EXPERIENCE OF THE UNITED STATES PHARMACOPEIA IN COMPOUNDING PREPARATIONS STANDARDIZATION AND MONOGRAPH DEVELOPMENT

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The United States Pharmacopeia Convention (USP) has been developing standards for compounding practitioners since its founding on January 1, 1820. The first publication, *The Pharmacopeia of the United States of America*, was published later that year on December 15 1820. It contained 217 formulas printed on 272 pages. To obtain the compounding formulas for publication, the founders of USP, divided the country into 4 districts and sought from medical schools and medical societies, recipes for "substances which possess medicinal power, those, the utility of which is most fully established and best understood" (today we call this "evidence-based medicine"). Today, nearly 200 years later, USP continues to develop and publish standardize compounded preparation monographs. USP continues to conduct surveys to obtain formulas that are commonly compounded by reaching out to national organizations such as the International Academy of Compounding Pharmacists (IACP), American Veterinary Medical Association (AVMA), and the American College of Veterinary Pharmacists (ACVP) as well as specialized pediatric and geriatric hospitals. All of USP's compounding standards are developed based on the expertise and knowledge of the USP Compounding Expert Committee.

USP publishes three types of standards affecting compounding:

- Monographs for bulk substances used in compounded preparations
- General Chapters describing practice and quality standards for compounding
- Compounded preparation monographs containing formulations for specific preparations.

There are currently six essential compounding General Chapters in the *United States Pharmacopeia–National Formulary*: <797> *Pharmaceutical Compounding—Sterile Preparations*, <795> *Pharmaceutical Compounding—Nonsterile Preparations*, <800> *Hazardous Drugs – Handling in Healthcare Settings*, <1160> *Pharmaceutical Calculations in Pharmacy Practice*, <1163> *Quality Assurance in Pharmaceutical Compounding*, <1176> *Prescription Balances and Volumetric Apparatus Used in Compounding*. One additional General Chapter is now in development, <1168> *Compounding for Investigational Studies*. General Chapters contain good compounding practices for sterile and nonsterile preparations and other information helpful to the compounding practitioner.

USP's Council of Experts and Expert Committees are responsible for developing and revising USP standards. USP's Expert Committees are elected on a 5-year cycle with the current one beginning on July 1, 2015. The committee responsible for developing compounded preparation monographs is the Compounding Expert Committee. The 18-member Compounding Expert Committee represents expertise across all compounding areas, including sterile and nonsterile compounding. As of *USP39-NF34*, there are over 175 official compounding monographs published for human and veterinary use. These include formulas for oral suspensions, oral solutions, suppositories, injections, topicals and ophthalmics.

Over the course of the last several decades, USP has developed monographs in different ways. Previously, USP developed monographs based on peer-reviewed literature studies published in major journals. These studies were evaluated against a 33 point criteria checklist developed by the Compounding Expert Committee. The checklist included 4 mandatory requirements and 29 supporting criteria. Since 2011, USP develops monographs based on work conducted by contract

laboratories. The contract laboratories develop and validate a stability-indicating method and conduct stability testing on the formulation to establish a beyond-use date.

The method validation confirms that the method meets certain criteria. The typical analytical characteristics used in method validation include accuracy, precision, specificity, linearity, range, and ruggedness, as outlined in general information chapter <1225> *Validation of Compendial Procedures*. The Compounding Expert Committee has developed a very extensive protocol that the analytical laboratories must follow for conducting these studies. Once the method is developed and validated, and stability testing is completed, the Compounding Expert Committee reviews the work and drafts a monograph for publication in the *Pharmacopeial Forum* for public comment. After the public comment process, the Compounding Expert Committee evaluates that public input and votes on the standard for publication into (*USP-NF*).

A USP Compounded preparation monograph contains the following 9 sections:

- **Title**
- **Definition**
  Lists the range of labeled amount of active ingredient
- **Formula**
  Ingredients and quantities
- **Compounding Procedures**
- **Stability-indicating Assay (majority of recent monographs)**
- **pH (when appropriate)**
- **Packaging and Storage**
- **Labeling**
- **Beyond-use dates**

USP standards - general chapters and monographs - contained in the *USP-NF* have long been recognized in various provisions of the United States Federal, Food, Drug and Cosmetic Act (FDCA). Any drug that is recognized in the *USP-NF* must adhere to USP standards for identity, strength, quality, purity, packaging and labeling or risk being deemed adulterated or misbranded. These provisions do not differentiate between manufactured or compounded medications.

Practitioners of the United States of America who compound should understand their responsibility to comply with USP standards. Compounding, while a part of federal law as described above, is largely regulated by the state boards of pharmacy. A number of states have incorporated USP's compounding General Chapters into their pharmacy laws and regulations, and require compliance with these standards.

USP began publication of the *Compounding Compendium* in 2012. The *Compounding Compendium* contains a subset of standards in the *USP-NF* as it is related to compounding. The publication offers compounding practitioners convenient access to all compounding-related General Chapters and monographs. The *USP Compounding Compendium* also features more than 40 supporting general chapters and more than 175 compounding monographs along with *USP–NF* General Notices and Requirements.

The U.S. Pharmacopeial Convention (USP) is a scientific nonprofit organization that sets public standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements manufactured, distributed and consumed worldwide. USP's drug standards are enforceable in the United States by the Food and Drug Administration and state regulatory authorities. These standards are used in more than 140 countries which supports our mission to improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.