



Secundum Artem

*Current & Practical Compounding
Information for the Pharmacist.*

USP Chapter <795>

Pharmaceutical Compounding - Nonsterile Preparations

GOALS AND OBJECTIVES

Goal: The goal of this article is to provide information on the historical development and practical implementation of USP Chapter <795> Pharmaceutical Compounding-Nonsterile Preparations.

Objectives: After reading and studying the article, the reader will be able to:

1. Discuss the history and development of the USP-NF and the USP-Pharmacists' Pharmacopeia.
2. List the five questions that should be considered concerning each compounded prescription.
3. Discuss the difference between a "product" and a "preparation" as well as the difference between an "expiration date" and a "beyond use date".
4. Discuss the various sections of USP Chapter <795> and their application.
5. List the two basic reasons or intent for developing USP Chapter <795>.

INTRODUCTION

What is USP Chapter <795>? Why should compounders be familiar with it? Where did it come from? From where did it derive its authority? Do I have to follow it? What happens if I don't? Is it really important? What if I have never had a problem before.....do I still need to comply with its standards? Who establishes these standards? Are they "set in stone" or do they change over time? What is the relationship between the USP and the U.S. government? What is the relationship between the USP and the Food and Drug Administration? Do the USP standards really contribute to patient safety?

All these are valid questions that deserve an answer. As we travel from looking at where the pharmacopeias came from and from where they derive their authority, we will look at how the USP-NF shapes pharmacy compounding and the pharmaceutical industry today.

Two things to keep in mind regarding the USP and these chapters; the intent is to protect both the patient AND the pharmacist. Protection of the patient is addressed when these standards are followed and the pharmacist when any adverse event might occur where patient harm and/or litigation results.

BACKGROUND

Pharmaceutical compounding is the history of pharmacy, spanning the past 5,000 years, until the early to mid 1900s when the pharmaceutical industry came into being. There are many recorded writings of formulas and methods of treating disease in pharmacy history books. The standards for uniformity and quality in pharmacy compounding started back in 1580 in Bergamo, Italy, where the term "pharmacopoeia" was first used in connection with a local book of drug standards. Many pharmacopeias were developed on local, city and

Loyd V. Allen, Jr., Ph.D., R.Ph., Professor Emeritus,
University of Oklahoma, HSC College of Pharmacy,
Oklahoma City, OK 73190



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national levels in Europe. Some of the best known were the London, Edinburgh and Dublin Pharmacopoeias which were official until 1864, when they were combined and replaced by the well-known British Pharmacopoeia.¹

The U.S. Pharmacopoeia (USP) was established in January 1820 by a group of physicians from the United States at the first Pharmacopoeial convention. The objective of the USP was to establish uniform standards for the medications they prescribed. In December 1820, they published the first U.S. Pharmacopoeia. Following this, the USP convention met every 10 years and produced a revision to the book; pharmacists were invited to join in 1850.¹

The USP is an independent organization where decisions about standards are made by the many volunteers serving on various expert committees. There are two committees that address compounding; one for nonsterile and one for sterile activities. Each committee consists of 10 to 12 volunteers from pharmacy practice, academia and related support companies. The expert committees meet with sufficient frequency to accomplish their goals (usually one to three times per year) and conduct much of their business via telephone, e-mails, etc. Each committee has a staff liaison at USP that is responsible for working with the committees.

The USP was mentioned as a “standard” in the Drug Importation Act of 1848 and the USP and NF were both established as official compendia for the United States in the Pure Food and Drug Act of 1906. Its’ status continues today. In 1938, the Food and Drug Administration (FDA) was born, having originally been the US Department of Agriculture Bureau of Chemistry, then the Food, Drug and Insecticide Administration and finally the FDA. The FDA can enforce the standards established by the USP for the pharmaceutical industry or the standards it develops. The USP is independent and has no relationship with either the federal government or the FDA. It is unique because other pharmacopoeias throughout the world are prepared by the government of the country, but not the USP.¹

The National Formulary (NF) was first published in 1888 by the American Pharmaceutical Association, listing standardized formulas including the ingredients and their quantities required for compounding purposes.¹

In 1940, the USP changed from the 10-year to a 5-year meeting cycle to adapt more rapidly to change. In 1975

the USP purchased the NF and in 1980 the first combined USP-NF was published and continually published the book every 5 years. In 2002, annual revisions were implemented. Today the USP-NF is published on an annual basis.¹

There was a change in the USP during the early-mid 1900s as the pharmaceutical industry began to grow and assume a major role in providing pharmaceuticals to the public. The USP changed its format from an orientation towards compounded pharmaceuticals to manufactured pharmaceuticals. This change continued throughout the 1900s and early into the 2000s. Also, during the 1800s and 1900s, the State Boards of Pharmacy enforced the standards of the USP and NF in pharmacies at the state level. However, as compounding diminished, the state boards did not necessarily require USP or NF volumes actually be in the required library of the pharmacies.

