CNSP should display the following information:

- Route of administration
- Indication that the preparation is compounded
- Any special handling instructions
- Any warning statements that are applicable
- Name, address, and contact information of the compounding facility if the CNSP is to be sent outside of the facility or healthcare system in which it was compounded

Labeling operations must be controlled to prevent labeling errors and CNSP mix-ups. A final check must be conducted to verify that the correct label has been affixed to the finished CNSP. All labels must also comply with laws and regulations of the applicable regulatory jurisdiction.

10. ESTABLISHING BEYOND-USE DATES

10.1 Terminology

Each CNSP label must state the date, or the hour and date, beyond which the preparation cannot be used and must be discarded (i.e., the BUD). BUDs for CNSPs are calculated in terms of hours, days, or months.

BUDs and expiration dates are not the same. An expiration date identifies the time during which a conventionally manufactured drug product, active ingredient, or added substance can be expected to meet the requirements of a compendial monograph, if one exists, or maintain expected quality provided it is kept under the specified storage conditions. The expiration date limits the time during which a conventionally manufactured product, API, or added substance may be dispensed or used (see *Labeling* ⟨7⟩*, Labels and Labeling for Products in Other Categories, Expiration Date and Beyond-Use Date*). Expiration dates are assigned by manufacturers based on analytical and performance testing of the sterility, chemical and physical stability, and packaging integrity of the product. Expiration dates are specific for a particular formulation in its container and at stated exposure conditions of illumination and temperature.

10.2 Parameters to Consider in Establishing a BUD

BUDs for CNSPs should be established conservatively to ensure that the preparation maintains its required characteristics to minimize the risk of contamination or degradation.

When establishing a BUD for a CNSP, it is critical that personnel carefully consider the possible ways that the physical or chemical characteristics of the CNSP could change over time. The following factors must be considered:

- The chemical and physical stability properties of the API and any added substances in the preparation (e.g., if the API and added substances in the preparation are known to degrade over time and/or under certain storage conditions, which would reduce the strength of the preparation and/or produce harmful impurities)
- The compatibility of the container–closure system with the finished preparation (e.g., leachables, interactions, adsorption, and storage conditions)
- Degradation of the container–closure system, which can lead to a reduction in integrity of the CNSP
- The potential for microbial proliferation in the CNSP

10.3 Establishing a BUD for a CNSP

The BUDs indicate the days after the CNSP is prepared and beyond which the CNSP must not be used. The day that the preparation is compounded is considered Day 1. The BUDs in *Table 3* are based on the ability of the CNSP to maintain chemical and physical stability and to suppress microbial growth. *Table 3* represents the maximum BUDs for CNSPs that are packaged in tight, light-resistant containers unless conditions under *10.4 CNSPs Requiring Shorter BUDs* or *10.5 Extending BUDs for CNSPs* apply.

The aqueous and nonaqueous dosage forms in *Table 3* are defined based on the water activity (Aw) of the most similar drug product described in *Application of Water Activity Determination to Nonsterile Pharmaceutical Products* ⟨1112⟩. In general,

the use of Aw aids in assessing the susceptibility of CNSPs to microbial contamination and the potential for API degradation due to hydrolysis. Reduced Aw greatly assists in the prevention of microbial proliferation in conventionally manufactured products and is expected to convey the same benefit to CNSPs. The list of manufactured products in *Application of Water Activity Determination to Nonsterile Pharmaceutical Products* ⟨1112⟩, *Table 2* is not exhaustive. However, it provides guidance on the Aw value of a particular CNSP and can assist personnel in determining the BUD by dosage form based on *Table 3*.

CNSPs with an Aw > 0.6 should contain suitable antimicrobial agents to protect against bacteria, yeast, and mold contamination from proliferation if inadvertently introduced during or after the compounding process. When antimicrobial preservatives are clinically contraindicated in a CNSP, storage of the preparation in a refrigerator is required if such storage does not change the physical or chemical properties of the CNSP (i.e., precipitation).

Table 3. Maximum BUD by Type of Preparation in the Absence of a *USP-NF* Compounded Preparation Monograph or CNSP-Specific Stability Information

Type of Preparation	BUDs (days)	Storage Temperature[a]
Non-preserved aqueous dosage forms[b]	14	Refrigerator
Preserved aqueous dosage forms[b]	35	Controlled room temperature or refrigerator
Nonaqueous dosage forms[c]	90	Controlled room temperature or refrigerator
Solid dosage forms[d]	180	Controlled room temperature or refrigerator

[a] See *Packaging and Storage Requirements* ⟨659⟩.
[b] An aqueous preparation is one that has an Aw of > 0.6 (e.g., emulsions, gels, creams, solutions, sprays, or suspensions).
[c] Any preparation other than solid dosage forms that have a reduced Aw of ≤0.6 (e.g., suppositories, ointments, fixed oils, or waxes).
[d] Capsules, tablets, granules, powders.

10.4 CNSPs Requiring Shorter BUDs

A shorter BUD must be established under the following circumstances:

- If the API or any other components in the CNSP have an expiration date that is earlier than the BUD that could be assigned from *Table 3*, the expiration date supersedes the BUD and must be the assigned shortest date
- If the CNSP includes components from conventionally manufactured product(s), the BUD of the CNSP must not exceed the shortest remaining expiration date of any of those conventionally manufactured product(s)
- If the CNSP includes components from other compounded preparations, the BUD of the final CNSP must not exceed the shortest remaining BUD of any of those compounded preparations
- If the formulation is known to require a shorter BUD

10.5 Extending BUDs for CNSPs

CNSPS WITH A *USP–NF* MONOGRAPH

If there is a *USP–NF* compounded preparation monograph for the CNSP, the BUD must not exceed the BUD specified in the monograph.

CNSPS WITH STABILITY INFORMATION

The BUDs specified in *Table 3* for aqueous dosage forms and nonaqueous dosage forms may be extended up to maximum of 180 days if there is a stability study (published or unpublished) using a stability-indicating assay for the API(s), CNSP, and type of container–closure that will be used.

If the BUD of the CNSP is extended beyond the BUDs in *Table 3*, an aqueous CNSP should be tested for antimicrobial effectiveness (see *Antimicrobial Effectiveness Testing* ⟨51⟩). The compounder may rely on 1) antimicrobial effectiveness testing that is conducted (or contracted for) once for each formulation in the particular container–closure system in which it will be packaged or 2) antimicrobial effectiveness testing results provided by an FDA-registered facility or published in peer-reviewed literature sources if the CNSP formulation (including any preservative) and container–closure system are exactly the same as those tested unless a bracketing study is performed. Antimicrobial effectiveness testing may be performed on a low concentration and a high concentration of the active ingredient in the formulation to establish preservative effectiveness across various strengths of the same formulation (e.g., bracketing). The concentration of all other ingredients (including preservatives) must be the same throughout the bracketing study.

11. SOPS

Facilities preparing CNSPs must develop SOPs on all aspects of the compounding operation. All personnel who conduct or oversee compounding activities must be trained in the SOPs and are responsible for ensuring that they are followed.

One or more person(s) must be designated to ensure that SOPs are fully implemented. The designated person(s) must ensure that follow-up occurs if problems, deviations, or errors are identified.

12. QUALITY ASSURANCE AND QUALITY CONTROL

Quality assurance and quality control programs are necessary to ensure that consistently high-quality CNSPs are prepared. QA is a system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards. QC is the sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the CNSP. See *Quality Assurance in Pharmaceutical Compounding* ⟨1163⟩.

A facility's QA and QC programs must be formally established and documented in SOPs that ensure that all aspects of the preparation of CNSPs are conducted in accordance with this chapter and laws and regulations of the applicable regulatory jurisdiction. A designated person must ensure that the facility has formal, written QA and QC programs that establish a system of:

1. Adherence to procedures
2. Prevention and detection of errors and other quality problems
3. Evaluation of complaints and adverse events
4. Appropriate investigations and corrective actions

The SOPs must describe the roles, duties, and training of the personnel responsible for each aspect of the QA program. Designated person(s) responsible for the QA program must have the training, experience, responsibility, and authority to perform these duties. The overall QA and QC program must be reviewed at least once every 12 months by the designated person(s). The results of the review must be documented and appropriate action must be taken if needed.

13. CNSP PACKAGING AND TRANSPORTING

13.1 Packaging of CNSPs

SOPs must describe packaging of CNSPs. Personnel should select and use packaging materials that will maintain the physical and chemical integrity and stability of the CNSPs. Packaging materials must protect CNSPs from damage, leakage, contamination, and degradation, while simultaneously protecting personnel from exposure.

13.2 Transporting CNSPs

If transporting CNSPs, the facility must have written SOPs to describe the mode of transportation, any special handling instructions, and whether temperature monitoring devices are needed.

14. COMPLAINT HANDLING AND ADVERSE EVENT REPORTING

Compounding facilities must develop and implement SOPs for complaint and adverse event report receipt, acknowledgment, and handling and designate one or more person(s) to be responsible for handling them. Complaints may include concerns or reports on the quality and labeling of, or possible adverse reactions to, a specific CNSP.

14.1 Complaint Handling

The designated person(s) must ensure that all complaints are reviewed to determine whether the complaint indicates a potential quality problem with the CNSP. If it does, a thorough investigation into the cause of the problem must be initiated and completed. The investigation must consider whether the quality problem extends to other CNSPs. Corrective action, if necessary, must be implemented for all potentially affected CNSPs. Consider whether to initiate a recall of potentially affected CNSPs and whether to cease nonsterile compounding processes until all underlying problems have been identified and corrected.

A readily retrievable written or electronic record of each complaint must be kept by the facility, regardless of the source of the complaint (e.g., e-mail, telephone, mail). The record must contain the name of the complainant or unique identifier, the date the complaint was received, the nature of the complaint, and the response to the complaint. In addition, to the extent that the information is known, the following should be recorded: the name and strength of the CNSP, the prescription or medication order number, and the lot number, if one is assigned.

The record must also include the findings of any investigation and any follow-up. Records of complaints must be easily retrievable for review and evaluation for possible trends and must be retained in accordance with the record-keeping requirements in *15. Documentation*. A CNSP that is returned in connection with a complaint must be quarantined until it is destroyed after completion of the investigation and in accordance with laws and regulations of the applicable regulatory jurisdiction.

14.2 Adverse Event Reporting

The designated person(s) must ensure that reports of potential adverse events involving a CNSP are reviewed. If the investigation into an adverse event reveals a quality problem with a CNSP that is likely to affect other patients, those patients and prescribers potentially affected must be informed. The designated person(s) must review all adverse event reports as part of the QA and QC programs (see *12. Quality Assurance and Quality Control*). Adverse events must be reported in accordance with facility SOPs and all laws and regulations of the applicable regulatory jurisdiction. In addition, adverse events associated

with a CNSP should be reported to the FDA through the MedWatch program for human drugs and through Form FDA 1932a for animal drugs.

15. DOCUMENTATION

All facilities where CNSPs are prepared must have and maintain written or electronic documentation to demonstrate compliance with the requirements in this chapter. This documentation must include, but is not limited to, the following:

- Personnel training, competency assessments, and corrective actions for any failures
- Equipment records (e.g., calibration, verification, and maintenance reports)
- COA
- Receipt of components
- SOPs, Master Formulation Records, and Compounding Records
- Release inspection and testing records
- Information related to complaints and adverse events including corrective actions taken
- Results of investigation and corrective actions

Documentation must comply with all laws and regulations of the applicable regulatory jurisdiction. Records must be legible and stored in a manner that prevents their deterioration and/or loss. All required compounding records for a particular CNSP (e.g., Master Formulation Record, Compounding Record, and release inspection and testing results) must be readily retrievable for at least 3 years after preparation or as required by the laws and regulations of the applicable regulatory jurisdiction, whichever is longer.

GLOSSARY

Active pharmaceutical ingredient (API): Any substance or mixture of substances intended to be used in the compounding of a preparation, thereby becoming the active ingredient in that preparation and furnishing pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and animals or affecting the structure and function of the body.

Added substances: Ingredients that are necessary to compound a preparation but are not intended or expected to cause a pharmacologic response if administered alone in the amount or concentration contained in a single dose of the compounded preparation. The term is used synonymously with the terms inactive ingredients, excipients, and pharmaceutical ingredients.

Biological safety cabinet (BSC): A ventilated cabinet which may be used for compounding. These cabinets divided into three general classes (Class I, Class II, and Class III). Class II BSCs are further divided into types (Type A1, Type A2, Type B1, and Type B2).

Certificate of Analysis (COA): A report from the supplier of a component, container, or closure that accompanies the supplier's material and contains the specifications and results of all analyses and a description of the material.

Cleaning: The process of removing soil (e.g., organic and inorganic material) from objects and surfaces, normally accomplished by manually or mechanically using water with detergents or enzymatic products.

Component: Any ingredient used in the compounding of a preparation, including any active ingredient, added substance, or conventionally manufactured product.

Compounded nonsterile preparation (CNSP): A preparation intended to be nonsterile created by combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering of a drug or bulk drug substance.

Compounder: Personnel trained to compound preparations.

Compounding: The process of combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering a drug or bulk drug substance to create a nonsterile medication.

Compounding area: A space that is specifically designated for nonsterile compounding. A visible perimeter should establish the boundaries of the nonsterile compounding area.

Container–closure system: Packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection.

Containment glove bag: A single-use disposable glove bag that is capable of containing airborne chemical particles.

Containment ventilated enclosure (CVE): A full or partial enclosure that uses ventilation principles to capture, contain, and remove airborne contaminants through high-efficiency particulate air (HEPA) filtration and to prevent their release into the work environment.

Conventionally manufactured product: A pharmaceutical dosage form, usually the subject of an FDA-approved application that is manufactured under current good manufacturing practice conditions.

Designated person(s): One or more individuals assigned to be responsible and accountable for the performance and operation of the facility and personnel for the preparation of CNSPs.

Hazardous drug (HD): Any drug identified by at least one of the following six criteria: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans, organ toxicity at low dose in humans or animals, genotoxicity, or new drugs that mimic existing HDs in structure or toxicity. See ⟨800⟩.

Label: A display of written, printed, or graphic matter on the immediate container of any article.

Labeling: All labels and other written, printed, or graphic matter that are 1) on any article or any of its containers or wrappers, or 2) accompanying such an article.

Purified Water: The minimal quality of source water for the production of Purified Water is drinking water whose attributes are prescribed by the US Environmental Protection Agency (EPA), the EU, Japan, or the World Health Organization (WHO). This source water may be purified using unit operations that include deionization, distillation, ion exchange, reverse osmosis, filtration, or other suitable purification procedures. (See *Water for Pharmaceutical Purposes* ⟨1231⟩*, 3. Waters Used for Pharmaceutical Manufacturing and Testing Purposes, 3.1 Bulk Monographed Waters and Steam, 3.1.1 Purified Water*.)

Preservative: A substance added to inhibit microbial growth.

Quality assurance (QA): A system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards.

Quality control (QC): The sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the CNSP.

Reconstitution: The process of adding a diluent to a conventionally manufactured product to prepare a solution or suspension.

Release inspection and testing: Visual inspection and testing performed to ensure that a preparation meets appropriate quality characteristics.

Sanitizing agent: An agent for reducing, on inanimate surfaces, the number of all forms of microbial life including fungi, viruses, and bacteria.

Specification: The tests, analytical methods, and acceptance criteria to which an API or other components, CNSP, container–closure system, equipment, or other material used in compounding CNSPs must conform to be considered acceptable for its intended use.

Stability: The extent to which a product or preparation retains physical and chemical properties and characteristics within specified limits throughout its expiration or BUD.

APPENDIX

Acronyms

API(s)	Active pharmaceutical ingredient(s)
ASHRAE	American Society of Heating, Refrigerating, and Air-Conditioning Engineers
Aw	Water activity
BSC(s)	Biological safety cabinet(s)
BUD(s)	Beyond-use date(s)
CETA	Controlled Environment Testing Association
CNSP(s)	Compounded nonsterile preparation(s)
COA	Certificate(s) of Analysis
CVE	Containment ventilated enclosure
FDA	Food and Drug Administration
HD(s)	Hazardous drug(s)
QA	Quality assurance
QC	Quality control
SDS(s)	Safety Data Sheet(s)
SOP(s)	Standard operating procedure(s)▲ USP 1-Dec-2019

2019

USP General Chapter <797> *Pharmaceutical Compounding – Sterile Preparations*

Reprinted from USP 42—NF 37

Links for Supplemental Resources

- Information on USP General Chapter <797>
- USP General Chapter <797> FAQs
- USP General Chapter <797> Education Courses
- Sign up for USP Updates

This text is a courtesy copy of General Chapter <797> Pharmaceutical Compounding – Sterile Preparations, intended to be used as an informational tool and resource only. Please refer to the current edition of the USP-NF for official text.

This chapter alone is not sufficient for a comprehensive approach to pharmaceutical compounding – sterile preparations. Additional chapters are required for complete implementation; see USP Compounding Compendium or USP-NF.

⟨797⟩ PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS

Change to read:

▲TABLE OF CONTENTS

1. INTRODUCTION AND SCOPE

This chapter describes the minimum standards to be followed when preparing compounded sterile human and animal drugs [compounded sterile preparations (CSPs)]. Sterile compounding is defined as combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug or bulk drug substance to create a sterile medication.

The requirements in this chapter must be followed to minimize harm, including death, to human and animal patients that could result from 1) microbial contamination (nonsterility), 2) excessive bacterial endotoxins, 3) variability from the intended strength of correct ingredients, 4) physical and chemical incompatibilities, 5) chemical and physical contaminants, and/or 6) use of ingredients of inappropriate quality.

Aseptic technique must be followed for preparing any sterile medication. Procedures must be in place to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other products or CSPs.

Pursuant to *General Notices, 2.30 Legal Recognition*, assuring compliance with *USP* standards is the responsibility of regulatory bodies. Accreditation or credentialing organizations may adopt and enforce *USP* standards. USP has no role in enforcement.

1.1 Scope

CSPS AFFECTED

The requirements in this chapter must be met to ensure the sterility of any CSP. Although the list below is not exhaustive, the following must be sterile:

- Injections, including infusions
- Irrigations for internal body cavities (i.e., any space that does not normally communicate with the environment outside of the body such as the bladder cavity or peritoneal cavity). [NOTE—Irrigations for the mouth, rectal cavity, and sinus cavity are not required to be sterile.]
- Ophthalmic dosage forms
- Preparations for pulmonary inhalation. [NOTE—Nasal dosage forms intended for local application are not required to be sterile.]
- Baths and soaks for live organs and tissues
- Implants

SPECIFIC PRACTICES

Repackaging: Repackaging of a sterile product or preparation from its original container into another container must be performed in accordance with the requirements in this chapter.