However, in the 1970s, there was a resurgence of pharmacy compounding and in 1985, the USP Convention passed two resolutions urging the USP to become active again in promoting standards for pharmacy compounding. This was followed with convention resolutions in 1990, 1995 and again in 2000.

In 1993, there was the formation of the Expert Advisory Panel and the Review Panel on Pharmacy Compounding Practices by the USP. The Expert Advisory Panel is divided into two groups; one to work on general chapters and the other to work on compounding monographs. In 1996, the USP published the chapter Pharmacy Compounding Practices <1161> to provide guidance to pharmacists and other compounding professionals on proper compounding practices and techniques.

When Congress enacted the FDA Modernization Act of 1997 (FDAMA97) that referred to pharmacy compounding, the FDA formed an internal FDA Steering Committee and an external FDA Compounding Advisory Committee to aid in implementing the compounding provisions of FDAMA97. Since FDAMA97 referred to USP and the enforceability of its contents, it was deemed necessary to renumber <1161> Pharmacy Compounding Practices from an informational chapter (numbered >1000), to <795> an enforceable chapter (numbered <1000) and ultimately its name was changed to Pharmaceutical Compounding-Nonsterile Preparations. It became official in January 2000 and remains so today.

In the mid-1990s, those involved with the USP pharmacy compounding activities saw the need to reorient part of the USP-NF back to pharmacy. It was evident that the regular USP-NF had grown so much and was so entrenched in the pharmaceutical industry, but yet much of it still applied to pharmacy practice. It was then that the idea of a separate compendium was born. In July 2005, the long-awaited USP-Pharmacists' Pharmacopoeia was published, containing official and authorized information for pharmacists.

TAKE A TOUR THROUGH <795>²

Walking through USP <795>, the first thing that is discussed is the responsibility of the compounder (which covers pharmacists, physicians, etc.). One has to have a facility in which to practice that meets certain minimum standards as well as equipment. One must also know about the stability of the compounded preparations and what kind of beyond-use date can be placed on the preparations. The next item concerns the selection of ingredients and their quality. There is a checklist that should be considered before compounding and then a discussion of procedures for different dosage forms. The compounding process is discussed as well as necessary records and documentation. The chapter concludes with short discussions on quality control, verification and patient counseling.

Before we look at some details, let's go over some terminology. We have "manufactured products" and "compounded preparations"; this distinguishes between the output of the pharmaceutical companies (products) and the pharmacies (preparations). Pharmacists compound "preparations"; the pharmaceutical industry manufactures "products". Also, products have "expiration dates" that are determined through extensive laboratory experimentation, statistical analysis, etc. Compounded preparations have "beyond-use dates" which are conservative reasonable estimates.

Let's briefly review the intent and/or emphasis of the various sections of <795>.

RESPONSIBILITY OF THE COMPOUNDER

The buck stops here! The primary emphasis on the responsibility of the compounder centers around assurance of quality in the areas of personnel, ingredients, finished preparations, processes, environment, stability, consistency, error-prevention and documentation.

FACILITY AND EQUIPMENT

Facilities and Equipment

The primary requirement here is adequate and appropriate space. These requirements are similar to those mandated by the state boards of pharmacy.

Equipment must simply be appropriate in design and size and suitable for the purpose for which it is used. It should not interact or interfere with the compounded preparation or process. It must be properly maintained, used, calibrated and cleaned.

STABILITY OF COMPOUNDED PREPARATIONS

Primary Packaging, Stability Criteria and Beyond-Use Dating, Beyond-Use Labeling

The beyond-use date is the responsibility of the compounder and is determined from the time of compounding, not the time of dispensing. Compounders can consult appropriate literature, manufacturers and work with analytical laboratories to determine an appropriate beyond-use date. In the event there is no data available, the chapter provides guidelines that can be used, as follows:²

- Solids and non-aqueous liquids prepared from commercially available dosage forms - 25% of the remaining expiration date of the commercial product, or 6 months, whichever is earlier.
- Solids and non-aqueous liquids prepared from bulk ingredients - up to 6 months.
- Water-containing formulations (prepared from ingredients in solid form) - up to 14 days when stored in a refrigerator.
- All other formulations - up to 30 days or the intended duration of therapy, whichever is earlier.

DEFINITIONS

The purpose of this section is merely to provide a definition for some terms used in the chapter.

INGREDIENT SELECTION

Sources

First and foremost, USP and NF grade ingredients should be used. If an item is not monographed in the USP or NF,

then the pharmacist must select a reasonable high-quality grade ingredient from a reliable source. Certificates of analysis can be useful in establishing quality of the ingredients used, both active and excipients. Items not to be compounded are those on the FDA negative list. However, one must read the negative list very carefully because in some cases, it is not all dosage forms of an active drug, but just a specific dosage form that is on the list and other dosage forms can be prepared.

CHECKLIST FOR ACCEPTABLE STRENGTH, QUALITY AND PURITY

A series of five questions are presented for consideration concerning each and every compounded preparation. While some of these questions are second nature, some may require some thought and even investigation, such as those related to local or systemic absorption. These questions are as follows: ²

1. Have the physical and chemical properties and medicinal, dietary, and pharmaceutical uses of the drug substances been reviewed?
2. Are the quantity and quality of each active ingredient identifiable?
3. Will the active ingredients be effectively absorbed, locally or systemically according to the prescribed purpose, from the preparation and route of administration?
4. Are there added substances, confirmed or potentially present from manufactured products, that may be expected to cause an allergic reaction, irritation, toxicity, or undesirable organoleptic response from the patient? Are there added substances, confirmed or potentially present, that may be unfavorable (e.g., unsuitable pH or inadequate solubility)?
5. Were all calculations and measurements confirmed to ensure that the preparation will be compounded accurately?

COMPOUNDED PREPARATIONS

Quality suggestions, clinical considerations and technical procedural hints are provided for solid, liquid and semisolid dosage forms.

COMPOUNDING PROCESS

Thirteen steps are presented to minimize error and maximize the prescriber's intent for the patient. These should all be covered in the standard operating procedures of the pharmacy and are good practice standards to follow. The steps are as follows: ²

1. Judge the suitability of the prescription to be compounded in terms of its safety and intended use. Determine what legal limitations, if any, are applicable.
2. Perform necessary calculations to establish the amounts of ingredients needed.
3. Identify equipment needed.
4. Wear the proper attire and wash hands.
5. Clean the compounding area and needed equipment.
6. Only one prescription should be compounded at one time in a specified compounding area.
7. Assemble all necessary materials to compound the prescription.
8. Compound the preparation following the formulation record or prescription, according to the art and science of pharmacy.
9. Assess weight variation, adequacy of mixing, clarity, odor, color, consistency and pH as appropriate.
10. Annotate the compounding log, and describe the appearance of the formulation.
11. Label the prescription containers to include the following items:
 - a) The name of the preparation
 - b) The internal identification number
 - c) The beyond-use date
 - d) The initials of the compounder who prepared the label
 - e) Any storage requirements
 - f) Any other statements required by law.
12. Sign and date the prescription affirming that all procedures were carried out to ensure uniformity, identity, strength, quantity, and purity.
13. Thoroughly and promptly clean all equipment, and store properly.

COMPOUNDING RECORDS AND DOCUMENTS

Formulation Record, Compounding Record, MSDS File

State boards of pharmacy have record keeping requirements that must be met. The following are practical for quality purposes and to enable another compounder to duplicate the preparation when prepared at a later time.

The formulation record generally will be either on the computer system, or may be an individual new prescription or request. This is where the process starts. The formulation record can be used to prepare the documentation for the compounding record.

The compounding record contains the sources and lot numbers of the ingredients, calculations, processes used, results of any testing done, an assigned beyond-use date, identification numbers, name of the compounder, quantity of the preparation compounded and other pertinent information. It contains all relevant information related to the actual compounding of the specific prescription. It is used for checking the final preparation for accuracy.

Material Safety Data Sheets (MSDSs) may be either hard copy or accessible electronically. They are needed for all drug substances or bulk chemicals located in the compounding pharmacy. If commercial products are used, the package insert can serve this purpose.

QUALITY CONTROL

All the paperwork from the first step to the final preparation should be reviewed along with observing the finished preparation.