Allergenic extracts: Licensed allergenic extracts are mixed and diluted to prepare prescription sets for administration to patients. A prescription set is a vial or set of vials of premixed licensed allergenic extracts for subcutaneous immunotherapy diluted with an appropriate diluent for an individual patient. Because of certain characteristics of allergenic extracts and allergy practice, preparation of allergenic extract prescription sets is not subject to the requirements in this chapter that are applicable to other sterile CSPs. The standards for compounding allergenic extracts are in *21. Compounding Allergenic Extracts* and are applicable only when:

1. The compounding process involves transfer via sterile needles and syringes of conventionally manufactured sterile allergen products and appropriate conventionally manufactured sterile added substances, and
2. Manipulations are limited to penetrating stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile vials

Otherwise, compounding of allergenic extracts prescription sets must meet the requirements for Category 1 or Category 2 CSPs, which are described in this chapter.

Hazardous drugs: Compounding of sterile hazardous drugs (HDs) must additionally comply with *Hazardous Drugs—Handling in Healthcare Settings* ⟨800⟩.

Blood-derived and other biological materials: When compounding activities require the manipulation of a patient's blood-derived or other biological material (e.g., autologous serum), the manipulations must be clearly separated from other compounding activities and equipment used in CSP preparation activities, and they must be controlled by specific standard operating procedures (SOPs) in order to avoid any cross-contamination. Handling of blood components must additionally comply with jurisdictional standards and guidelines.

Sterile radiopharmaceuticals: Compounding of radiopharmaceuticals is not required to meet the standards of this chapter for Category 1 and Category 2 CSPs and is subject to the requirements in *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging* ⟨825⟩.

PERSONNEL AND SETTINGS AFFECTED

This chapter describes the minimum requirements that apply to all persons who prepare CSPs and all places where CSPs are prepared. This includes, but is not limited to, pharmacists, technicians, nurses, physicians, veterinarians, dentists, naturopaths, and chiropractors in all places including, but not limited to, hospitals and other healthcare institutions, medical and surgical patient treatment sites, infusion facilities, pharmacies, and physicians' or veterinarians' practice sites. Any person, whether preparing a CSP or not, entering a sterile compounding area must meet the requirements in *3. Personal Hygiene and Garbing*.

The compounding facility must designate one or more individuals [i.e., the designated person(s)] to be responsible and accountable for the performance and operation of the facility and personnel in the preparation of CSPs and for performing other functions as described in this chapter.

1.2 Administration

For the purposes of this chapter, administration means the direct application of a sterile medication to a single patient by injecting, infusing, or otherwise providing a sterile medication in its final form. Administration of medication is out of the scope of this chapter. Standard precautions such as the Centers for Disease Control and Prevention's (CDC's) safe injection practices apply to administration.

1.3 Immediate Use CSPs

Compounding of CSPs for direct and immediate administration to a patient is not subject to the requirements for Category 1 or Category 2 CSPs when all of the following are met:

1. Aseptic processes are followed and written procedures are in place to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other conventionally manufactured products or CSPs.
2. The preparation is performed in accordance with evidence-based information for physical and chemical compatibility of the drugs (e.g., FDA-approved labeling, stability studies).
3. The preparation involves not more than 3 different sterile products.
4. Any unused starting component from a single-dose container must be discarded after preparation for the individual patient is complete. Single-dose containers must not be used for more than 1 patient.
5. Administration begins within 4 hours following the start of preparation. If administration has not begun within 4 hours following the start of preparation, it must be promptly, appropriately, and safely discarded.
6. Unless administered by the person who prepared it or administration is witnessed by the preparer, the CSP must be labeled with the names and amounts of all active ingredients, the name or initials of the person who prepared the preparation, and the exact 4-hour time period within which administration must begin.

1.4 Preparation Per Approved Labeling

Compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling [21 USC 353a (e)].

Preparing a conventionally manufactured sterile product in accordance with the directions in the manufacturer's approved labeling is out of scope of this chapter only if:

1. The product is prepared as a single dose for an individual patient, and
2. The approved labeling includes information for the diluent, the resultant strength, the container closure system, and storage time.

PROPRIETARY BAG AND VIAL SYSTEMS

Docking and activation of proprietary bag and vial systems (e.g., addEASE, ADD-Vantage, Mini Bag Plus) in accordance with the manufacturer's labeling for *immediate* administration to an individual patient is not considered compounding and may be performed outside of an International Organization for Standardization (ISO) 5 environment.

Docking of the proprietary bag and vial systems for *future activation* and administration is considered compounding and must be performed in accordance with this chapter, with the exception of *14. Establishing Beyond-Use Dates*. Beyond-use dates (BUDs) for proprietary bag and vial systems must not be longer than those specified in the manufacturer's labeling.

1.5 CSP Categories

This chapter distinguishes two categories of CSPs, Category 1 and Category 2, primarily based on the conditions under which they are made, the probability for microbial growth, and the time period within which they must be used. Category 1 CSPs are those assigned a BUD of 12 hours or less at controlled room temperature or 24 hours or less when refrigerated if made in accordance with all of the applicable requirements for Category 1 CSPs in this chapter. Category 2 CSPs are those that may be assigned a BUD of greater than 12 hours at controlled room temperature or greater than 24 hours if refrigerated (see *14. Establishing Beyond-Use Dates*) if made in accordance with all of the applicable requirements for Category 2 CSPs in this chapter.

The requirements that are not specifically described as applicable to Category 1 or Category 2, such as training, competency testing, and personal hygiene for personnel, are applicable to the compounding of all CSPs.

CSPs can be compounded either by using only sterile starting ingredients or by using some or all nonsterile starting ingredients. If all of the components used to compound a drug are sterile to begin with, the sterility of the components must be maintained during compounding to produce a CSP. If one or more of the starting components being used to compound is not sterile, the sterility of the compounded preparation must be achieved through a sterilization process (e.g., terminal sterilization in the final sealed container) or sterilizing filtration, and then maintained if the CSP is subsequently manipulated. When compounding with nonsterile starting components, supplies, or equipment, the quality of the components and the effectiveness of the sterilization step are critical to achieving a sterile preparation.

2. PERSONNEL TRAINING AND EVALUATION

All personnel involved in the compounding of CSPs must be initially trained and qualified by demonstrating proficiency in compounding CSPs. A designated person must oversee the training of personnel. Training and observation may be performed by the designated person(s) or an assigned trainer. Personnel must complete training every 12 months in appropriate sterile compounding principles and practices.

Each compounding facility must develop a written training program that describes the required training, the frequency of training, and the process for evaluating the performance of individuals involved in preparing CSPs. This program should

equip personnel with the appropriate knowledge and train them in the required skills necessary to perform their assigned tasks. Training and evaluation of personnel must be documented.

2.1 Demonstrating Proficiency in Core Competencies

Before beginning to prepare CSPs independently, all compounding personnel must complete training and be able to demonstrate knowledge of principles and proficiency of skills for performing sterile manipulations and achieving and maintaining appropriate environmental conditions. Competency must be demonstrated every 12 months in at least the following:

- Hand hygiene
- Garbing
- Cleaning and disinfection
- Calculations, measuring, and mixing
- Aseptic technique
- Achieving and/or maintaining sterility and apyrogenicity
- Use of equipment
- Documentation of the compounding process (e.g., master formulation and compounding records)
- Principles of high-efficiency particulate air (HEPA)-filtered unidirectional airflow within the ISO Class 5 area
- Proper use of primary engineering controls (PECs)
- Principles of movement of materials and personnel within the compounding area

All compounding personnel must complete written or electronic testing every 12 months. Any other personnel handling CSPs and/or accessing the compounding area must complete training and demonstrate competency in maintaining the quality of the environment in which they are performing their assigned task. The designated person(s) must ensure that any person who enters the sterile compounding area maintains the quality of the environment.

If the facility has only one person in the compounding operation, that person must document that they have obtained training and demonstrated competency, and they must comply with the other requirements of this chapter.

2.2 Demonstrating Competency in Garbing and Hand Hygiene

All compounding personnel must be visually observed initially and every 6 months while performing hand hygiene and garbing procedures (see *3. Personal Hygiene and Garbing*). The visual audit must be documented and the documentation maintained to provide a record of personnel competency.

Initial gloved fingertip and thumb sampling evaluates a compounder's competency in correctly performing hand hygiene and garbing (see *Box 2-1*). Before being allowed to independently compound, all compounders must successfully complete an initial competency evaluation, including visual observation and gloved fingertip and thumb sampling on both hands, no fewer than 3 separate times. Each fingertip and thumb evaluation must occur after performing a separate and complete hand hygiene and full garbing procedure. After the initial competency evaluation, compounding personnel must successfully complete gloved fingertip and thumb sampling at least every 6 months after completing the media-fill test (see *2.3 Competency Testing in Aseptic Manipulation*).

Initial gloved fingertip and thumb sampling must be performed on donned sterile gloves in a classified area or segregated compounding area (SCA). Subsequent gloved fingertip and thumb sampling must be performed on donned sterile gloves inside of an ISO Class 5 PEC. If conducting gloved fingertip and thumb sampling in a compounding aseptic isolator (CAI), compounding aseptic containment isolator (CACI), or a pharmaceutical isolator, samples must be taken from the sterile gloves placed over the gloves attached to the restricted-access barrier system (RABS) sleeves.

Successful completion of initial gloved fingertip and thumb sampling is defined as zero colony-forming units (cfu). Successful completion of subsequent gloved fingertip and thumb sampling after media-fill testing is defined as ≤3 cfu (total from both hands). Action levels for gloved fingertip and thumb sampling results are shown in *Table 1*.

Failure is indicated by visual observation of improper hand hygiene and garbing procedures and/or gloved fingertip and thumb sampling results that exceed the action levels in *Table 1*. Results of the evaluation and corrective actions, in the event of failure, must be documented and the documentation maintained to provide a record and long-term assessment of personnel competency. Documentation must at a minimum include the name of the person evaluated, evaluation date/time, media and components used including manufacturer, expiration date and lot number, starting temperature for each interval of incubation, dates of incubation, the results, and the identification of the observer and the person who reads and documents the results.

Box 2-1. Gloved Fingertip and Thumb Sampling Procedures

- Use one sampling device per hand (e.g., plates, paddles, or slides) containing general microbial growth agar [e.g., trypticase soy agar (TSA)] supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) as this agar supports both bacterial and fungal growth.
- Label each sampling device with a personnel identifier, whether it was from the right or left hand, and the date and time of sampling.
- Do not apply sterile 70% isopropyl alcohol (IPA) to gloves immediately before touching the sampling device because this could cause a false-negative result.
- Using a separate sampling device for each hand, collect samples from all gloved fingers and thumbs from both hands by rolling finger pads and thumb pad over the agar surface.
- Incubate the sampling device at a temperature of 30°–35° for no less than 48 hours and then at 20°–25° for no less than 5 additional days. Store media devices during incubation to prevent condensate from dropping onto the agar and affecting the accuracy of the cfu reading (e.g., invert plates).
- Record the number of cfu per hand (left hand, right hand).
- Determine whether the cfu action level is exceeded by counting the total number of cfu from both hands.

Table 1. Action Levels for Gloved Fingertip and Thumb Sampling[a]

Gloved Fingertip and Thumb Sampling	Action Levels (total number of cfu from both hands)
Initial sampling after garbing	>0
Subsequent sampling after media-fill testing (every 6 months)	>3

[a] Action levels are based on the total cfu count from both hands.

2.3 Competency Testing in Aseptic Manipulation

All compounding personnel must perform media-fill testing to assess their sterile technique and related practices (see *Box 2-2*) initially and every 6 months thereafter. Gloved fingertip and thumb sampling must be performed inside of an ISO Class 5 PEC following media-fill tests to evaluate the ability of the compounder to demonstrate acceptable aseptic processing.

When performing a media-fill test, simulate the most difficult and challenging compounding procedures and processing conditions encountered by the person replacing all the components used in the CSPs with soybean–casein digest media.

If using commercial sterile microbial growth media, a certificate of analysis (COA) must be obtained from the supplier stating that the lot of the growth media will support the growth of microorganisms. Store microbial growth media in accordance with manufacturer instructions and initiate the media-fill test before the expiration date of the media. If preparing sterile microbial growth media in-house for sterile-to-sterile media-fill testing, the growth promotion capability of the media must be demonstrated for each batch and documented as described in *Sterility Tests* ⟨71⟩*, Culture Media and Incubation Temperatures, Growth Promotion Test of Aerobes, Anaerobes, and Fungi*.

Failure is indicated by visible turbidity or other visual manifestations of growth in the media in one or more container–closure unit(s) on or before the end of the incubation period.

Results of the evaluation and corrective actions, in the event of failure, must be documented and the documentation maintained to provide a record and long-term assessment of personnel competency. Documentation must at a minimum include the name of the person evaluated, evaluation date/time, media and components used including manufacturer, expiration date and lot number, starting temperature for each interval of incubation, dates of incubation, the results, and the identification of the observer and the person who reads and documents the results.

Box 2-2. Media-Fill Testing Procedures

- If all of the starting components are sterile to begin with, manipulate them in a manner that simulates sterile-to-sterile compounding activities, and transfer the sterile soybean–casein digest media into the same types of container–closure systems commonly used at the facility. Do not further dilute the media unless specified by the manufacturer.
- If some of the starting components are nonsterile to begin with, use a nonsterile soybean–casein digest powder to make a solution. Dissolve nonsterile commercially available soybean–casein digest medium in nonbacteriostatic water to make a 3% nonsterile solution. Manipulate it in a manner that simulates nonsterile-to-sterile compounding activities. Prepare at least 1 container as the positive control to demonstrate growth promotion, which is indicated by visible turbidity upon incubation.
- Once the compounding simulation is completed and the final containers are filled with the test media, incubate them in an incubator for 7 days at 20°–25° followed by 7 days at 30°–35° to detect a broad spectrum of microorganisms.
- Failure is indicated by visible turbidity or other visual manifestations of growth in the media in one or more container–closure unit(s) on or before 14 days.

3. PERSONAL HYGIENE AND GARBING

Personal hygiene and garbing are essential to maintain microbial control of the environment. Most microorganisms detected in cleanrooms are transferred from individuals. Squamous cells are normally shed from the human body at a rate of 10^6 or more per hour, and those skin particles are covered with microorganisms.[1, 2] Individuals entering a compounding area must be properly garbed and must maintain proper personal hygiene to minimize the risk of contamination to the environment and/or CSPs.

Individuals that may have a higher risk of contaminating the CSP and the environment (e.g., personnel with rashes, recent tattoos, oozing sores, conjunctivitis, or active respiratory infection) must report these conditions to the designated person(s).

[1] Agalloco J, Akers JE. Aseptic processing: a vision of the future. *Pharm Technol*. 2005; Aseptic Processing supplement, s16.
[2] Eaton T. Microbial risk assessment for aseptically prepared products. *Am Pharm Rev*. 2005;8(5):46–51.

The designated person(s) is responsible for evaluating whether these individuals should be excluded from working in compounding areas before their conditions have resolved because of the risk of contaminating the CSP and the environment.

3.1 Personnel Preparation

Individuals entering a compounding area must take appropriate steps to minimize microbial contamination of the environment and the CSPs, including hand hygiene (*3.2 Hand Hygiene*), garbing (*3.3 Garbing Requirements*), and consideration of needed materials to be brought into the compounding area. Before entering a compounding area, individuals must remove any items that are not easily cleanable or that are not necessary for compounding. At a minimum, individuals must:

- Remove personal outer garments (e.g., bandanas, coats, hats, jackets, sweaters, vests).
- Remove all cosmetics because they shed flakes and particles.
- Remove all hand, wrist, and other exposed jewelry including piercings that could interfere with the effectiveness of garbing (e.g., the fit of gloves, cuffs of sleeves, and eye protection) or otherwise increase the risk of contamination of the CSP. Cover any jewelry that cannot be removed.
- Not wear earbuds or headphones.
- Not bring electronic devices that are not necessary for compounding or other required tasks into the compounding area.
- Keep nails clean and neatly trimmed to minimize particle shedding and avoid glove punctures. Nail products (e.g., polish, artificial nails, and extenders) must not be worn.
- Wipe eyeglasses, if worn.

The designated person(s) may permit accommodations as long as the quality of the CSP and environment will not be affected.

3.2 Hand Hygiene

Personnel must wash hands and forearms up to the elbows with soap and water before initiating compounding activities *Box 3-1*). Brushes must not be used for hand hygiene. Hand dryers must not be used. A closed system of soap (i.e., non-refillable container) to minimize the risk of extrinsic contamination must be readily available or in close proximity to the sink.

Box 3-1. Hand Washing Procedures

- Remove visible debris from underneath fingernails under warm running water using a disposable nail cleaner.
- Wash hands and forearms up to the elbows with soap and water for at least 30 seconds.
- Dry hands and forearms to the elbows completely with low-lint disposable towels or wipers.

The order of hand washing and garbing depends on the placement of the sink (see *4.4 Water Sources*). The order of garbing must be determined by the facility and documented in the facility's SOP. Hands must be sanitized with alcohol-based hand rub before donning sterile gloves (see *Box 3-2*). Sterile gloves must be donned in a classified room or SCA.

Box 3-2. Hand Sanitizing Procedures

- Apply an alcohol-based hand rub to dry skin following the manufacturer's instructions for the volume of product to use.
- Apply product to one hand and rub hands together, covering all surfaces of hands and fingers, until hands are dry.
- Allow hands to dry thoroughly before donning sterile gloves.

3.3 Garbing Requirements

Any person entering a compounding area must be properly garbed in accordance with the facility's SOPs. Garb must be donned and doffed in an order that reduces the risk of contamination. The order of garbing must be determined by the facility and documented in the facility's SOP. Sterile gloves must be donned in a classified room or SCA. Skin must not be exposed inside the ISO Class 5 PEC (e.g., gloves must not be donned or doffed inside the ISO Class 5 PEC exposing bare hands). Donning and doffing garb should not occur in the ante-room or the SCA at the same time. The minimum garbing requirements include:

- Low-lint garment with sleeves that fit snugly around the wrists and that is enclosed at the neck (e.g., gowns or coveralls)
- Low-lint, disposable covers for shoes
- Low-lint, disposable covers for head that cover the hair and ears, and if applicable, disposable cover for facial hair
- Face mask
- Sterile powder-free gloves
- If using a RABS, such as a CAI or CACI, disposable gloves (e.g., cotton, nonsterile, sterile) should be worn inside gloves attached to the RABS sleeves. Sterile gloves must be worn over gloves attached to the RABS sleeve

Garb must be replaced immediately if it becomes visibly soiled or if its integrity is compromised. Gowns and other garb must be stored in a manner that minimizes contamination (e.g., away from sinks to avoid splashing). When personnel exit

the compounding area, garb except for gowns cannot be reused and must be discarded. Gowns may be re-used within the same shift if the gown is maintained in a classified area or inside the perimeter of an SCA.

If compounding a HD, appropriate personal protective equipment (PPE) must be worn and disposed of in accordance with ⟨800⟩.