Standard Operating Procedures (SOPs) are documents that describe how to perform routine tasks in the environment of formulation development, purchasing, compounding, testing, maintenance, materials handling, quality assurance and dispensing. They contain step-by-step instructions to perform tasks reliably and consistently; including how a task will be performed, who will do the task, who is responsible, why it will be performed and any limits associated with the task.

VERIFICATION

Verification, not validation, is what is required. Verification involves checking to ensure that all the processes were appropriate and accurately performed. Validation is much more involved and time-consuming.

PATIENT COUNSELING

As with any prescription, patient counseling is important. It is especially important with compounded preparations where the beyond-use date may be rather short. Patients should be counseled about use, storage and evidence of instability (visual changes, odor, etc.).

SUMMARY

There is no question that the standards of the USP serve to enhance patient safety and also protect the pharmacist. There are many general chapters in the USP that either directly or indirectly affect pharmacy compounding. The primary chapters are <795> Pharmaceutical Compounding-Nonsterile Preparations, <797> Pharmaceutical Compounding Compounding-Sterile Preparations, <1075> Good Compounding Practices, and <1160> Pharmaceutical Calculations in Prescription Compounding.

REFERENCES

1. Allen Jr LV, Popovich NG, Ansel HC. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 8th Ed. Baltimore MD, Lippincott, Williams & Wilkins, 2005, pp 7-12.
2. U.S. Pharmacopoeial Convention, Inc. USP-Pharmacists' Pharmacopeia, Rockville MD, U.S. Pharmacopoeial Convention, Inc., 2005, pp 408-413.

Copies of the individual USP Chapter <795> Pharmaceutical Compounding-Nonsterile Preparations or the new USP-Pharmacists' Pharmacopeia, can be obtained online at www.usp.org or by calling 1-800-227-8772.

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Please circle the most appropriate answer for each of the following questions. There is only ONE correct answer per question.

- The first U.S. Pharmacopeia was established in 1820 by a group of:
 - pharmacists.
 - physicians.
 - government agents.
 - state boards.
 - physicians and dentists.
- Today, the USP/NF standards are applicable to:
 - pharmaceutical companies
 - compounding pharmacies
 - health food/nutrition stores
 - I only
 - III only
 - I and II only
 - II and III only
 - I, II and III.
- The USP began to reorient its activities to include pharmacy compounding again in:
 - 1965
 - 1970
 - 1975
 - 1980
 - 1985
- The terminology applied to compounded prescriptions and the date after which they should not be used are:
 - products, expiration date
 - products, beyond use date
 - preparations, expiration date
 - preparations, beyond use date
 - none of the above
- The ultimate responsibility for compliance with all the USP/NF standards for compounding rest with the:
 - prescribing physician
 - owner
 - compounder
 - technician
 - all the above
- If no valid data is available for an aqueous, oral compounded suspension, the beyond use date to be applied is:
 - 24 hours at room temperature
 - 72 hours at refrigerated temperature
 - 1 week at room temperature
 - 2 weeks at refrigerated temperature
 - 6 months at refrigerated temperature
- Which of the following is NOT on the checklist for acceptable strength, quality and purity?
 - Have the physical and chemical properties and medicinal, dietary, and pharmaceutical uses of the drug substances been reviewed?
 - Are the quantity and quality of each active ingredient identifiable?
 - Will the active ingredients be effectively absorbed, locally or systemically according to the prescribed purpose, from the preparation and route of administration?
 - Has the bioavailability of the compounded preparation been demonstrated?
 - Were all calculations and measurements confirmed to ensure that the preparation will be compounded accurately?
- The purposes of the thirteen steps in the Compounding Process are to:
 - minimize errors
 - maximize the prescribers' intent for the patient
 - provide shortcuts in compounding
 - I only
 - III only
 - I and II only
 - II and III only
 - I, II and III.
- Which of the following records is where the information concerning the ingredients used in compounding a prescription, such as the manufacturer, lot numbers, expiration dates of chemicals, are recorded?
 - formulation record
 - compounding record
 - material safety data sheet
 - certificate of analysis
 - none of the above
- The purpose of the compounding standards of the USP are to:
 - ensure third party reimbursement
 - enhance patient safety
 - protect the pharmacist
 - I only
 - III only
 - I and II only
 - II and III only
 - I, II and III.
- My practice setting is:
 - Community-based
 - Managed care-based
 - Hospital-based
 - Consultant and other
- The quality of the information presented in this article was:
 - Excellent
 - Good
 - Fair
 - Poor
- The test questions correspond well with the information presented.
 - Yes
 - No
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