GLOVES

Gloves must be sterile and powder free. Application of sterile 70% IPA to gloves must occur regularly throughout the compounding process and whenever nonsterile surfaces (e.g., vials, counter tops, chairs, or carts) are touched.

All gloves must be inspected for holes, punctures, or tears and must be replaced immediately if such defects are detected. The RABS sleeves and gloves and the pharmaceutical isolator gauntlet sleeves and gloves should be changed per the manufacturer's recommendations and as defined in the facility's SOP.

4. FACILITIES AND ENGINEERING CONTROLS

Sterile compounding facilities must be designed, outfitted, and maintained properly to minimize the risk of contamination of CSPs. The required air quality must be achieved and maintained through PECs and secondary engineering controls (SECs). The ante-room, buffer room, and SCA must be separated from areas not directly related to compounding. The ante-room and buffer room must be appropriately controlled to achieve and maintain the required air quality classifications. The design of the facility should take into account the number of personnel and their movements, and the equipment, supplies, and components to maintain and facilitate the maintenance of air quality. The number of operations being performed, the equipment (e.g., PECs, carts, computers), the personnel in the compounding area (and in adjacent areas), and the complexity of the compounding procedures are critical considerations for maintaining control of environmental conditions in the facility.

4.1 Protection from Airborne Contaminants

Sterile compounding facilities must be designed to minimize the risk of airborne contamination of the area in which sterile compounding occurs. Proper design and controls are required to minimize the risk of exposure of CSPs to airborne contaminants.

AIR QUALITY STANDARDS

The ISO standards for air quality in controlled environments are provided in *Table 2* and referenced throughout this chapter.

Table 2. ISO Classification of Particulate Matter in Room Air[a]

ISO Class	Particle Count[b] /m³
3	35.2
4	352
5	3520
6	35,200
7	352,000
8	3,520,000

[a] Adapted from ISO 14644-1, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness by particle concentration.
[b] Limits for number of particles ≥0.5 µm measured under dynamic operating conditions.

DESIGN REQUIREMENTS TO MAINTAIN AIR QUALITY

Facilities used for compounding CSPs must be designed so that air quality improves with movement through separate operational areas to the PEC. Classified areas in which the air quality is controlled (see *Table 2*) include ante-rooms, buffer rooms, and PECs.

- Ante-rooms providing access to positive pressure buffer rooms must meet at least ISO Class 8 classification. Ante-rooms providing access to negative pressure buffer rooms must meet at least ISO Class 7 classification (see ⟨800⟩). Typically, personnel hand hygiene and garbing procedures, staging of components, and other activities that potentially generate higher levels of particulates are performed in the ante-room. Ante-rooms are also transition areas to ensure that proper air classification and pressure relationships are maintained between classified and unclassified areas.
- A buffer room must meet at least ISO Class 7 air quality. Activities in the buffer room must be controlled to minimize any effects on air quality in the area where CSPs are prepared.
- Category 1 and Category 2 CSPs must be prepared in an ISO Class 5 or better PEC.

If compounding only Category 1 CSPs, the PEC may be placed in an unclassified SCA.

4.2 Facility Design and Environmental Controls

In addition to minimizing airborne contamination, sterile compounding facilities must be designed and controlled to provide a well-lighted and comfortable working environment (see *Physical Environments That Promote Safe Medication Use* ⟨1066⟩). The cleanroom suite should be maintained at a temperature of 20° or cooler and a relative humidity below 60% to minimize the risk for microbial proliferation and provide comfortable conditions for compounding personnel attired in the required garb. The temperature and humidity must be monitored in each room of the cleanroom suite each day that compounding is performed, either manually or by a continuous recording device. The results of the temperature and humidity readings must be documented at least once daily or stored in the continuous recording device, and must be retrievable. The temperature and humidity readings must be reviewed as described in the facility's SOPs. Temperature and humidity in the cleanroom suite must be controlled through a heating, ventilation, and air conditioning (HVAC) system. Free-standing humidifiers/dehumidifiers and air conditioners must not be used within the classified area or within the perimeter of the SCA. Temperature and humidity monitoring devices must be verified for accuracy at least every 12 months or as required by the manufacturer.

The designated person(s) is responsible for ensuring that each area related to CSP preparation meets the classified air quality standard appropriate for the activities to be conducted in that area. The designated person(s) must also ensure that the ISO Class 5 areas are located, operated, maintained, monitored, and certified to have appropriate air quality.

TYPES OF SECS AND DESIGN

The PEC must be located in the buffer room of the cleanroom suite or the SCA in a manner that minimizes conditions that could increase the risk of microbial contamination. For example, strong air currents from opened doors, personnel traffic, or air streams from the HVAC system(s) can disrupt the unidirectional airflow of an open-faced PEC such as a laminar airflow workbench (LAFW). Access to the SEC must be restricted to authorized personnel and required materials.

Cleanroom suite: The ISO-classified ante-room and buffer room must be separated from the surrounding unclassified areas of the facility by fixed walls and doors, and controls must be in place to minimize the flow of lower-quality air into the more controlled areas. Air supplied to the cleanroom suite must be introduced through HEPA filters that are located in the ceiling of the buffer and ante-rooms.

Air returns in the cleanroom suite must be low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow where particulate will accumulate. This smoke study along with environmental monitoring must be repeated whenever a change to the placement of equipment within the room is made or any other alteration is performed within the cleanroom suite that affects the quality of the air (e.g., HVAC alterations, change of HEPA filter units).

The classified rooms must be equipped with a pressure-differential monitoring system. The ante-room must have a line of demarcation to separate the clean side from the dirty side. Alternatively, facilities may be designed with two separate ante-rooms, a clean ante-room and a dirty ante-room. The ante-room is entered through the dirty side/room, and the clean side/room is the area closest to the buffer room. Required garb must be donned prior to entering the clean side/room of the ante-room (see *3. Personal Hygiene and Garbing*).

It is also critical to control materials (e.g., supplies and equipment) as they move from classified areas of lower quality to those of higher quality (e.g., ISO Class 8 ante-room to ISO Class 7 buffer room to ISO Class 5 PEC) to minimize the influx of contaminants. Airlocks and interlocking doors may be used to facilitate better control of air balance between areas of differing ISO classification (e.g., between the buffer room and ante-room), or between a classified area and an unclassified area (e.g., between the ante-room and an unclassified area such as a hallway). If a pass-through is used, both doors must never be opened at the same time, and doors should be interlocking.

Due to the interdependence of the various rooms or areas that make up a sterile compounding facility, it is essential to carefully define and control the dynamic interactions permitted between areas and rooms. Consider the placement of door closures, door surfaces, and the movement of the doors, all of which can affect airflow. Seals and sweeps should not be installed at doors between buffer and ante-rooms. Access doors should be hands-free. Tacky mats must not be placed within ISO-classified areas.

Segregated compounding area (SCA): A PEC may be located within an unclassified area, without an ante-room or buffer room. This type of design is called an SCA. Only Category 1 CSPs can be compounded in an SCA. The SCA must be located away from unsealed windows, doors that connect to the outdoors, and traffic flow, all of which may adversely affect the air quality in the PEC. An SCA must not be located where environmental control challenges (e.g., restrooms, warehouses, or food preparation areas) could negatively affect the air quality of the PEC within the SCA. The impact of activities (e.g., patient care activities) that will be conducted around or adjacent to the SCA must be considered carefully when designing such an area. A visible perimeter must establish the boundaries of the SCA.

THE CSP COMPOUNDING ENVIRONMENT

The PEC must be certified to meet ISO Class 5 or better conditions (see *Table 2*) during dynamic operating conditions and must be designed to prevent contamination during compounding of CSPs.

Unidirectional airflow must be maintained in the PEC. HEPA-filtered air must be supplied by the PEC at a velocity sufficient to sweep particles away from critical sites and maintain unidirectional airflow during operations. Proper design, control, and use minimizes turbulence and creation of eddies or stagnant air in the PEC.

TYPES OF PECS AND PLACEMENT

Proper placement of the PEC is critical to ensuring an ISO Class 5 environment for preparing CSPs. Placement of the PEC must allow for cleaning around the PEC. See *Table 3* for a summary of minimum requirements for the placement of PECs for preparing non-HD CSPs.

Types of PECs and their placement include the following.

Laminar airflow system (LAFS): An LAFS provides an ISO Class 5 or better environment for sterile compounding. The LAFS provides unidirectional HEPA-filtered airflow that is designed to prevent contamination of a sterile compounding environment. The unidirectional airflow within the LAFS helps protect the direct compounding area (DCA) from process-generated contamination (e.g., opening wrappings of sterile containers, compounder movement) as well as from outside sources.

Types of LAFS: Examples of LAFS include LAFWs, integrated vertical laminar flow zones (IVLFZs), and biological safety cabinets (BSCs).

LAMINAR AIRFLOW WORKBENCH (LAFW): An LAFW is a device that provides an ISO Class 5 or better environment for sterile compounding. The LAFW provides either horizontal or vertical unidirectional HEPA-filtered airflow. [NOTE—An LAFW must not be used for preparation of antineoplastic and/or active pharmaceutical ingredient (API) HDs (see ⟨800⟩).]

INTEGRATED VERTICAL LAMINAR FLOW ZONE (IVLFZ): An IVLFZ is a designated ISO Class 5 area serving as the PEC within an ISO Class 7 or cleaner buffer room. In the IVLFZ, unidirectional airflow is created by placing HEPA filters over the entire surface of the work tables and effective placement of air returns. The unidirectional HEPA-filtered zone must be separated from the ISO Class 7 area with a physical barrier to direct the airflow downward over the work area to separate the DCA from potential sources of contamination. Strategic location of air returns in addition to full coverage of HEPA filters above the work surface is required. Both static and dynamic smoke studies verifying a continuous flow of HEPA-filtered air void of turbulence, dead air zones, and refluxing from the HEPA filters to and across the entire work area and to the air returns must be documented (e.g., with video). [NOTE—Dynamic airflow smoke pattern tests have shown that it is difficult to achieve this type of design and also achieve and maintain unidirectional airflow under dynamic operating conditions.] [NOTE—A IVLFZ must not be used for preparation of antineoplastic and/or API HDs (see ⟨800⟩).]

CLASS II BIOLOGICAL SAFETY CABINET (BSC): A Class II BSC is a ventilated cabinet with an open front and inward and downward unidirectional HEPA-filtered airflow and HEPA-filtered exhaust. The BSC is designed to provide worker protection from exposure to airborne drugs and to provide an ISO Class 5 or better environment for preparing CSPs. [NOTE—The exhaust air from the BSC must be externally vented for preparation of antineoplastic and/or API HDs (see ⟨800⟩).]

Placement of LAFS: The LAFS must be located out of traffic patterns and away from room air currents that could disrupt the intended airflow patterns inside the PEC. If used to prepare only Category 1 CSPs, the ISO Class 5 PEC may be located in an unclassified SCA. If used to prepare Category 2 CSPs, the LAFS must be located within a cleanroom suite with an ISO Class 7 or better buffer room with an ISO Class 8 or better ante-room. A dynamic airflow smoke pattern test must be performed in the PEC initially and at least every 6 months to ensure that 1) the LAFS is properly placed into the facility and 2) compounders understand how to utilize the unidirectional airflow to maintain first air in the DCA.

Restricted-access barrier system (RABS): A RABS is an enclosure that provides HEPA-filtered ISO Class 5 unidirectional air. It allows for the ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of environmental air contamination, and that generally are not to be opened during compounding operations.

Types of RABS: Examples of RABS include CAIs and CACIs. In a CAI or CACI, glove ports are used to provide physical separation between the surrounding area and the aseptic manipulations.

COMPOUNDING ASEPTIC ISOLATOR (CAI): A CAI is designed for compounding non-HD CSPs. It is designed to maintain an ISO Class 5 environment throughout the compounding and material transfer processes. Air exchange into the CAI from the surrounding environment must not occur unless the air has first passed through a HEPA filter. [NOTE—A CAI must not be used for preparation of antineoplastic and/or API HDs (see ⟨800⟩).]

COMPOUNDING ASEPTIC CONTAINMENT ISOLATOR (CACI): A CACI is designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes, and to maintain an ISO Class 5 environment for compounding sterile HD preparations (see ⟨800⟩).

Placement of RABS: If used to prepare only Category 1 CSPs, the ISO Class 5 environment may be achieved by placing the RABS in an unclassified SCA. If used to prepare Category 2 CSPs, the RABS must be located within a cleanroom suite with an ISO Class 7 or better buffer room with an ISO Class 8 or better ante-room. For placement of a CACI used for the preparation of antineoplastic and/or API HDs, see ⟨800⟩.

When a RABS is used, the recovery time after opening the transfer chamber to achieve ISO Class 5 air quality must be documented (e.g., by the manufacturer), and internal procedures must be developed to ensure that adequate recovery time is allowed after opening and closing the RABS, both before and during compounding operations. A dynamic airflow smoke pattern test must be performed in the PEC under dynamic operating conditions initially and at least every 6 months to ensure that 1) the RABS is properly integrated into the facility and 2) compounders understand how to utilize the unidirectional airflow to maintain first air in the DCA.

Pharmaceutical isolator: A pharmaceutical isolator provides isolation from the surrounding area and maintains ISO Class 5 air quality during dynamic operating conditions. [NOTE—A CAI or CACI is not a pharmaceutical isolator.] A pharmaceutical isolator comprises four elements:

1. Controlled workspace
2. Transfer device(s)
3. Access device(s)
4. Integral decontamination system

Placement of pharmaceutical isolators: A pharmaceutical isolator used to prepare only Category 1 CSPs can be placed in an unclassified SCA. If the pharmaceutical isolator is used to prepare Category 2 CSPs, the pharmaceutical isolator must be placed in an ISO Class 8 or better room. [NOTE—An ante-room is not required when using a pharmaceutical isolator.] A dynamic airflow smoke pattern test must be performed in the PEC initially and at least every 6 months to ensure that 1) the pharmaceutical isolator is properly placed into the facility and 2) compounders understand how to utilize the unidirectional airflow to maintain first air in the work zone. For placement of a pharmaceutical isolator used for the preparation of HDs, see ⟨800⟩.

Table 3. Summary of Minimum Requirements for Placement of PEC for Compounding Non-HD CSPs[a]

PEC Type	Device Type	Placement for Compounding Category 1 CSPs	Placement for Compounding Category 2 CSPs
LAFS	LAFW	Unclassified SCA	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room
	IVLFZ	N/A[b]	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room
	BSC	Unclassified SCA	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room
RABS	CAI or CACI	Unclassified SCA	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room
Pharmaceutical isolator	Pharmaceutical isolator	Unclassified SCA	ISO Class 8 positive pressure room

[a] For compounding HDs, refer to ⟨800⟩.
[b] An IVLFZ must not be used in an unclassified area.

If a robotic enclosure is used as the PEC, a dynamic airflow smoke pattern test must be performed initially and every 6 months thereafter to ensure 1) that it is properly integrated into the facility, 2) that there is no turbulence or refluxing at any critical site, 3) that room air does not enter the PEC where sterile products and/or preparations may be exposed, and 4) that all processes can be performed without introducing contamination to the DCA(s).

AIR EXCHANGE REQUIREMENTS

For cleanroom suites, adequate HEPA-filtered airflow to the buffer room(s) and ante-room(s) is required to maintain the appropriate ISO classification during compounding activities. Airflow is measured in terms of the number of air changes per hour (ACPH). The ACPH may need to be higher to maintain the required ISO classification and microbial state of control depending on the following factors:

- number of personnel permitted to work in the area
- number of particulates that may be generated from activities and processes in the area
- the equipment located in the room
- the room pressure
- the effects of temperature

See *Table 4* for a summary of ACPH requirements for non-HD sterile compounding areas.

A minimum of 30 total HEPA-filtered ACPH must be supplied to ISO Class 7 rooms:

- The total HEPA-filtered air change rate must be adequate to maintain ISO Class 7 during dynamic operating conditions considering the factors listed above
- At least 15 ACPH of the total air change rate in a room must come from the HVAC through HEPA filters located in the ceiling
- The HEPA-filtered air from the PEC, when added to the HVAC-supplied HEPA-filtered air, increases the total HEPA-filtered ACPH to at least 30 ACPH
- If the PEC is used to meet the minimum total ACPH requirements, the PEC must not be turned off except for maintenance
- Rooms where activity levels are high may require more HEPA-filtered ACPH to maintain ISO Class 7 air quality under dynamic operating conditions
- The ACPH from HVAC, ACPH contributed from the PEC, and the total ACPH must be documented on the certification report

A minimum of 20 total HEPA-filtered ACPH must be supplied to ISO Class 8 rooms:

- The total HEPA-filtered air change rate must be adequate to maintain ISO Class 8 under dynamic operating conditions considering the factors listed above
- At least 15 ACPH of the total air change rate in a room must come from the HVAC through HEPA filters located in the ceiling

- Rooms where activity levels are high may require more HEPA-filtered ACPH to maintain ISO Class 8 air quality under dynamic operating conditions
- The total ACPH must be documented on the certification report

Table 4. Summary of ACPH Requirements for Non-HD Sterile Compounding Areas

Compounding Area	ACPH Requirement
Unclassified SCA	No requirement
ISO Class 7 room(s)	≥30 ACPH
ISO Class 8 room(s)	≥20 ACPH

ESTABLISHING AND MAINTAINING PRESSURE DIFFERENTIALS

Continuous differential positive pressure is required to minimize airflow from an area with lower air-quality classification to an area of higher air-quality classification. In a cleanroom suite, a minimum differential positive pressure of 0.020-inch water column is required between each ISO classified area (e.g., between the buffer room and ante-room). The pressure differential between the ante-room and the unclassified area must not be less than 0.020-inch water column. No pressure differential is required between the SCA and the surrounding area. See ⟨800⟩ for pressure requirements for compounding HD CSPs.

Where pressure differentials are required, a pressure differential monitoring device must be used to continuously monitor the pressure differentials. The quantitative results from the pressure monitoring device must be reviewed and documented at least daily on the days when compounding is occurring.

FACILITIES PREPARING CSPS FROM NONSTERILE STARTING INGREDIENT(S) OR COMPONENT(S)

Weighing, measuring, or otherwise manipulating components could generate airborne chemical particles (e.g., API, added substances). If preparing a Category 2 CSP from nonsterile component(s), presterilization procedures, such as weighing and mixing, must be completed in no worse than an ISO Class 8 environment (e.g., ante-room, buffer room). Presterilization procedures must be performed in single-use containment glove bags, containment ventilated enclosure (CVE) , BSC, or CACI to minimize the risk of airborne contamination. CVE, BSC, or CACI used for presterilization procedures must be certified at least every 6 months.

Presterilization procedures must not adversely affect the required air quality of the SEC as demonstrated during certification under dynamic operating conditions. Personnel must follow the hygiene and garbing requirements as described in *3. Personal Hygiene and Garbing* during presterilization procedures.

4.3 Creating Areas to Achieve Easily Cleanable Conditions

CLEANROOM SUITE

The surfaces of ceilings, walls, floors, doors, door frames, fixtures, shelving, work surfaces, counters, and cabinets in the classified area must be smooth, impervious, free from cracks and crevices, and non-shedding so they can be cleaned and disinfected and to minimize spaces in which microorganisms and other contaminants can accumulate. Surfaces should be resistant to damage by cleaning agents, disinfectants, sporicidal agents, and tools used to clean. Junctures between the ceiling and the walls and between the walls and the floor must be sealed to eliminate cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, the panels must be caulked around each panel to seal them to the support frame.

Walls must be constructed of, or may be covered with, durable material (e.g., epoxy painted walls or heavy-gauge polymer) and the integrity of the surface must be maintained. Panels must be joined together and sealed to each other and the support structure. Floors must include coving to the sidewall, or the juncture between the floor and the wall must be caulked. Classified areas should minimize dust-collecting overhangs such as utility pipes and ledges such as windowsills. If overhangs or ledges are present, they must be easily cleanable. The exterior lens surface of ceiling light fixtures must be smooth, mounted flush, and sealed. Any other penetrations through the ceiling or walls must be sealed.

SCA

The SCA and all surfaces (e.g., walls, floors, counters, and equipment) in the SCA must be clean, uncluttered, and dedicated to compounding. Surfaces in the SCA should be smooth, impervious, free from cracks and crevices, and non-shedding so they can be easily cleaned and disinfected and to minimize spaces in which microorganisms and other contaminants can accumulate. Surfaces should be resistant to damage by cleaning agents, disinfectants, sporicidal agents, and tools used to clean. Dust-collecting overhangs such as utility pipes and ledges such as windowsills should be minimized. If overhangs or ledges are present, they must be easily cleanable.

4.4 Water Sources

The facility where CSPs are prepared must be designed so that activities such as hand hygiene and garbing will not adversely affect the ability of the PEC to function as designed. Sinks should enable hands-free use. Surfaces of sink(s) must be cleaned and disinfected at least daily and a sporicidal agent must be applied at least monthly (see *7.1 Cleaning, Disinfecting,*

and Sporicidal Agents). If compounding is not performed daily, cleaning and disinfecting of the sink must be completed before initiating compounding.

In facilities with a cleanroom suite, the sink used for hand hygiene may be placed either inside or outside of the ante-room. If the sink is located outside of the ante-room, it must be located in a clean space to minimize the risk of bringing in contaminants into the ante-room. If the sink is located inside the ante-room, it may be placed on either the clean side or the dirty side of the ante-room. [NOTE—The order of hand washing and garbing depends on the placement of the sink (see *3.2 Hand Hygiene*).] The buffer room must not contain plumbed water sources [e.g., sink(s), eyewash(es), shower(s), or floor drain(s)]. The ante-room must not contain floor drain(s). If installed, sprinkler systems should be recessed and covered, and the covers should be easily cleanable.

In a facility with an SCA design, the sink must be accessible but located at least 1 meter away from the PEC. The sink must not be located inside the perimeter of the SCA.

4.5 Placement and Movement of Materials

Only furniture, equipment, and other materials necessary for performing compounding activities are permitted in a classified area or SCA, and they should be low-shedding and easily cleaned and disinfected. Their number, design, location, and manner of installation must not impact environmental air quality and must promote effective cleaning and disinfecting. No shipping carton(s) or other corrugated or uncoated cardboard are allowed in a classified area or SCA.

Carts used to transport components or equipment into classified areas must be constructed from nonporous materials with cleanable casters and wheels to promote mobility and ensure ease of cleaning and disinfection. In a cleanroom suite, carts must not be moved from the dirty side to the clean side of the ante-room unless the entire cart, including casters, is cleaned and disinfected.

Only equipment necessary for performing compounding activities is permitted in the PEC. Proper placement of equipment in a PEC must be initially verified by a dynamic airflow smoke pattern test to demonstrate minimal disruption in airflow. The dynamic airflow smoke pattern test must be repeated if equipment is placed in a different location. Equipment and other items used in a classified area or an SCA should not be removed except for calibration, servicing, cleaning, or other activities associated with maintenance. If removed, these items must be cleaned and wiped with sterile 70% IPA or a suitable disinfectant before they are returned to the classified area or inside the perimeter of the SCA.

5. CERTIFICATION AND RECERTIFICATION

Before a compounding area is used to compound either Category 1 or Category 2 CSPs, it must be certified using procedures in the current Controlled Environment Testing Association (CETA) certification guide for *Sterile Compounding Facilities* or an equivalent guideline. Certification indicates that the compounding area is meeting its design and air quality specifications (see *Table 2*). It is important to place special emphasis on certifying the ISO Class 5 areas.

Certification of the classified areas including the PEC must be performed initially, and recertification must be performed at least every 6 months and must include:

- Airflow testing: Airflow testing is performed to determine acceptability of the air velocity and volume, the air exchange rate, and the room pressure differential in doorways between adjacent rooms to ensure consistent airflow and that the appropriate quality of air is maintained under dynamic operating conditions. The ACPH from HVAC, ACPH contributed from the PEC, and the total ACPH must be documented on the certification report.
- HEPA filter integrity testing: HEPA filters must be leak tested at the factory and then leak tested again after installation and as part of recertification.
- Total particle count testing (see *5.1 Total Airborne Particle Sampling*): Total particle count testing must be performed under dynamic operating conditions using calibrated electronic equipment.
- Dynamic airflow smoke pattern test: Smoke pattern tests must be performed for each PEC during dynamic operating conditions to demonstrate unidirectional airflow and sweeping action over and away from the preparation(s).

Classified areas additionally must be recertified if there are changes to the area such as redesign, construction, replacement or relocation of any PEC, or alteration in the configuration of the room that could affect airflow or air quality.

All certification and recertification records must be reviewed by the designated person(s) to ensure that the classified environments meet the minimum requirements in this chapter. The number of personnel present in each PEC and SEC during total particle count tests and dynamic airflow smoke pattern tests must be documented. Records must be maintained in accordance with the requirements in *20. Documentation*.

A corrective action plan must be implemented and documented in response to any out-of-range results. Data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective.

5.1 Total Airborne Particle Sampling

It is imperative that all engineering control equipment function as designed and that the levels of total airborne particles remain within acceptable limits during compounding (see *Table 2*). A monitoring program for total airborne particles must be developed and implemented to measure the performance of the engineering controls that are being used to provide the specified levels of air cleanliness (e.g., in the ISO Class 5 PEC and ISO Class 7 and 8 rooms).

Total airborne particle count testing must be conducted in all classified areas during dynamic operating conditions at least every 6 months.

Total airborne particle sampling sites must be selected in all classified areas. Measurements of total airborne particles must be taken in each PEC at locations where there is greatest risk to the exposed CSPs, containers, and closures. When conducting sampling of the PEC, care should be taken to avoid disturbing the unidirectional airflow within the PEC. All sampling sites and procedures must be described in the facility's SOP. Measurements of total airborne particles in other classified areas, including the buffer room(s) and ante-room(s), should be taken at representative locations that reflect the quality of air in the room(s).

DATA EVALUATION AND ACTION LEVELS

If levels measured during the total air sampling program exceed the criteria in *Table 2* for the ISO classification of the area sampled, the cause must be investigated and corrective action taken and documented. Data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective. Some examples of corrective action include process or facility improvements or HEPA filter replacement or repair. The extent of the investigation should be consistent with the deviation and should include an evaluation of trends.

6. MICROBIOLOGICAL AIR AND SURFACE MONITORING

An effective microbiological air and surface monitoring program provides information on the environmental quality of the compounding area. In addition, an effective microbiological air and surface monitoring program identifies environmental quality trends over time, identifies potential routes of contamination, and allows for implementation of corrective actions to minimize the risk of CSP contamination. Sterile compounding facilities must develop and implement written procedures for microbiological air and surface monitoring (see *17. SOPs*). All microbiological air and surface monitoring procedures, the test results, and the corrective actions must be documented, and the records must be maintained in accordance with the requirements in *20. Documentation*. Data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective.

6.1 General Monitoring Requirements

The microbiological air and surface monitoring program must include 1) viable impact volumetric airborne particulate sampling and 2) surface sampling. The goals of a microbiological air and surface monitoring program are to determine whether contamination is present at unacceptable levels and to assess whether proper personnel practices are being followed, cleaning and disinfecting agents are effective, and environmental quality is maintained.

The microbiological air and surface monitoring program involves the collection and evaluation of samples from various air and surface locations to detect airborne and surface contaminants. The data from microbiological airborne and surface sampling are then used to assess risks for contamination, potential routes of contamination, and the adequacy of cleaning and disinfecting agents and procedures. Regular review of the sampling data must be performed to detect trends and the results of the review must be documented.

In addition, results from microbiological air and surface sampling must be reviewed in conjunction with personnel data (i.e., training records, visual observations, competency assessments) to assess the state of control and to identify potential risks of contamination. Corrective action in response to any adverse findings is required to maintain the necessary environmental quality for preparation of CSPs. Data must also be reviewed following corrective actions to confirm that the actions taken have been effective in achieving the required microbiological air and surface quality levels (see *Table 2*, *Table 5*, and *Table 6*).

Microbiological air and surface monitoring must be performed initially for sterile compounding facilities to establish a baseline level of environmental quality. After initial sampling, the environment in which sterile compounding activities are performed must be monitored according to the minimum frequencies described in this section to ensure that the environment remains suitable for sterile compounding. Evaluating results collected over a period of time can be useful in identifying trends or determining that a significant change has occurred, even when the results fall within the specified levels.

Microbiological air and surface monitoring must be conducted in all classified areas during dynamic operating conditions to confirm that the required environmental quality is maintained. In addition to the specific sampling frequencies described in this section, sampling must be performed in the following circumstances:

- In conjunction with the certification of new facilities and equipment
- After any servicing of facilities or equipment (see *4. Facilities and Engineering Controls*)
- In response to identified problems (e.g., positive growth in sterility tests of CSPs)
- In response to identified trends (e.g., repeated positive gloved fingertip and thumb sampling results, failed media fill testing, or repeated observations of air or surface contamination)
- In response to changes that could impact the sterile compounding environment (e.g., change in cleaning agents)

The microbiological air and surface monitoring program must be clearly described in the facility's SOPs, which must include a diagram of the sampling locations, procedures for collecting samples, frequency of sampling, size of samples (e.g., surface area, volume of air), time of day of sampling in relation to activities in the compounding area, and action levels that will trigger corrective action.

The times and locations of sampling should be carefully selected based on their relationship to the activities performed in the area. It is important to obtain samples from locations that pose the highest possible risk of contamination to the CSP and that are likely to be representative of the conditions throughout the area. To obtain air and surface samples that are representative of the typical compounding conditions at the facility, in all PECs and classified rooms, air sampling must be

conducted during dynamic operating conditions and surface sampling must be performed at the end of a compounding activity or shift, but before the area has been cleaned and disinfected. The monitoring program must be designed and conducted in a manner that minimizes the chance that the sampling itself will contribute to contamination of the CSP or the environment.

It is important that personnel are trained in the proper operation of the air and surface sampling equipment to ensure accurate and reproducible sampling. All active air sampling devices must be serviced and calibrated as recommended by the manufacturer.

6.2 Monitoring Air Quality for Viable Airborne Particles

A monitoring program for viable airborne particles must be developed and implemented to assess microbiological air quality in all classified areas.

VIABLE AIR SAMPLING—TIMING AND LOCATIONS

Volumetric active air sampling of all classified areas using an impaction device must be conducted in each classified area [e.g., ISO Class 5 PEC and ISO Class 7 and 8 room(s)] during dynamic operating conditions at least every 6 months. Air sampling sites must be selected in all classified areas.

SAMPLING PROCEDURES

When conducting sampling of the PEC, care should be taken to avoid disturbing unidirectional airflow. See *Box 6-1* for active air sampling procedures. A general microbiological growth media that supports the growth of bacteria and fungi must be used (e.g., TSA). COAs from the manufacturer must verify that the media meets the expected growth promotion, pH, and sterilization requirements. Samples must be incubated in an incubator at temperatures that will promote growth of bacteria and fungi. The incubator temperature must be monitored during incubation, either manually or by a continuous recording device, and the results must be reviewed and documented as described in the facility's SOPs. The incubator must be placed in a location outside of the sterile compounding area.

Box 6-1. Active Air Sampling Procedures for Viable Airborne Monitoring

- Follow the manufacturer's instructions for operation of the active air sampling device, including placement of media.
- Using the sampling device, test at least 1 cubic meter or 1000 liters of air from each location sampled.
- At the end of the sampling, retrieve the media devices and cover them.
- Invert the media and incubate at 30°–35° for no less than 48 hours. Examine for growth. Record the total number of discrete colonies of microorganisms on each media device as cfu per cubic meter of air on an environmental sampling form based on sample type (i.e., viable air), sample location, and sample date.
- Then incubate the inverted media at 20°–25° for no less than 5 additional days. Examine the media devices for growth. Record the total number of discrete colonies of microorganisms on each media device as cfu per cubic meter of air on an environmental sampling form based on sample type (i.e., viable air), sample location, and sample date.
- Alternatively, to shorten the overall incubation period, two samples may be collected for each sample location and incubated concurrently.
  - Both samples could be TSA or one sample could be TSA and the other fungal media (e.g., malt extract agar (MEA) or sabouraud dextrose agar (SDA)).
  - Incubate each sample in a separate incubator. Incubate one sample at 30°–35° for no less than 48 hours, and incubate the other sample at 20°–25° for no less than 5 days.
    - If fungal media are used as one of the samples, incubate the fungal media sample at 20°–25° for no less than 5 days.
  - Count the total number of discrete colonies of microorganisms on each sample, and record these results as cfu per cubic meter of air.
  - Record the results of the sampling on an environmental sampling form based on sample type (i.e., viable air), and include the sample location, and sample date.

DATA EVALUATION AND ACTION LEVELS

Evaluate cfu counts against the action levels in *Table 5*, and examine counts in relation to previous data to identify adverse results or trends. If two devices of media are collected at a single location, all recovered growth on each must be documented and action levels applied to each media device. If levels measured during the viable air monitoring program exceed the levels in *Table 5* for the ISO classification levels of the area sampled, the cause must be investigated and corrective action must be taken. Data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective. The corrective action plan must be dependent on the cfu count and the microorganism recovered. Some examples of corrective action include process or facility improvements, personnel training, cleaning and disinfecting, or HEPA filter replacement and/or repair. The extent of the investigation should be consistent with the deviation and should include an evaluation of trends. The corrective action plan must be documented. If levels measured during viable air sampling exceed the levels in *Table 5*, an attempt must be made to identify any microorganisms recovered to the genus level (see *Microbial Characterization, Identification, and Strain Typing* ⟨1113⟩) with the assistance of a microbiologist.

Table 5. Action Levels for Viable Airborne Particle Air Sampling[a]

ISO Class	Air Sampling Action Levels [cfu per cubic meter (1000 liters) of air per plate]
5	>1

Table 5. Action Levels for Viable Airborne Particle Air Sampling[a] *(continued)*

ISO Class	Air Sampling Action Levels [cfu per cubic meter (1000 liters) of air per plate]
7	>10
8	>100

[a] Adapted from *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*. U.S. Department of Health and Human Services, FDA, September 2004.

6.3 Monitoring Surfaces for Viable Particles

Surface sampling is an important tool used to assist in maintenance of a suitably controlled environment for compounding CSPs. Surface sampling is useful for evaluating facility cleaning and material handling procedures, work surface cleaning and disinfecting procedures, and personnel competency in work practices such as cleaning and disinfecting of component and/or vial surfaces. All sampling sites and procedures must be described in the facility's SOP.

SURFACE SAMPLING: TIMING AND LOCATIONS

Surface sampling of all classified areas and pass-through chambers connecting to classified areas for microbial contamination must be conducted at least monthly (see *Microbiological Control and Monitoring of Aseptic Processing Environments* ⟨1116⟩). Each classified area must be sampled, including the following:

- The interior of the PEC and the equipment contained in it
- Staging or work area(s) near the PEC
- Frequently touched surfaces

When conducted, surface sampling must be performed at the end of compounding activity or shift, but before the area has been cleaned and disinfected.

SAMPLING PROCEDURES

See *Box 6-2* for the procedures for surface sampling on flat surfaces. Surface sampling devices (e.g., plates, paddles, or slides) containing microbial growth media must be used for sampling flat surfaces. COAs from the manufacturer must verify that the devices meet the expected growth promotion, pH, and sterilization requirements. Surface sampling devices must contain general microbial growth media (e.g., TSA) supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) to neutralize the effects of any residual disinfecting agents. Surface sampling devices must have a raised convex surface. Sterile swabs wetted with sterile water or a sterile neutralizing buffer may be used when sampling irregular surfaces and difficult-to-reach locations, such as crevices, corners, and spaces between surfaces. After sampling, the sampled area must be thoroughly cleaned and disinfected (see *7. Cleaning, Disinfecting, and Applying Sporicidal Agents in Compounding Areas*).

Samples must be incubated in a calibrated incubator at temperatures that will promote growth of bacteria and fungi. The incubator temperature must be monitored during incubation, either manually or by a continuous recording device, and the results must be reviewed and documented. The incubator must be placed in a location outside of the sterile compounding area.

Box 6-2. Surface Sampling Procedures

- Remove the cover from the surface sampling device. Using a rolling motion, firmly press the media surface onto the surface to be sampled. The surface sampling device will leave a residue of growth media on the sample site. After sampling, remove the residue from the surface using sterile 70% IPA.
- Cover each surface sampling device. Store media devices during incubation to prevent condensate from dropping onto the agar and affecting the accuracy of the cfu reading (e.g., invert plates).
- Incubate the surface sampling devices at 30°–35° for no less than 48 hours. Examine for growth. Record the total number of discrete colonies of microorganisms on each device as cfu per sample on an environmental sampling form based on sample type (i.e., surface), sample location, and sample date.
- Incubate the surface sampling device at 20°–25° for no less than 5 additional days. Examine the device for growth. Record the total number of discrete colonies of microorganisms on each media device (cfu per sample) on the environmental sampling record based on sample type (i.e., surface), sample location, and sample date.
- Alternatively, to shorten the overall incubation period, two samples may be collected for each sample location and incubated concurrently.
  - Both samples could be TSA or one sample could be TSA and the other fungal media (e.g., MEA or SDA).
  - Incubate each sample in a separate incubator. Incubate one sample at 30°–35° for no less than 48 hours, and incubate the other sample at 20°–25° for no less than 5 days.
    - If fungal media are used as one of the samples, incubate the fungal media sample at 20°–25° for no less than 5 days.
  - Count the total number of discrete colonies of microorganisms on each sample, and record these results as cfu per sample.
  - Record the results of the sampling on an environmental sampling form based on sample type (i.e., surface), and include the sample location, and sample date.

DATA EVALUATION AND ACTION LEVELS

Evaluate cfu counts against the action levels in *Table 6*, and examine counts in relation to previous data to identify adverse results or trends. If two devices were collected at a single location, all recovered growth on each must be documented and action levels are applied to each device of media. If levels measured during surface sampling exceed the levels in *Table 6* for the ISO classification levels of the area sampled, the cause must be investigated and corrective action must be taken. Data

collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective. The corrective action plan must be dependent on the cfu count and the microorganism recovered. Some examples of corrective action include process or facility improvements, personnel training, cleaning and disinfecting, or HEPA filter replacement and/or repair. The extent of the investigation should be consistent with the deviation and should include an evaluation of trends. The corrective action plan must be documented. If levels measured during surface sampling exceed the levels in *Table 6*, an attempt must be made to identify any microorganism recovered to the genus level (see ⟨1113⟩) with the assistance of a microbiologist.

Table 6. Action Levels for Surface Sampling

ISO Class	Surface Sampling Action Levels (cfu/device or swab)
5	>3
7	>5
8	>50

7. CLEANING, DISINFECTING, AND APPLYING SPORICIDAL AGENTS IN COMPOUNDING AREAS

Cleaning, disinfecting, and applying a sporicidal agent are important because surfaces in classified areas and SCA are a potential source of microbial contamination of CSPs. The process of cleaning involves removing organic and inorganic materials from surfaces, usually with a manual or mechanical process and a cleaning agent. The process of disinfecting involves destruction of microorganisms, usually with a chemical agent.

Surfaces must be cleaned prior to being disinfected unless an Environmental Protection Agency (EPA)-registered (or equivalent) one-step disinfectant cleaner is used to accomplish both the cleaning and disinfection in one step. A sporicidal agent must be applied to destroy bacterial and fungal spores. Some EPA-registered (or equivalent) one-step disinfectant cleaners may have sporicidal properties. After cleaning and disinfecting or the application of a one-step disinfectant cleaner, or the application of a sporicidal agent in a PEC, apply sterile 70% IPA to remove any residue. See *Table 7* for a summary of the purposes of the cleaning, disinfectant, and sporicidal agents.

Table 7. Purpose of Cleaning, Disinfecting, and Sporicidal Agents

Type of Agent	Purpose
Cleaning agent	An agent used for the removal of residues (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.
Disinfectant	A chemical or physical agent used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria.
Sporicidal agent	A chemical or physical agent that destroys bacterial and fungal spores when used at a sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

Cleaning and disinfecting surfaces and applying a sporicidal agent must occur at the minimum frequencies specified in *Table 8* or, if compounding is not performed daily, cleaning and disinfecting must be completed before initiating compounding.

All cleaning and disinfecting activities must be performed by trained and appropriately garbed personnel using facility-approved agents and procedures, which must be described in written SOPs. Personnel must be trained if there are any changes in the cleaning and disinfecting procedures. Cleaning must be performed in the direction of clean to dirty areas. The frequency, method(s), and location(s) of cleaning, disinfecting, and sporicidal agent use must be established in written SOPs, in accordance with the manufacturer's instructions, and must be followed by all cleaning personnel. The manufacturer's directions or published data for the minimum contact time must be followed for the cleaning, disinfecting, and sporicidal agents used. When sterile 70% IPA is used, it must be allowed to dry. All cleaning, disinfecting, and application of sporicidal agents must be documented according to facility SOPs.

Table 8. Minimum Frequency for Cleaning and Disinfecting Surfaces and Applying Sporicidal Agents in Classified Areas and within the Perimeter of the SCA[a]

Site	Cleaning	Disinfecting	Applying Sporicidal
PEC(s) and equipment inside the PEC(s)	Equipment and all interior surfaces of the PEC daily and when surface contamination is known or suspected.	• Equipment and all interior surfaces of the PEC daily and when surface contamination is known or suspected. • Apply sterile 70% IPA to the horizontal work surface at least every 30 minutes if the compounding process takes 30 minutes or less. If the compounding process takes more than 30 minutes, compounding must not be disrupted and the work surface of the PEC must be disinfected immediately after compounding.	Monthly
Removable work tray of the PEC	• Work surface of the tray daily • All surfaces and the area underneath the work tray monthly	• Work surface of the tray daily • All surfaces and the area underneath the work tray monthly	• Work surface of the tray monthly • All surfaces and the area underneath the work tray monthly
Pass-through(s)	Daily	Daily[b]	Monthly
Work surface(s) outside the PEC	Daily	Daily[b]	Monthly
Floor(s)	Daily	Daily[b]	Monthly
Wall(s), door(s), and door frame(s)	Monthly	Monthly[b]	Monthly
Ceiling(s)[c]	Monthly	Monthly[b]	Monthly
Storage shelving and bins	Monthly	Monthly[b]	Monthly
Equipment outside the PEC(s)	Monthly	Monthly[b]	Monthly

[a] Cleaning of sinks is described in *4.4 Water Sources*.
[b] Many disinfectants registered by the EPA are one-step cleaning and disinfecting agents, which means that the disinfectant has been formulated to be effective in the presence of light to moderate soiling without a separate cleaning step.
[c] Ceilings of the SCA are required to be cleaned, disinfected, and applied with sporicidal agent only when visibly soiled and when surface contamination is known or suspected.

7.1 Cleaning, Disinfecting, and Sporicidal Agents

Cleaning and disinfecting agents must be selected and used with careful consideration of compatibilities, effectiveness, and user safety. Considerations when selecting and using disinfectants include their antimicrobial activity, inactivation by organic matter, residue, shelf life, preparation requirements of the agent, and suitability for surfaces being disinfected. After the disinfectant or sporicidal agent is applied to the surface, the agent must be allowed to dwell for the minimum contact time specified by the manufacturer.

7.2 Cleaning Supplies

All cleaning supplies (e.g., wipers, sponges, and mop heads) with the exception of tool handles and holders must be low-lint. Wipers, pads, and mop heads should be disposable. If disposable cleaning supplies are used, they must be discarded after each cleaning activity. Reusable cleaning tools must be made of cleanable materials (e.g., no wooden handles) and must be cleaned and disinfected before and after each use. Reusable cleaning tools must be dedicated for use in the classified areas or SCA and must not be removed from these areas except for disposal. They must be discarded as determined based on the condition of the tools. Dispose of cleaning supplies used in the classified areas and SCAs in a manner that minimizes the potential for dispersing contaminants into the air (e.g., with minimal agitation, away from work surfaces).

7.3 Cleaning, Disinfecting, and Applying Sporicidal Agents in the PEC

Clean, disinfect, and apply a sporicidal agent to equipment and all interior surfaces in the PEC at the minimum frequencies specified in *Table 8*. See *Box 7-1* and *Box 7-2* for procedures for cleaning, disinfecting, and applying a sporicidal agent in the PEC.

Box 7-1. Procedures for Cleaning and Disinfecting the PEC

- Remove visible particles, debris, or residue with an appropriate solution (e.g., *Sterile Water for Injection* or *Sterile Water for Irrigation*) using sterile, low-lint wipers.
- Using a low-lint wiper, apply a cleaning agent, followed by a disinfecting agent, or apply an EPA-registered (or equivalent) one-step disinfectant cleaner to equipment and all interior surfaces of the PEC.
- Ensure the contact time specified by the manufacturer is achieved.
- Using a low-lint wiper, apply sterile 70% IPA to equipment and all interior surfaces in the PEC.
- Allow the surface to dry completely before beginning compounding.

Box 7-2. Procedures for Applying a Sporicidal Agent in the PEC

- Remove visible particles, debris, or residue with an appropriate solution (e.g., *Sterile Water for Injection* or *Sterile Water for Irrigation*) using sterile, low-lint wipers.
- After cleaning and disinfecting (*Box 7-1*), apply the sporicidal agent using a low-lint wiper to all surfaces and the area underneath the work tray. If the sporicidal agent is an EPA-registered (or equivalent) one-step disinfectant sporicidal cleaner, separate cleaning and disinfecting steps are not required.
- Ensure the contact time specified by the manufacturer is achieved.
- Using a low-lint wiper, apply sterile 70% IPA to all interior surfaces, including underneath the work tray.
- Allow the surface to dry completely before beginning compounding.

8. INTRODUCING ITEMS INTO THE SEC AND PEC

8.1 Introducing Items into the Cleanroom Suite and SCAs

Before any item is introduced into the clean side of ante-room(s), placed into pass-through(s), or brought inside the perimeter SCA and when packaging integrity will not be compromised, it must be wiped with a sporicidal agent, EPA-registered disinfectant, or sterile 70% IPA using low-lint wipers by personnel wearing gloves. If an EPA-registered disinfectant or sporicidal agent is used, the agent must be allowed to dwell for the minimum contact time specified by the manufacturer. If sterile 70% IPA is used, it must be allowed to dry. The wiping procedure must not render the product label unreadable.

8.2 Introducing Items into the PEC

Just before any item is introduced into the PEC, it must be wiped with sterile 70% IPA using low-lint wipers and allowed to dry before use. When sterile items are received in sealed containers designed to keep them sterile until opening, the sterile items may be removed from the covering as the supplies are introduced into the ISO Class 5 PEC without the need to wipe the individual sterile supply items with sterile 70% IPA. The wiping procedure must not render the product label unreadable.

8.3 Use of Sterile 70% IPA on Critical Sites within the PEC

Critical sites (e.g., vial stoppers, ampule necks, and intravenous bag septums) must be wiped with sterile 70% IPA in the PEC to provide both chemical and mechanical actions to remove contaminants. The sterile 70% IPA must be allowed to dry before entering or puncturing stoppers/septums or breaking the necks of ampules.

9. EQUIPMENT, SUPPLIES, AND COMPONENTS

9.1 Equipment

PECs are described in *4.2 Facility Design and Environmental Controls, Types of PECs and Placement*. Other equipment used in compounding CSPs [e.g., automated compounding devices (ACDs) and balances] should be of suitable composition such that the surfaces that contact components are not reactive or sorptive. Equipment that must be brought into classified areas must be wiped with a sporicidal agent, EPA-registered disinfectant, or sterile 70% IPA using low-lint wipers.

Equipment must be placed in a manner that facilitates sterile compounding operations. The equipment must be capable of operating properly and within required performance parameters. Compounding personnel must follow established SOPs for the calibration, maintenance, cleaning, and use of the equipment based on the manufacturer's recommendations. Personnel must maintain records from equipment calibration, verification, and maintenance in accordance with the requirements in *20. Documentation*.

ACDs and other similar equipment are designed to assist in the compounding of preparations by delivering specific volumes of solution(s) automatically under computerized control.

Before using ACDs or other similar equipment, compounding personnel must conduct an accuracy assessment before the first use and again each day the equipment is used to compound CSPs. The precision of the equipment can be monitored based on an assessment of day-to-day variations in its accuracy measures. Compounding personnel must maintain a daily record of the accuracy measurements on the days the equipment is in use. Corrective actions must be implemented if accuracy measurements are outside the manufacturer's specification.

9.2 Supplies

Supplies (e.g., beakers, utensils, needles, syringes, filters, and tubing sets) should be of suitable composition such that the surfaces that contact components are not reactive or sorptive. Supplies in direct contact with the CSP must be sterile and depyrogenated.

9.3 Components

Compounding personnel must follow facility SOPs, which must address the selection, receipt, evaluation, handling, storage, and documentation of all CSP components, including all ingredients, containers, and closures.

COMPONENT SELECTION

Conventionally manufactured sterile products should be used when available and appropriate for the intended CSP.
APIs:

- Must comply with the criteria in the *USP–NF* monograph, if one exists
- Must have a COA that includes the specifications and test results and shows that the API meets the specifications
- Must be obtained from an FDA-registered facility

All components other than APIs:

- Must comply with the criteria in the *USP–NF* monograph, if one exists
- Must be accompanied by documentation (e.g., COA, labeling) that includes the specifications and test results and shows that the component meets the specifications
- Should be obtained from an FDA-registered facility
    - If it cannot be obtained from an FDA-registered facility, the designated person(s) must select an acceptable and reliable source (see *Good Distribution Practices for Bulk Pharmaceutical Excipients* ⟨1197⟩). The compounding facility must establish the identity, strength, purity, and quality of the ingredients obtained from that supplier by reasonable means. Reasonable means may include, but is not limited to, visual inspections, evaluation of a COA supplied by the manufacturer, and/or verification by analytically testing a sample to determine conformance with the COA or other specifications.

All APIs and other components used must be evaluated for suitability for use in sterile drug preparation. Components labeled with "not for pharmaceutical use", "not for injectable use", "not for human use" or an equivalent statement must not be used to compound for these purposes.

Each lot of commercially available sterile, depyrogenated containers and container–closure systems must be accompanied by a COA or other documentation showing conformance with established specifications (i.e., sterility and depyrogenation requirements). If sterilization and depyrogenation of supplies or container–closure systems are performed on site, the efficacy of each process must be established and documented (see *Sterilization of Compendial Articles* ⟨1229⟩).

COMPONENT RECEIPT

Upon receipt of each lot of a component, the external packaging must be examined for evidence of deterioration and other aspects of unacceptable quality. Facility personnel must verify the labeling and condition of the component [e.g., whether the outer packaging is damaged and whether temperature-sensing indicators show that the component has been exposed to excessive temperature(s)].

Any component found to be of unacceptable quality must be promptly rejected, clearly labeled as rejected, and segregated to prevent use before appropriate disposal. Any other lots of that component from that vendor must be examined to determine whether other lots have the same defect.

The date of receipt by the compounding facility must be clearly marked on each API or added substance package that lacks a vendor expiration date. Packages of components (i.e., API and added substances) that lack a vendor's expiration date must be assigned a conservative expiration date, not to exceed 1 year after receipt by the compounding facility.

COMPONENT EVALUATION BEFORE USE

Compounding personnel must ascertain before use that components for CSPs are of the correct identity, appropriate quality, within expiry date, and have been stored under appropriate conditions. The following information should be used to make this determination: prescription or medication order, compounding record, master formulation record (if used), vendor labels, COAs of API(s) and other component(s), product labeling of conventionally manufactured sterile products, labeling of CSPs, and documentation of the compounding facility storage conditions and practices.

All components must be re-inspected before use. All packages must be re-inspected to detect container breaks, looseness of the cap or closure, and deviation from the expected appearance, aroma, and texture of the contents that might have occurred during storage. Sterile container–closures must be visually re-inspected to ensure that they are free from defects that could compromise sterility and are otherwise suitable for their intended use.

Any component found to be of unacceptable quality must be promptly rejected, clearly labeled as rejected, and segregated to prevent use before appropriate disposal. Any other lots of that component from that vendor must be examined to determine whether other lots have the same defect.

COMPONENT HANDLING AND STORAGE

All components must be handled and stored in a manner that prevents contamination, mix-ups, and deterioration. Components must be stored in closed containers under temperature, humidity, and lighting conditions consistent with those indicated in official monographs or specified by the suppliers and/or manufacturer.

Personnel must monitor temperature in the area(s) where components are stored either manually at least once daily on days that the facility is open or by a continuous temperature recording device to determine whether the temperature remains within the appropriate range. The results of the temperature readings must be documented on a temperature log or stored in the continuous recording device, and must be retrievable. All monitoring equipment must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer.

10. STERILIZATION AND DEPYROGENATION

When selecting the sterilization method for CSPs prepared from one or more nonsterile starting components or using nonsterile supplies or devices, personnel must take into consideration the nature of the component(s), their physical and chemical properties, and the intended container–closure system. The sterilization method used must sterilize the CSP without degrading its physical and chemical stability (e.g., affecting its strength, purity, and quality) or the packaging integrity. See also the ⟨1229⟩ family of chapters.

The following must be considered when selecting an appropriate sterilization method:

- Terminal sterilization (e.g., dry heat, steam, or irradiation) is the preferred method unless the specific CSP or container–closure system cannot tolerate terminal sterilization.
- Steam sterilization is not an option if moisture, pressure, or the temperatures used would degrade the CSP or if there is insufficient moisture to sterilize the CSP within the final, sealed container–closure system.
- Filtration is not an option when compounding a suspension if the suspended drug particles are removed by the filter being used.

CSPs that are terminally sterilized (e.g., dry heat, steam, or irradiation) must use a process intended to achieve a probability of a nonsterile unit (PNSU) of 10^{-6}. [NOTE—This is also called the sterility assurance level (SAL).] A PNSU of 10^{-6} is equivalent to a probability that 1 unit in a million is nonsterile. A PNSU value cannot be applied to CSPs that are aseptically filled into a sterile container following sterilization by filtration because sterilization by filtration is not terminal sterilization.

Injectable compounded preparations that contain nonsterile components or that come into contact with nonsterile devices (e.g., containers, tubing) during any phase of the compounding procedure must be sterilized within 6 hours after completing the preparation to minimize the generation of bacterial endotoxins in CSPs.

A description of the terminal sterilization and depyrogenation process, including the temperature, pressure (if applicable), duration, permissible load conditions for each cycle, and the use of biological indicators and endotoxin challenge vials (ECVs) must be included in the facility's SOPs.

SOPs must include training and competency of personnel on all sterilization methods and equipment used by the facility. In addition, the SOPs must include a schedule and method for establishing and verifying the effectiveness of the terminal sterilization and depyrogenation methods selected, as well as the methods for maintaining and cleaning the sterilizing and depyrogenation equipment.

10.1 Depyrogenation

See *Dry Heat Depyrogenation* ⟨1228.1⟩. Dry heat depyrogenation must be used to render glassware, metal, and other thermostable containers and components pyrogen-free. Depyrogenation processes typically operate at a range of temperatures, from approximately 170° up to about 400°, depending on the exposure time (e.g., a cycle might hold the items at 250° for 30 minutes to achieve sterility and depyrogenation). The duration of the exposure period must include sufficient time for the items to reach the depyrogenation temperature. The items must remain at the depyrogenation temperature for the duration of the depyrogenation period.

The effectiveness of the dry heat depyrogenation cycle must be established initially and verified annually using ECVs to demonstrate that the cycle is capable of achieving a ≥3-log reduction in endotoxins (see *Bacterial Endotoxins Test* ⟨85⟩). The effectiveness of the depyrogenation cycle must be re-established if there are changes to the depyrogenation cycle described in SOPs (e.g., changes in load conditions, duration, temperature). This verification must be documented.

Items that are not thermostable must be depyrogenated by rinsing with sterile, non-pyrogenic water (e.g., *Sterile Water for Injection*, *Sterile Water for Irrigation*) and then thoroughly drained or dried immediately before use in compounding.

10.2 Sterilization by Filtration

See *Sterilizing Filtration of Liquids* ⟨1229.4⟩. Sterilizing filters must be sterile, depyrogenated, have a nominal pore size of 0.22 µm or smaller, and include labeling for pharmaceutical use. Sterilizing filters with labeling that states "for laboratory use only" or an equivalent statement must not be used for compounding CSPs. Sterilizing filters must be certified by the manufacturer to retain at least 10^7 microorganisms of a strain of *Brevundimonas diminuta* per square centimeter of upstream filter surface area under conditions similar to those in which the CSPs will be filtered (i.e., pressure, flow rate, and volume filtered).

The designated person(s) must ensure—from available published information, from supplier documentation, or through direct challenge (e.g., filtering the CSP)—that the filters 1) are chemically and physically compatible with all ingredients in

the CSP (e.g., water-miscible alcohols may damage filter integrity); 2) are chemically stable at the pressure and temperature conditions that will be used; and 3) have enough capacity to filter the required volumes. The filter dimensions and the CSP to be sterilized by filtration should permit the sterilization process to be completed without the need for replacement of the filter during the process. Filter units used to sterilize CSPs must be subjected to the manufacturers' recommended integrity testing, such as a post-use bubble point test. If multiple filters are required for the compounding process, each of the filters must pass a filter-integrity test.

When CSPs are known to contain excessive particulate matter, a prefiltration step must be performed using a filter of larger nominal pore size (e.g., 1.2 µm) or a separate filter of larger nominal pore size should be placed upstream of (i.e., prior to) the sterilizing filter to remove gross particulate contaminants before the CSP is passed through the sterilizing-grade filter. Excessive particulate matter requiring a prefiltration step could potentially be a signal of an inappropriate formulation, and therefore the formulation and the process should be assessed and, if necessary, modified. CSPs that were prepared using a filter that failed integrity tests must be discarded or, after investigating the cause of the failure and selection of an appropriate filter, refiltered for sterilization no more than one additional time.

10.3 Sterilization by Steam Heat

Temperatures used to achieve sterilization by steam heat are lower than those used to achieve depyrogenation. The process of thermal sterilization using saturated steam under pressure (i.e., autoclaving) is the preferred method for terminal sterilization of aqueous CSPs in their final, sealed container–closure system (see *Steam Sterilization by Direct Contact* ⟨1229.1⟩). Steam sterilization is not an option if moisture, pressure, or the temperatures used would degrade the CSP.

To achieve sterility when steam sterilization is used, all materials must be directly exposed to steam under adequate pressure for the length of time necessary, as determined by use of appropriate biological indicators, to render the items sterile (e.g., between 20 and 60 minutes at 121° saturated steam under a pressure of 15 psi, depending on the volume or size of the CSP being sterilized). The duration of the exposure period must include sufficient time for the entire contents of the CSP and other items to reach the sterilizing temperature. The CSP and other items must remain at the sterilizing temperature for the duration of the sterilization period.

CSPs must be placed in the autoclave to allow steam to reach the CSPs without entrapment of air. Flat, stainless steel trays with low sides or ventilated bottoms will permit steam contact. When preparing items for steam sterilization that must be wrapped, wrap them in low-lint protective fabric or paper or sealed in envelopes that will permit steam penetration and that are designed to prevent post-sterilization microbial contamination. For CSPs, immediately before filling ampules and vials that will be steam sterilized, solutions must be passed through a filter with a nominal pore size of not larger than 1.2 µm for removal of particulate matter.

Sealed containers must be able to generate steam internally. Stoppered and crimped empty vials must contain a small amount of sterile water to generate steam. Deep containers, such as beakers and graduated cylinders, must be inverted or placed on their sides at a downward-sloping angle to minimize air entrapment and to facilitate condensate drainage, or must have a small amount of sterile water placed in them before steam sterilization. Porous materials and those items with occluded pathways (e.g., tubing) must only be sterilized by steam if the autoclave chamber has suitable cycles for dry goods, such as a pre-vacuum process to remove air before steam is sent into the chamber. Elastomeric closures and many other dry goods will need a drying cycle after steam exposure to remove condensed or absorbed moisture.

The effectiveness of steam sterilization must be verified and documented with each sterilization run or load by using appropriate biological indicators, such as spores of *Geobacillus stearothermophilus*, ATCC 12980, ATCC 7953, or equivalent (see *Biological Indicators for Sterilization* ⟨1229.5⟩), and other confirmation methods such as physicochemical indicators and integrators (see *Physicochemical Integrators and Indicators for Sterilization* ⟨1229.9⟩).

The steam supplied must be free of contaminants and generated using water per the manufacturer's recommendation. A calibrated data recorder or chart must be used to monitor each cycle and to examine for cycle irregularities (e.g., deviations in temperature or pressure). The date, run, and load numbers of the steam sterilizer used to sterilize a CSP must be documented in the compounding record.

10.4 Sterilization by Dry Heat

Dry heat may be used for those items that cannot be sterilized by steam or other means, when either the moisture would damage the material or the wrapping material is impermeable (see *Dry Heat Sterilization* ⟨1229.8⟩). Sterilization by dry heat requires higher temperatures and longer exposure times than sterilization by steam. The duration of the exposure period must include sufficient time for the entire contents of CSPs and other items to reach the sterilizing temperature. The CSP and other items must remain at the sterilizing temperature for the duration of the sterilization period.

Dry heat sterilization is usually performed in an oven designed for sterilization at a temperature of 160° or higher. If lower temperatures are used, they must be shown to achieve effective sterilization (see *Dry Heat Sterilization* ⟨1229.8⟩*, Validation of Dry Heat Sterilization, Biological Indicators*).

Heated air must be evenly distributed throughout the chamber, which is typically accomplished by an air blower. The calibrated oven must be equipped with temperature controls and a timer. During sterilization, sufficient space must be left between materials to allow for circulation of the hot air. A calibrated data recorder or chart must be used to monitor each cycle and the data must be reviewed to identify cycle irregularities (e.g., deviations in temperature or exposure time).

The effectiveness of the dry heat sterilization method must be verified and documented with each sterilization run or load using appropriate biological indicators such as spores of *Bacillus atrophaeus*, ATCC 9372 (see ⟨1229.5⟩), and other confirmation methods (e.g., temperature-sensing devices). The date, run, and load numbers of the dry heat oven used to sterilize a CSP must be documented in the compounding record.

11. MASTER FORMULATION AND COMPOUNDING RECORDS

11.1 Creating Master Formulation Records

A Master Formulation Record is a detailed record of procedures that describes how the CSP is to be prepared. A Master Formulation Record must be created for CSPs prepared for more than 1 patient and for CSPs prepared from nonsterile ingredient(s). Any changes or alterations to the Master Formulation Record must be approved and documented according to the facility's SOP. *Box 11-1* lists the information that must be included in a Master Formulation Record.

Box 11-1. Master Formulation Records

A Master Formulation Record must include at least the following information:

- Name, strength or activity, and dosage form of the CSP
- Identities and amounts of all ingredients
- Type and size of container–closure system(s)
- Complete instructions for preparing the CSP, including equipment, supplies, a description of the compounding steps, and any special precautions
- Physical description of the final CSP
- BUD and storage requirements
- Reference source to support the stability of the CSP
- Quality control (QC) procedures (e.g., pH testing, filter integrity testing)
- Other information as needed to describe the compounding process and ensure repeatability (e.g., adjusting pH and tonicity, sterilization method (e.g., steam, dry heat, irradiation, or filter)

11.2 Creating Compounding Records

A Compounding Record documents the compounding of each CSP. A Compounding Record must be created for all CSPs. The Compounding Record must be created to document the compounding process or repackaging process. A prescription or medication order or label may serve as the compounding record. If an ACD, workflow management system, or other similar equipment is used, the required information in the compounding record may be stored electronically as long as it is retrievable and contains the required information (see *Box 11-2*). A Master Formulation Record can serve as the basis for preparing the Compounding Record. For example, a copy of the Master Formulation Record can be made that contains spaces for recording the information needed to complete the Compounding Record. *Box 11-2* lists the information that must be included in a Compounding Record.

Box 11-2. Compounding Records

Compounding Records must include at least the following information:

- Name, strength or activity, and dosage form of the CSP
- Date and time of preparation of the CSP
- Assigned internal identification number (e.g., prescription, order, or lot number)
- A method to identify the individuals involved in the compounding process and verifying the final CSP
- Name of each component
- Vendor, lot number, and expiration date for each component for CSPs prepared for more than 1 patient and for CSPs prepared from nonsterile ingredient(s)
- Weight or volume of each component
- Strength or activity of each component
- Total quantity compounded
- Assigned BUD and storage requirements
- Results of QC procedures (e.g., visual inspection, filter integrity testing, pH testing)

If applicable, the Compounding Record must also include:

- Master Formulation Record reference for the CSP
- Calculations made to determine and verify quantities and/or concentrations of components

12. RELEASE INSPECTIONS AND TESTING

All release testing procedures (e.g., visual inspections and testing) must be included in the facility's documentation (see *11. Master Formulation and Compounding Records* and *17. SOPs*). Any out-of-specification results must be investigated, and a corrective action plan must be implemented and documented as part of the quality assurance (QA) and QC program (see *18. Quality Assurance and Quality Control*).

12.1 Visual Inspection

At the completion of compounding, before release and dispensing, the CSP must be visually inspected to determine whether the physical appearance of the CSP is as expected (e.g., it is inspected for evidence of inappropriate visible particulates or other foreign matter, discoloration, or other defects). The CSP must be visually inspected to confirm that the CSP and its labeling match the prescription or medication order. The inspection also must include a visual inspection of container–closure integrity (e.g., checking for leakage, cracks in the container, or improper seals). CSPs with observed

defects must be discarded, or marked and segregated from acceptable units in a manner that prevents them from being released or dispensed.

When a CSP will not be released or dispensed on the day of preparation, a visual inspection must be conducted immediately before it is released or dispensed to make sure that the CSP does not exhibit any defects, such as precipitation, cloudiness, or leakage, which could develop during storage. A CSP with such defects must be immediately discarded, or marked and segregated from acceptable units in a manner that prevents it from being released or dispensed. Any defect may indicate sterility or stability problems, which should be investigated to determine the cause (see *18. Quality Assurance and Quality Control*).

12.2 Sterility Testing

Sterility testing is not required for Category 1 CSPs (see *Table 10*). If a Category 2 CSP is assigned a BUD that requires sterility testing (see *Table 11*), the testing must be performed according to ⟨71⟩ or a validated alternative method (see *Validation of Alternative Microbiological Methods* ⟨1223⟩) that is non-inferior to ⟨71⟩ testing.

If sterility testing is performed, the minimum quantity of each container to be tested for each media is specified in *Sterility Tests* ⟨71⟩, *Table 2*, and the number of containers required to be tested in relation to the batch size is specified in *Sterility Tests* ⟨71⟩, *Table 3*, except as described below.

If the number of CSPs to be compounded in a single batch is less than the number of CSPs needed for testing as specified in *Sterility Tests* ⟨71⟩, *Table 3*, additional units must be compounded to be able to perform sterility testing as follows:

- If between 1 and 39 CSPs are compounded in a single batch, the sterility testing must be performed on a number of units equal to 10% of the number of CSPs prepared, rounded up to the next whole number. For example:
  - If 1 CSP is compounded, 10% of 1 rounded up to the next whole number would indicate that 1 additional CSP must be prepared for sterility testing.
  - If 39 CSPs are compounded, 10% of 39 rounded up to the next whole number would indicate that 4 additional CSPs must be prepared for sterility testing.

If more than 40 CSPs are prepared in a single batch, the sample sizes specified in *Sterility Tests* ⟨71⟩, *Table 3* must be used.

If sterility testing is performed according to ⟨71⟩, a *Sterility Tests* ⟨71⟩*, Method Suitability Test* must be performed to ensure that contamination can be recovered. If performing sterility testing according to ⟨71⟩, the *Sterility Tests* ⟨71⟩*, Test for Sterility of the Product to Be Examined, Membrane Filtration* method is the method of choice when the CSP formulation permits. The preferred alternative is the ⟨71⟩*, Test for Sterility of the Product to be Examined, Direct Inoculation of the Culture Medium* method. If an alternative method is used for sterility testing, the method must be validated (see ⟨1223⟩) and demonstrated to be suitable for that CSP formulation.

Sterility tests resulting in failures must prompt an investigation into the possible causes and must include identification of the microorganism, as well as an evaluation of the sterility testing procedure, compounding facility, process, and/or personnel that may have contributed to the failure. The source(s) of the contamination, if identified, must be corrected, and the facility must determine whether the conditions causing the sterility failure affect other CSPs. The investigation and resulting corrective actions must be documented.

12.3 Bacterial Endotoxins Testing

Category 2 injectable CSPs made from one or more nonsterile component(s) and assigned a BUD that requires sterility testing (see *Table 11*) must be tested to ensure that they do not contain excessive bacterial endotoxins (see ⟨85⟩). Category 2 injectable CSPs made from one or more nonsterile component(s) and assigned a BUD that does not require sterility testing should be tested for bacterial endotoxins. In the absence of a bacterial endotoxins limit in an official monograph or other CSP formula source, the CSP must not exceed the endotoxins limit calculated as described in ⟨85⟩ for the appropriate route of administration for humans. CSPs for non-human species must not exceed the endotoxin reference limits calculated as described in ⟨85⟩ based on the weight of the target animal unless a different limit is scientifically supported. CSPs administered epidurally should have the same endotoxin limit as that of intrathecally administered CSPs. See also *Guidelines on the Endotoxins Test* ⟨1085⟩.

13. LABELING

CSPs must be labeled with legible identifying information to prevent errors during storage, dispensing, and use. The term labeling designates all labels and other written, printed, or graphic matter on the immediate container or on, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term label designates that part of the labeling that is on the immediate container. See *Labeling* ⟨7⟩.

The label on the immediate container of the CSP must, at a minimum, display prominently and legibly the following information:

- Assigned internal identification number (e.g., barcode, prescription, order, or lot number)
- Active ingredient(s) and their amounts, activities, or concentrations
- Storage conditions if other than controlled room temperature
- BUD
- Route of administration

- Total amount or volume if it is not obvious from the container
- If it is a single-dose container, a statement stating such when space permits
- If it is a multiple-dose container, a statement stating such

The labeling on the CSP should indicate that the preparation is compounded.

If the CSP is to be sent outside of the facility in which it was compounded, the labeling must include the contact information of the compounding facility. The labeling of the CSP must also provide any applicable special handling instructions or warning statements.

Labeling procedures must be followed as described in the facility's SOPs to prevent labeling errors and CSP mix-ups. The label of the CSP must be verified to ensure that it conforms with the:

1. Prescription or medication order;
2. Master Formulation Record, if required (see *11.1 Creating Master Formulation Records*); and
3. Compounding Record (see *11.2 Creating Compounding Records*)

All labels must also comply with laws and regulations of the applicable regulatory jurisdiction.

14. ESTABLISHING BEYOND-USE DATES

14.1 Terminology

Each CSP label must state the BUD, which is the date, or the hour and date, beyond which the preparation must not be used and must be discarded. The BUD is determined from the date/time that preparation of the CSP is initiated. The BUD is not intended to limit the time during which the CSP is administered (e.g., infused).

BUDs and expiration dates are not the same. An expiration date identifies the time during which a conventionally manufactured product, API, or added substance can be expected to meet the requirements of a compendial monograph, if one exists, or maintain expected quality provided it is kept under the specified storage conditions. The expiration date limits the time during which the conventionally manufactured product, API, or added substance may be dispensed or used (see *Labeling ⟨7⟩, Labels and Labeling for Products in Other Categories, Expiration Date and Beyond-Use Date*). Expiration dates are assigned by manufacturers based on analytical and performance testing of the sterility, chemical and physical stability, and packaging integrity of the product. Expiration dates are specific for a particular formulation in its container and at stated exposure conditions of illumination and temperature. See *Table 9* for a summary of terms.

Table 9. Summary of Terms

Term	Definition	Applicability
BUD	Either the date, or hour and date, after which a CSP must not be used. The BUD is determined from the date/time that preparation of the CSP is initiated.	Applies to all CSPs
Expiration Date	The time during which a product can be expected to meet the requirements of the compendial monograph, if one exists, or maintain expected quality provided it is kept under the specified storage conditions.	Applies to all conventionally manufactured products, APIs, and added substances

14.2 Parameters to Consider in Establishing a BUD

Multiple factors that affect sterility and chemical and physical stability must be considered when establishing BUDs for CSPs. BUDs should be established conservatively for CSPs to ensure that the drug maintains its required characteristics (i.e., stability and sterility) until its BUD.

When establishing a BUD for a CSP, compounders must consider factors that may affect stability, including but not limited to:

- The chemical and physical properties of the drug and/or its formulation
- The compatibility of the container–closure system with the finished preparation (e.g., leachables, interactions, and storage conditions)

The BUDs for CSPs in *Table 10* and *Table 11* are based primarily on factors that affect the achievement and maintenance of sterility, which include, but are not limited to, the following:

- Environment in which the CSP is prepared (e.g., PEC in a cleanroom suite or SCA)
- Aseptic processing and sterilization method
- Starting components (e.g., sterile or nonsterile starting ingredients)
- Whether or not sterility testing is performed
- Storage conditions (e.g., packaging and temperature)

ASEPTIC PROCESSING AND STERILIZATION METHODS

A CSP may be prepared by the following methods (see *10. Sterilization and Depyrogenation*):

1. **Aseptic processing**, which includes either 1) compounding with only sterile starting ingredient(s), or 2) compounding with nonsterile ingredient(s) followed by sterilization by filtration. [NOTE—Sterilization by filtration is not a form of terminal sterilization.]
2. **Terminal sterilization**, which includes compounding with sterile and/or nonsterile starting ingredient(s) and subsequent sterilization with a process intended to achieve a PNSU of 10^{-6} (e.g., dry heat, steam, irradiation).

Terminal sterilization is the preferred method of sterilization, unless the specific CSP or container–closure system cannot tolerate terminal sterilization. *Table 11* allows for longer BUDs for CSPs that are terminally sterilized than for aseptically processing CSPs because terminal sterilization using a verified method provides reasonable assurance that a CSP will be sterile.

STARTING COMPONENTS

The use of one or more nonsterile starting component(s) is a risk factor to be considered when preparing a CSP. A longer BUD is permitted in *Table 11* for CSPs that are aseptically processed from conventionally manufactured sterile starting component(s) than from one or more nonsterile starting component(s).

STERILITY TESTING

Sterility testing (see *12.2 Sterility Testing*) of a CSP can provide additional assurance of the absence of contamination, although passing a sterility test does not guarantee that all units of a batch of CSPs are sterile because contamination may not be uniformly distributed throughout the batch. A longer BUD is permitted in *Table 11* if sterility testing results are within acceptable limits.

STORAGE CONDITIONS

Storage in colder conditions [i.e., in a refrigerator or freezer (see *Packaging and Storage Requirements* ⟨659⟩)] has been shown to slow the growth of most microorganisms. However, the chemical and physical stability of the CSP and its components must be considered when storing in colder conditions (e.g., some formulations may precipitate when stored in a refrigerator or freezer). A longer BUD is permitted in *Table 10* and *Table 11* for CSPs stored in colder conditions than for CSPs stored at controlled room temperature.

If the CSP will be stored in a frozen state, the container–closure system must be able to withstand the physical stress (i.e., without breaking or cracking) during storage in a freezer. The CSP must be thawed in appropriate conditions to avoid compromising the physical and chemical stability of the preparation and its components (e.g., do not heat in a microwave). Once the CSP is thawed, the CSP must not be re-frozen.

CSPs may be stored under different storage conditions before they are used (e.g., CSPs may first be frozen, and then thawed in the refrigerator, and finally kept at controlled room temperature before administration). The storage time of a CSP must not exceed the original BUD placed on the CSP for its labeled storage condition, and BUDs must not be additive. For example, an aseptically processed CSP prepared from one or more nonsterile starting component(s) cannot be stored for 45 days in a freezer, then 4 days refrigerated, and then 1 day at controlled room temperature for a total of 50 days. Once a CSP has been stored under a condition that would require a shorter BUD (i.e., controlled room temperature), the CSP must be used within the time frame for that storage condition (in this example, 1 day).

14.3 Establishing a BUD for a CSP

BUDs for CSPs must be established in accordance with *Table 10* for Category 1 CSPs and *Table 11* for Category 2 CSPs. One day is equivalent to 24 hours.

The BUDs in *Table 10* and *Table 11* for CSPs are based on the risk of microbial contamination or not achieving sterility despite implementation of the requirements in this chapter. Therefore, it is assumed that the CSP formulation will remain chemically and physically stable, and its packaging will maintain its integrity for the duration of the BUD.

A shorter BUD must be assigned when the stability of the CSP or its components is less than the hours or days stated in *Table 10* or *Table 11*. Additionally, the BUD must not exceed the shortest remaining expiration date or BUD of any of the starting components, regardless of the source.

Table 10 establishes the longest permitted BUDs for Category 1 CSPs. Category 1 CSPs may be prepared in an SCA or cleanroom suite (see *4.2 Facility Design and Environmental Controls*).

Table 10. BUDs for Category 1 CSPs

Storage Conditions		
	Controlled Room Temperature (20°–25°)	**Refrigerator (2°–8°)**
BUD	≤12 hours	≤24 hours

Table 11 establishes the longest permitted BUDs for Category 2 CSPs. Category 2 CSPs must be prepared in a cleanroom suite (see *4.2 Facility Design and Environmental Controls*).

Table 11. BUDs for Category 2 CSPs

Preparation Characteristics		Storage Conditions		
Compounding Method	**Sterility Testing Performed and Passed**	**Controlled Room Temperature (20°–25°)**	**Refrigerator (2°–8°)**	**Freezer (–25° to –10°)**
Aseptically processed CSPs	No	Prepared from one or more nonsterile starting component(s): 1 day	Prepared from one or more nonsterile starting component(s): 4 days	Prepared from one or more nonsterile starting component(s): 45 days
		Prepared from only sterile starting components: 4 days	Prepared from only sterile starting components: 10 days	Prepared from only sterile starting components: 45 days
	Yes	30 days	45 days	60 days
Terminally sterilized CSPs	No	14 days	28 days	45 days
	Yes	45 days	60 days	90 days

14.4 Multiple-Dose CSPs

A compounded multiple-dose container is designed to contain more than 1 dose, intended to be entered or penetrated multiple times, and usually contains a preservative. A preservative is intended to inhibit the growth of microorganisms and minimize the risk of contamination. The use of preservatives must be appropriate for the CSP formulation and the route of administration. For example, the preservative must not be inactivated by any ingredients in the CSP and some preservatives are not always appropriate for the patient (e.g., neonates) or route of administration (e.g., intrathecal or ophthalmic injections). The use of preservatives, however, must not be considered a substitute for aseptic technique.

A multiple-dose CSP must be prepared as a Category 2 CSP. A multiple-dose CSP must additionally pass antimicrobial effectiveness testing in accordance with *Antimicrobial Effectiveness Testing* ⟨51⟩. The compounder may rely on 1) antimicrobial effectiveness testing that is conducted (or contracted for) once for each formulation in the particular container–closure system in which it will be packaged or 2) antimicrobial effectiveness testing results provided by an FDA-registered facility or published in peer-reviewed literature sources if the CSP formulation (including any preservative) and container–closure system are exactly the same as those tested unless a bracketing study is performed. Antimicrobial effectiveness testing may be performed on a low concentration and a high concentration of the active ingredient in the formulation to establish preservative effectiveness across various strengths of the same formulation (e.g., bracketing). The concentration of all other ingredients (including preservatives) must be the same throughout the bracketing study.

After a multiple-dose container is initially entered or punctured, the multiple-dose container must not be used for longer than the assigned BUD or 28 days if supported by antimicrobial effectiveness testing results (see ⟨51⟩) on the CSP, whichever is shorter.

The container–closure system used to package the multiple-dose CSP must be evaluated for and conform to container–closure integrity (see *Package Integrity Evaluation—Sterile Products* ⟨1207⟩). The container–closure integrity test needs to be conducted only once on each formulation and fill volume in the particular container–closure system in which the multiple-dose CSP will be packaged.

15. USE OF CONVENTIONALLY MANUFACTURED PRODUCTS AS COMPONENTS

This section addresses the time within which an entered or punctured conventionally manufactured product must be used.

15.1 Use of Conventionally Manufactured Single-Dose Containers

A conventionally manufactured single-dose container is a container–closure system that holds a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. If a single-dose vial is entered or punctured only in an ISO Class 5 or cleaner air, it may be used up to 12 hours after initial entry or puncture as long as the storage requirements during that 12-hour period are maintained. Opened single-dose ampules must not be stored for any time period.

15.2 Use of Conventionally Manufactured Multiple-Dose Containers

A conventionally manufactured product in a multiple-dose container is intended to contain more than 1 dose of a drug product (see *Packaging and Storage Requirements* ⟨659⟩*, General Definitions, Injection Packaging Systems*). Once initially entering or puncturing the multiple-dose container, the multiple-dose container must not be used for more than 28 days (see ⟨51⟩) unless otherwise specified by the manufacturer on the labeling.

15.3 Use of Conventionally Manufactured Pharmacy Bulk Packages

A conventionally manufactured pharmacy bulk package is a container of a sterile product for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the sterile preparation of admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile containers. The pharmacy bulk package must be used according to the manufacturer's labeling (see *Packaging and Storage Requirements* ⟨659⟩*, General Definitions, Injection Packaging Systems*). The pharmacy bulk package must be entered or punctured only in an ISO Class 5 PEC.

16. USE OF CSPs AS COMPONENTS

This section addresses the use of CSPs (e.g., multiple-dose CSPs, single-dose CSPs, and compounded stock solutions) as components to prepare finished CSPs.

When a CSP is used as a component, care must be taken to minimize the risk of contamination of both the starting component CSP and the finished CSP(s). The BUD of a CSP prepared from one or more compounded components may not exceed the shortest BUD of any of the individual starting components (see *14. Establishing Beyond-Use Dates*).

16.1 Use of Compounded Multiple-Dose CSPs

A multiple-dose CSP is designed to contain more than 1 dose of medication, intended to be entered or punctured multiple times, and usually contains a preservative. Multiple-dose CSPs are required to meet the criteria for antimicrobial effectiveness testing (see ⟨51⟩) and the requirements in *14.4 Multiple-Dose CSPs*. Multiple-dose CSPs must be stored under the conditions upon which its BUD is based (e.g., refrigerator, controlled room temperature). After a multiple-dose CSP is initially entered or punctured, the multiple-dose CSP must not be used for longer than the assigned BUD or 28 days, whichever is shorter.

16.2 Use of Compounded Single-Dose CSPs and CSP Stock Solutions

When a compounded single-dose CSP or CSP stock solution is used as a component to compound additional CSPs, the original compounded single-dose CSP or CSP stock solution must be entered or punctured in ISO Class 5 or cleaner air, and must be stored under the conditions upon which its BUD is based (e.g., refrigerator, controlled room temperature). The component CSP may be used for sterile compounding for up to 12 hours or its assigned BUD, whichever is shorter, and any remainder must be discarded.

17. SOPs

Facilities that prepare CSPs must develop SOPs for the compounding process and other support activities. A designated person must ensure that SOPs are appropriate and are implemented, which includes ensuring that personnel demonstrate competency in performing every procedure that relates to their job function. A designated person must follow up to ensure that corrective actions are taken if problems, deviations, failures, or errors are identified. The corrective action must be documented.

All personnel who perform or oversee compounding or support activities must be trained in the SOPs. All compounding personnel must:

- Be able to recognize potential problems, deviations, failures, or errors associated with preparing a CSP (e.g., those related to equipment, facilities, materials, personnel, the compounding process, or testing) that could potentially result in contamination or other adverse impact on CSP quality
- Report any problems, deviations, failures or errors to the designated person(s)

SOPs must be reviewed at least every 12 months by the designated person(s) to ensure that they reflect current practices, and the review must be documented. Any changes or alterations to an SOP must be made only by a designated person and must be documented. Revisions to SOPs must be communicated to all personnel involved in these processes and procedures, and personnel should document acknowledgment of the communication.

18. QUALITY ASSURANCE AND QUALITY CONTROL

QA is a system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards. QC is the sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the CSP. See *Quality Assurance in Pharmaceutical Compounding* ⟨1163⟩.

A facility's QA and QC programs must be formally established and documented in SOPs that ensure that all aspects of the preparation of CSPs are conducted in accordance with the requirements in this chapter and laws and regulations of the applicable regulatory jurisdiction. A designated person must ensure that the facility has formal, written QA and QC programs that establish a system of:

1. Adherence to procedures
2. Prevention and detection of errors and other quality problems
3. Evaluation of complaints and adverse events

4. Appropriate investigations and corrective actions

The SOPs must describe the roles, duties, and training of the personnel responsible for each aspect of the QA program. The overall QA and QC program must be reviewed at least once every 12 months by the designated person(s). The results of the review must be documented and appropriate action must be taken if needed.

18.1 Notification About and Recall of Out-of-Specification Dispensed CSPs

If a CSP is dispensed or administered before the results of release testing are known, the facility must have procedures in place to:

1. Immediately notify the prescriber of a failure of specifications with the potential to cause patient harm (e.g., sterility, strength, purity, bacterial endotoxin, or other quality attributes), and
2. Determine whether a recall is necessary

An SOP for recall of out-of-specification dispensed CSPs must contain:

- Procedures to determine the severity of the problem and the urgency for implementation and completion of the recall
- Procedures to determine the distribution of any affected CSP, including the date and quantity of distribution
- Procedures to identify patients who have received the CSP
- Procedures for disposition and reconciliation of the recalled CSP

The sterile compounding facility must document the implementation of the recall procedures. The recall must be reported to appropriate regulatory bodies as required by laws and regulations of the applicable regulatory jurisdiction (e.g., state board of pharmacy, state health department).

18.2 Complaint Handling

Compounding facilities must develop and implement SOPs for handling complaints. Complaints may include, but are not limited to, concerns or reports on the quality, labeling, or possible adverse reactions related to a specific CSP.

A designated person must review all complaints to determine whether the complaint indicates a potential quality problem with the CSP. If it does, a thorough investigation into the cause of the problem must be initiated and completed. The investigation must consider whether the quality problem extends to other CSPs. Corrective action, if necessary, must be implemented for all potentially affected CSPs. Consider whether to initiate a recall of potentially affected CSPs and whether to cease sterile compounding processes until all underlying problems have been identified and corrected.

A readily retrievable written or electronic record of each complaint must be kept by the facility, regardless of the source of the complaint (e.g., email, telephone, mail). The record must contain the name of the complainant or unique identifier, the date the complaint was received, the nature of the complaint, and the response to the complaint. In addition, to the extent that the information is known, the following should be recorded: the name and strength of the CSP and the assigned internal identification number (e.g., prescription, order, or lot number).

The record must also include the findings of any investigation and any follow-up. Records of complaints must be easily retrievable for review and evaluation for possible trends and must be retained in accordance with the record-keeping requirements in *20. Documentation*. A CSP that is returned in connection with a complaint must be quarantined until it is destroyed after completion of the investigation and in accordance with laws and regulations of the applicable regulatory jurisdiction.

18.3 Adverse Event Reporting

Adverse events potentially associated with the quality of CSPs must be reported in accordance with facility SOPs and all laws and regulations of the applicable regulatory jurisdiction. In addition, adverse events potentially associated with the quality of the CSP should be reported to the applicable jurisdictional regulatory body (e.g., state boards of pharmacy, state health departments, FDA's MedWatch program for human drugs, or FDA Form 1932a for animal drugs).

19. CSP HANDLING, STORAGE, PACKAGING, SHIPPING, AND TRANSPORT

Processes and techniques for handling, storing, packaging, and transporting CSPs must be outlined in SOPs. Personnel who will be handling, storing, packaging, and transporting CSPs within the facility must be trained in accordance with the relevant SOPs, and the training must be documented.

19.1 Handling and Storing CSPs

CSPs must be handled in a manner that maintains CSP quality and packaging integrity. To help ensure that CSP quality is maintained during storage at the compounding facility, personnel must monitor conditions in the storage areas. A controlled temperature area (see ⟨659⟩) must be established and monitored to ensure that the temperature remains within the appropriate range for the CSP. The temperature must be monitored each day, either manually or by a continuous recording device. The results of the temperature readings must be documented in a temperature log at least once daily or stored in the continuous temperature recording device, and must be retrievable. Temperature monitoring devices must be verified for accuracy at least every 12 months or as required by the manufacturer.

The compounding facility must detect and minimize temperature excursions that are outside the temperature limits within the controlled temperature areas. When it is known that a CSP has been exposed to temperatures either below or above the storage temperature limits for the CSP, a designated person must determine (e.g., by consulting literature or analytical testing) whether the CSP is expected to retain its integrity or quality. If this cannot be determined, it must be discarded.

19.2 Packaging of CSPs

Packaging materials should protect CSPs from damage, leakage, contamination, degradation, and adsorption while preventing inadvertent exposure to transport personnel. The facility must select appropriate shipping containers and packaging materials based on the product specifications, information from vendors, and the mode of transport.

Alternative modes of transport and/or special packaging (e.g., tamper-evident closures) may be needed to protect the quality of CSPs. If the CSP is sensitive to light, light-resistant packaging materials must be used. In some cases, the CSP must be packaged in a special container (e.g., a cooler) to protect it from temperature fluctuations.

19.3 Shipping and Transporting CSPs

Compounding personnel must select modes of transport that are expected to deliver properly packed CSPs in an undamaged, sterile, and stable condition. Inappropriate transport can adversely affect the quality of CSPs. For example, preparation-specific considerations should be given to physical shaking that might occur during pneumatic tube transport or undue exposure to heat, cold, or light. When shipping or transporting CSPs that require special handling (e.g., CSPs with stability concerns), personnel must include specific handling instructions on the exterior of the container.

20. DOCUMENTATION

All facilities where CSPs are prepared must have and maintain written or electronic documentation to demonstrate compliance with the requirements in this chapter. This documentation must include, but is not limited to, the following:

- Personnel training, competency assessments, and qualification records including corrective actions for any failures
- Certification reports, including corrective actions for any failures
- Environmental air and surface monitoring procedures and results
- Equipment records (e.g., calibration, verification, and maintenance reports)
- Receipt of components
- SOPs, Master Formulation Records (when used), and Compounding Records
- Release inspection and testing records
- Information related to complaints and adverse events
- Results of investigations and corrective actions

Documentation must comply with all laws and regulations of the applicable jurisdiction. Records must be legible and stored in a manner that prevents their deterioration and/or loss. All required compounding records for a particular CSP (e.g., Master Formulation Record, Compounding Record, and release testing results) must be readily retrievable for at least 3 years after preparation or as required by laws and regulations of the applicable regulatory jurisdiction, whichever is longer.

21. COMPOUNDING ALLERGENIC EXTRACTS

Licensed allergenic extracts are mixed and diluted into prescription sets for an individual patient, even though these allergenic extract combinations are not specified in the approved licenses for the licensed biological products [e.g., Biological License Applications (BLA)]. Because patients must be maintained on a maintenance dose of prepared concentrated allergenic extracts for a period of time longer than the BUDs specified for Category 1 and Category 2, longer BUDs are required for prescription sets to achieve effective therapy.

Allergenic extracts prescription sets must follow standards at least as stringent as those in this section:

Personnel Qualifications

1. A designated person with training and expertise in allergen immunotherapy is responsible for ensuring that personnel who will be preparing allergen immunotherapy are trained, evaluated, and supervised.
2. Before beginning to independently prepare allergenic extracts, all compounding personnel must complete training and be able to demonstrate knowledge of principles and skills for sterile compounding.
3. Annual personnel training and competency must be documented. Personnel must demonstrate proficiency in these procedures by passing written or electronic testing before they can be allowed to compound allergenic extract prescription sets.
4. Before being allowed to independently compound, all compounders must successfully complete gloved fingertip and thumb sampling on both hands (see *Box 2-1* and *Table 1*), no fewer than 3 separate times. Each fingertip and thumb evaluation must occur after performing separate and complete hand hygiene and garbing procedure. After the initial competency evaluation, compounding personnel must successfully complete gloved fingertip and thumb sampling at least every 12 months thereafter.

5. Compounding personnel must have their sterile technique and related practices evaluated every 12 months as demonstrated by successful completion of a media-fill test (see *Box 2-2*).

6. Personnel who fail competency evaluations must successfully pass reevaluations in the deficient area(s) before they can resume compounding of allergenic extract prescription sets. The designated person(s) must identify the cause of failure and determine appropriate retraining requirements.

7. Personnel who have not compounded an allergenic extract prescription set in more than 6 months must be evaluated in all core competencies before resuming compounding duties.

Personnel Hygiene and Garbing

8. Before beginning compounding of allergen immunotherapy prescription sets, personnel must perform hand hygiene (see *Box 3-1*) and garbing procedures according to facility SOPs.

9. The minimum garb requirements include:

- Low-lint garment with sleeves that fit snugly around the wrists and that is enclosed at the neck (e.g., gowns or coveralls)
- Low-lint, disposable covers for head that cover the hair and ears and, if applicable, disposable cover for facial hair
- Face mask
- Sterile powder-free gloves

10. Compounding personnel must rub sterile 70% IPA onto all surfaces of the gloves and allow them to dry thoroughly throughout the compounding process.

Facilities

11. The compounding process must occur in an ISO Class 5 PEC or in a dedicated allergenic extracts compounding area (AECA). The PEC or AECA used to compound prescription sets must be located away from unsealed windows, doors that connect to the outdoors, and traffic flow, all of which may adversely affect the air quality. Neither a PEC nor an AECA may be located where environmental control challenges (e.g., restrooms, warehouses, or food preparation areas) could negatively affect the air quality. The PEC or the work surfaces in the AECA must be located at least 1 meter away from a sink. The impact of activities that will be conducted around or adjacent to the PEC or AECA must be considered carefully when designing such an area.

- If used, the PEC must be certified every 6 months (see *5. Certification and Recertification*).
- If used, a visible perimeter must establish the boundaries of the AECA.
  - Access to the AECA during compounding must be restricted to authorized personnel.
  - During compounding activities, no other activity is permitted in the AECA.
  - The surfaces of walls, floors, fixtures, shelving, counters, and cabinets in the AECA must be cleanable.
  - Carpet is not allowed in the AECA.
  - Surfaces should be resistant to damage by cleaning and sanitizing agents.
  - The surfaces in the AECA upon which the allergenic extract prescription sets are prepared must be smooth, impervious, free from cracks and crevices, and non-shedding to allow for easy cleaning and disinfecting.
  - Dust-collecting overhangs such as utility pipes, ledges, and windowsills should be minimized. If overhangs or ledges are present, they must be easily cleanable.
  - The AECA must be designed and controlled to provide a well-lighted working environment, with temperature and humidity controls for the comfort of compounding personnel wearing the required garb.

Cleaning and Disinfecting

12. In a PEC, all interior surfaces of the PEC must be cleaned and disinfected daily and when surface contamination is known or suspected. Apply sterile 70% IPA to the horizontal work surface between each prescription set.

13. In an AECA, all work surfaces in the AECA where direct compounding is occurring must be cleaned and disinfected daily and when surface contamination is known or suspected. Apply sterile 70% IPA to the horizontal work surface between each prescription set.

- If present, walls, doors, and door frames within the perimeter of the AECA must be cleaned and disinfected monthly and when surface contamination is known or suspected.
- Ceilings within the perimeter of the AECA must be cleaned and disinfected when visibly soiled and when surface contamination is known or suspected.

14. Vial stoppers on packages of conventionally manufactured sterile ingredients must be wiped with sterile 70% IPA to ensure that the critical sites are wet and allowed to dry before they are used to compound allergenic extracts prescription sets.

Establishing BUDs

15. The BUD for the prescription set must be no later than the earliest expiration date of any allergenic extract or any diluent that is part of the prescription set, and the BUD must not exceed 1 year from the date the prescription set is mixed or diluted.

Labeling

16. The label of each vial of an allergenic extract prescription set must display the following prominently and understandably:

- Patient name
- Type and fractional dilution of each vial, with a corresponding vial number
- BUD
- Storage conditions

Shipping and Transport

17. If shipping or transporting allergenic extract prescription sets, compounding personnel must select modes of transport that are expected to deliver properly packed prescription sets in an undamaged, sterile, and stable condition. Inappropriate transport can adversely affect the quality of allergenic extract prescription sets.

18. When shipping or transporting allergenic extract prescription sets that require special handling, personnel must include specific handling instructions on the exterior of the container.

Documentation

19. All facilities where allergenic extract prescription sets are prepared must have and maintain written or electronic documentation to include, but not limited to, the following:

- SOPs describing all aspects of the compounding process
- Personnel training records, competency assessments, and qualification records including corrective actions for any failures
- Certification reports of the PEC, if used, including corrective actions for any failures
- Temperature logs for the refrigerator(s)
- Compounding records for individual allergenic extract prescription sets (see *Box 21-1*)
- Information related to complaints and adverse events
- Investigations and corrective actions

Box 21-1. Compounding Records for Individual Allergenic Extract Prescription Sets

Compounding Records must include at least the following information:

- Name, concentration, volume, vendor or manufacturer, lot number, and expiration date for each component
- Date and time of preparation of the allergenic extract
- Assigned internal identification number
- A method to identify the individuals involved in the compounding process and verifying the final CSP
- Total quantity compounded
- Assigned BUD and storage requirements
- Results of QC procedures (e.g., visual inspection, second verification of quantities)

GLOSSARY

Active pharmaceutical ingredient (API): Any substance or mixture of substances intended to be used in the compounding of a preparation, thereby becoming the active ingredient in that preparation and furnishing pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and animals or affecting the structure and function of the body.

Added substances: Ingredients that are necessary to compound a preparation but are not intended or expected to cause a pharmacologic response if administered alone in the amount or concentration contained in a single dose of the compounded preparation. The term is used synonymously with the terms inactive ingredients, excipients, and pharmaceutical ingredients.

Administration: The direct application of a sterile medication to a single patient by injecting, infusing, or otherwise providing a sterile medication in its final form.

Airlock: A space with interlocked doors, constructed to maintain air pressure control when items move between two adjoining areas (generally with different air cleanliness standards). The intent of an airlock is to prevent ingress of particulate matter and microbial contamination from a lesser-controlled area.

Allergenic extract prescription set: Combinations of licensed allergenic extracts which would be mixed and diluted to provide subcutaneous immunotherapy to an individual patient, even though these allergenic extract combinations are not specified in the approved BLAs for the licensed biological products.

Allergenic extracts: Biological substances used for the diagnosis and/or treatment of allergic diseases such as allergic rhinitis, allergic sinusitis, allergic conjunctivitis, bee venom allergy, and food allergy.

Allergenic extracts compounding area (AECA): A designated, unclassified space, area, or room with a visible perimeter that is suitable for preparation of allergenic extract prescription sets.

Ante-room: An ISO Class 8 or cleaner room with fixed walls and doors where personnel hand hygiene, garbing procedures, and other activities that generate high particulate levels may be performed. The ante-room is the transition room between the unclassified area of the facility and the buffer room.

Aseptic processing: A method by which separate, sterile components (e.g., drugs, containers, or closures) are brought together under conditions that maintain their sterility. The components can either be purchased as sterile or, when starting with nonsterile components, can be separately sterilized prior to combining (e.g., by membrane filtration, autoclave).

Aseptic technique: A set of methods used to keep objects and areas free of microorganisms and thereby minimize infection risk to the patient. It is accomplished through practices that maintain the microbe count at an irreducible minimum.

Biological safety cabinet (BSC), Class II: A ventilated cabinet with an open front and inward and downward unidirectional HEPA-filtered airflow and HEPA-filtered exhaust. A BSC used to prepare a CSP must be capable of providing an ISO Class 5 or better environment for preparation of the CSPs.

Blood components: Any therapeutic constituent of blood separated by physical or mechanical means (e.g., white cells, red cells, platelets, plasma, serum). It is not intended to include plasma-derived products (e.g., albumin, coagulation factors, immunoglobulins) manufactured under an approved BLA or equivalent.

Buffer room: An ISO Class 7 or cleaner room with fixed walls and doors where PEC(s) that generate and maintain an ISO Class 5 environment are physically located. The buffer room may only be accessed through the ante-room.

Category 1 CSP: A CSP that is assigned a BUD of 12 hours or less at controlled room temperature or 24 hours or less refrigerated that is compounded in accordance with all applicable requirements for Category 1 CSPs in this chapter.

Category 2 CSP: A CSP that is assigned a BUD of greater than 12 hours at controlled room temperature or greater than 24 hours refrigerated that is compounded in accordance with all applicable requirements for Category 2 CSPs in this chapter.

Certificate of analysis (COA): A report from the supplier of a component, container, or closure that accompanies the supplier's material and contains the specifications and results of all analyses and a description of the material.

Classified area: An area that maintains an air quality classification based on the ISO standards (see also the definition for *ISO class*).

Cleaning agent: An agent for the removal of residues (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.

Cleanroom suite: A classified area that consists of both an ante-room and buffer room.

Component: Any ingredient used in the compounding of a preparation, including any active ingredient, added substance, or conventionally manufactured product.

Compounded sterile preparation (CSP): A preparation intended to be sterile that is created by combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance.

Compounded stock solution: A sterile mixture of components that is used to compound additional CSPs.

Compounding: The process of combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug or bulk drug substance to create a sterile medication.

Compounding area: The area where compounding is occurring (i.e., a cleanroom suite, inside the perimeter of the SCA, or AECA).

Compounding aseptic containment isolator (CACI): A type of RABS that uses HEPA filtration to provide an ISO Class 5 unidirectional air environment designed for the compounding of sterile HDs.

Compounding aseptic isolator (CAI): A type of RABS that uses HEPA filtration to provide an ISO Class 5 unidirectional air environment designed for compounding of sterile non-HDs.

Container–closure system: Packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection.

Containment ventilated enclosure: A full or partial enclosure that uses ventilation principles to capture, contain, and remove airborne contaminants through HEPA filtration and prevent their release into the work environment.

Conventionally manufactured product: A pharmaceutical dosage form, usually the subject of an FDA-approved application, and manufactured under current good manufacturing practice conditions.

Critical site: A location that includes any component or fluid pathway surfaces (e.g., vial septa, injection ports, and beakers) or openings (e.g., opened ampules and needle hubs) that are exposed and at risk of direct contact with air (e.g., ambient room or HEPA filtered), moisture (e.g., oral and mucosal secretions), or touch contamination.

Designated person(s): One or more individuals assigned to be responsible and accountable for the performance and operation of the compounding facility and personnel in the preparation of CSPs.

Direct compounding area (DCA): A critical area within the ISO Class 5 PEC where critical sites are exposed to unidirectional HEPA-filtered air, also known as first air.

Disinfectant: A chemical or physical agent used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria. Sporicidal disinfectant agents are considered a special class of disinfectants that also are effective against bacterial and fungal spores.

Dynamic airflow smoke pattern test: A PEC test in which a visible source of smoke, which is neutrally buoyant, is used to observe air patterns within the unidirectional space (i.e., the DCA) under dynamic operating conditions (see *Dynamic operating conditions*). This test is not appropriate for ISO Class 7 or ISO Class 8 cleanrooms that do not have unidirectional airflow (see *Visual smoke study*).

Dynamic operating conditions: Conditions in the compounding area in which operating personnel are present and simulating or performing compounding. The conditions should reflect the largest number of personnel and highest complexity of compounding expected during routine operations as determined by the designated person(s).

Excipients: See *Added substances*.

Filter integrity test: A test (e.g., bubble point test) of the integrity of a sterilizing grade filter performed after the filtration process to detect whether the integrity of the filter has been compromised.

First air: The air exiting the HEPA filter in a unidirectional air stream.

Formulation: The specific qualitative and quantitative composition of the final CSP.

Garb: Items such as gloves, garments (e.g., gowns, coveralls), shoe covers, head and facial hair covers, masks, and other items designed to reduce particle-shedding from personnel and minimize the risk of contamination of CSP(s).

Hazardous drug (HD): Any drug identified by at least one of the following six criteria: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans, organ toxicity at low dose in humans or animals, genotoxicity, or new drugs that mimic existing HDs in structure or toxicity.

High-efficiency particulate air (HEPA) filtration: Being, using, or containing a filter designed to remove 99.97% of airborne particles measuring 0.3-micron or greater in diameter passing through it.

Integrated vertical laminar flow zone (IVLFZ): A designated ISO Class 5 area serving as the PEC within an ISO Class 7 or cleaner buffer room. In the IVLFZ, unidirectional airflow is created by placing HEPA filters over the entire surface of the work tables and effective placement of air returns.

ISO class: An air-quality classification from the International Organization for Standardization.

Laminar airflow system (LAFS): A device or zone within a buffer area that provides an ISO Class 5 or better air quality environment for sterile compounding. The system provides a unidirectional HEPA-filtered airflow.

Laminar airflow workbench (LAFW): A device that is a type of LAFS that provides an ISO Class 5 or better air quality environment for sterile compounding. The device provides a unidirectional HEPA-filtered airflow.

Line of demarcation: A visible line on the floor that separates the clean and dirty sides of the ante-room.

Low-lint wiper: A wiper exhibiting few, if any, fibers or other contamination, visible without magnification, which is separate from, or easily removed from, the wiper material in a dry condition.

Media-fill test: A simulation used to qualify processes and personnel engaged in sterile compounding to ensure that the processes and personnel are able to prepare CSPs without contamination.

Multiple-dose container: A container of sterile medication for parenteral administration (e.g., injection or infusion) that is designed to contain more than 1 dose of the medication. A multiple-dose container is usually required to meet the antimicrobial effectiveness testing criteria. See *Packaging and Storage Requirements* ⟨659⟩*, Injection Packaging Systems, Multiple-dose container*.

One-step disinfectant cleaner: A product with an EPA-registered (or equivalent) claim that it can clean and disinfect a non-porous surface in the presence of light to moderate organic soiling without a separate cleaning step.

Pass-through: An enclosure with sealed doors on both sides that should be interlocked. The pass-through is positioned between two spaces for the purpose of minimizing particulate transfer while moving materials from one space to another.

Perimeter: A visible demarcation that defines the boundaries of the SCA or AECA (e.g. a visible line or wall).

Pharmacy bulk package: A conventionally manufactured sterile product for parenteral use that contains many single doses intended for use in a pharmacy admixture program. A pharmacy bulk package may either be used to prepare admixtures for infusion or, through a sterile transfer device, for filling sterile containers. See *Packaging and Storage Requirements* ⟨659⟩*, Injection Packaging Systems, Pharmacy bulk package*.

Pharmaceutical isolator: An enclosure that provides HEPA-filtered ISO Class 5 unidirectional air operated at a continuously higher pressure than its surrounding environment and is decontaminated using an automated system. It uses only decontaminated interfaces or rapid transfer ports for materials transfer. [NOTE—A CAI or CACI is not a pharmaceutical isolator.]

Positive-pressure room: A room that is maintained at higher pressure than the adjacent spaces, and therefore the net airflow is out of the room.

Preservative: A substance added to inhibit microbial growth.

Primary engineering control (PEC): A device or zone that provides an ISO Class 5 air quality environment for sterile compounding.

Probability of a nonsterile unit (PNSU): The probability of an item being nonsterile after it has been exposed to a verified sterilization process. A PNSU value can only be applied to terminal sterilization. [NOTE—This is also called the sterility assurance level (SAL).]

Pyrogen: A substance that induces a febrile reaction in a patient.

Quality assurance (QA): A system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards.

Quality control (QC): The sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the CSP.

Reconstitution: The process of adding a diluent to a conventionally manufactured product to prepare a sterile solution or suspension.

Release inspection and testing: Visual inspection and testing performed to ensure that a preparation meets appropriate quality characteristics.

Repackaging: The act of removing a sterile product or preparation from its original primary container and placing it into another primary container, usually of smaller size without further manipulation.

Restricted-access barrier system (RABS): An enclosure that provides HEPA-filtered ISO Class 5 unidirectional air that allows for the ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of contamination, and that generally are not to be opened during operations. Examples of RABS include CAIs and CACIs.

Secondary engineering control (SEC): The area where the PEC is placed (e.g., a cleanroom suite or an SCA). It incorporates specific design and operational parameters required to minimize the risk of contamination within the compounding area.

Segregated compounding area (SCA): A designated, unclassified space, area, or room with a defined perimeter that contains a PEC and is suitable for preparation of Category 1 CSPs only.

Single-dose containers: A container of sterile medication for parenteral administration (e.g., injection or infusion) that is designed for use with a single patient as a single injection/infusion. A single-dose container usually does not contain a preservative. See *Packaging and Storage Requirements* ⟨659⟩*, Injection Packaging Systems, Single-dose container*.

Specification: The tests, analytical methods, and acceptance criteria to which an API or other components, CSP, container–closure system, equipment, or other material used in compounding CSPs must conform to be considered acceptable for its intended use.

Sporicidal agent: A chemical or physical agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

Stability: The extent to which a product or preparation retains physical and chemical properties and characteristics within specified limits throughout its expiration or BUD.

Sterility: The absence of viable microorganisms.

Sterility assurance level (SAL): See *Probability of a nonsterile unit (PNSU)*.

Sterilization by filtration: Passage of a gas or liquid through a sterilizing-grade membrane to yield filtrates that are sterile.

Sterilizing-grade membranes: Filter membranes that are documented to retain 100% of a culture of 10^7 microorganisms of a strain of *Brevundimonas diminuta* per square centimeters of membrane surface under a pressure of not less than 30 psi. Such filter membranes are nominally 0.22-µm or 0.2-µm pore size.

Terminal sterilization: The application of a lethal process (e.g., dry heat, steam, irradiation) to sealed containers for the purpose of achieving a predetermined PNSU of greater than 10^{-6} or a probability of less than one in one million of a nonsterile unit.

Unclassified space: A space not required to meet any air cleanliness classification based on the ISO.

Unidirectional airflow: Air within a PEC moving in a single direction in a uniform manner and at sufficient velocity to sweep particles away from the DCA.

Workflow management system: Technology comprised of hardware and software that allows for automation to assist in the verification of components of, and preparation of, CSPs and to document components and processes.

Verify: To confirm that a method, process, system, or equipment will perform as expected under the conditions of actual use.

Visual smoke study: A test, used in ISO Class 7 and ISO Class 8 rooms that do not have unidirectional airflow, in which a visible source of smoke, which is neutrally buoyant, is used to verify an absence of stagnant airflow where particulates can accumulate. This test does not need to be performed under dynamic operating conditions and is not appropriate for PECs (see *Dynamic airflow smoke pattern test*).

APPENDIX

Acronyms

ACD	Automated compounding device
ACPH	Air changes per hour
AECA	Allergenic extracts compounding area
APIs	Active pharmaceutical ingredient(s)
BLA	Biological License Application
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BSC(s)	Biological safety cabinet(s)
BUD(s)	Beyond-use date(s)
CACI	Compounding aseptic containment isolator
CAI	Compounding aseptic isolator
CDC	Centers for Disease Control and Prevention
CETA	Controlled Environment Testing Association
cfu	Colony-forming units
COA(s)	Certificate(s) of analysis
CSP(s)	Compounded sterile preparation(s)
CVE	Containment ventilated enclosure
DCA(s)	Direct compounding area(s)
ECV(s)	Endotoxin challenge vial(s)
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
HD(s)	Hazardous drug(s)
HEPA	High-efficiency particulate air
HVAC	Heating, ventilation, and air conditioning

Acronyms *(continued)*

IPA	Isopropyl alcohol
ISO	International Organization for Standardization
IVLFZ	Integrated vertical laminar flow zone
LAFS	Laminar airflow system
LAFW(s)	Laminar airflow workbench(es)
MEA	Malt extract agar
PEC(s)	Primary engineering control(s)
PNSU	Probability of a nonsterile unit
PPE	Personal protective equipment
QA	Quality assurance
QC	Quality control
RABS	Restricted-access barrier system
SAL	Sterility assurance level
SCA	Segregated compounding area
SDA	Sabouraud dextrose agar
SEC(s)	Secondary engineering control(s)
SOP(s)	Standard operating procedure(s)
TSA	Trypticase soy agar ▲ USP 1-Dec-2019