



WHITE PAPER

A MODEL SYSTEM TO PROMOTE ACCESS TO GOOD QUALITY COMPOUNDED MEDICINES

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COUNCIL OF THE CONVENTION SECTION ON
THE QUALITY OF COMPOUNDED MEDICINES

INTRODUCTION

Extemporaneous compounding of preparations is a worldwide practice dating back centuries. Today, compounding is commonly defined as the preparation of a medicine in accordance with a licensed practitioner's prescription or medication order. This definition evolves from a triad—the prescribing practitioner, the compounding professional, and the patient/consumer. Historically, what was once viewed as an art is now deeply rooted in the scientific study of how to prepare and assess compounded preparations, together with provision of stability data to allow assignment of a beyond-use date (BUD).

In the following white paper, USP's Council of the Convention Section on the Quality of Compounded Medicines provides a general description of non-governmental and governmental approaches to provide compounding standards and conformity assessment to these standards. Conformity assessments may be conducted by various parties—first (compounding group/individual), second (purchasing group/individual), or third (group/individual independent of first or second party). While data are limited, all types of conformity assessments are likely to be conducted in the United States. The white paper then articulates a proposal for a model system of standards and conformity assessments to standards that assure access to good quality compounded preparations.¹

¹This paper is intended to address both compounding for human use and compounding for veterinary use. However, there are some significant differences between the two, including differences in the relevant laws. The federal laws regulating veterinary compounding are found in the Animal Drug Amendment of 1968 and the Animal Medicinal Drug Use Clarification Act of 1996 (and related regulations and guidances) which are intended to protect consumers of foods of or from animals, as well as the animals themselves that might be treated with drugs, including compounded preparations. As with compounding for human use, there is controversy surrounding the distinction between legitimate compounding and manufacturing; the scope of the FDA's role in regulating veterinary compounding; and the efficacy, safety, and appropriate labeling of these products, as well as other issues. A detailed discussion of the particular considerations that apply in the veterinary context is beyond the scope of this paper, but USP is committed to providing standards for compounding of preparations for both human and animal use, and the information and model system proposed herein is generally applicable to both human and veterinary compounding.



UNITED STATES NON-GOVERNMENTAL APPROACHES

1. USP: PREPARATION AND PROCESS STANDARDS

The compounding of the most “fully established and best understood” preparations for patient use was a founding principle for USP’s volunteer practitioners in 1820. USP still takes an active role in supporting the public’s access to the type of customized therapy offered by compounding and works to ensure the quality of such therapy by creating national standards and guidelines for compounding both sterile and nonsterile medications. These standards are process standards in that they provide appropriate techniques and procedures to guide practitioners in compounding. They also are product standards (commonly referred to as *preparation* standards to distinguish compounded formulations from manufactured products) to allow testing, both of the materials used in a compounded preparation and also the compounded preparations themselves, to assess quality and establish a BUD. Taken together, these preparation and process standards appear in official compendia of the United States—the *United States Pharmacopeia (USP)* and *National Formulary (NF)*. Just like manufactured medicines, compounded preparations must comply with the product standards in the *USP* and *NF*, which are recognized as official compendia in federal food and drug law. In addition, a number of States recognize USP’s process standards for compounding and require compliance with these standards. These legal requirements are discussed further below.

In the 2005-2010 cycle, USP supported two Expert Committees that provided these compounding standards. The Compounding Pharmacy Expert Committee of USP’s Council of Experts is composed of 10 experts, with proven extemporaneous compounding expertise representing varied pharmacy environments such as hospital, ambulatory, academia, veterinary practice, and private practice. The Sterile Compounding Expert Committee of USP’s Council of Experts is composed of 12 experts, also representing a wide range of pharmacy disciplines and infection control. These two Expert Committees: 1) develop compounded preparation monographs that can be used every day by pharmacists to prepare medications for patients requiring customized drug therapy, and 2) develop and revise General Chapters that describe good compounding practices.

As an emanation of the standards from USP’s two Expert Committees in the Council of Experts, USP supports several compounding constituencies through publication of the *Pharmacists’ Pharmacopeia (P2)*, now in its second edition. *P2* contains more than 115 compounding monographs, for use in both humans and animal patients, and 75 supporting General Chapters, all of which were excerpted from the *USP* and *NF*. In USP’s ongoing effort to develop more preparation monographs, academic and other laboratories are performing method development and stability studies for both sterile and nonsterile preparations. When these studies are completed, they provide information to support decisions of the compounding Expert Committees relative to a BUD designation. Currently, 17 compounded preparations are under study. USP also is reaching out to professional organizations and others to obtain candidate formulations, materials, tests, procedures, and acceptance criteria for the two compounding Expert Committees. The total universe of formulations needed for compounded preparations is unknown, but is well over 1,000. USP is attempting to focus on those that are most commonly compounded or that present the most significant risk.



2. PROCESS STANDARDS/CONFORMITY ASSESSMENTS FOR SITE ACCREDITATION

The Pharmacy Compounding Accreditation Board (PCAB) was launched in 2004 by eight pharmacy-related organizations (including USP) as a voluntary accrediting body to assess compounding pharmacies against high quality standards for compounding. The founders of PCAB, and the pharmacists they represent, believed that standards against which compounding pharmacies can be tested are not only good for patients, but also good for the practice of pharmacy.² To date, PCAB has accredited 65 compounding pharmacies. Each PCAB-accredited pharmacy undergoes a rigorous review of its policies and procedures and an onsite inspection against PCAB standards, which incorporate USP standards.

The pharmacies that have achieved the milestone of PCAB accreditation have demonstrated their commitment to quality standards and procedures. However, participation levels in PCAB are less than hoped for among U.S. pharmacies, which include approximately 3000 to 4000 pharmacies that emphasize compounding capability. This may be attributed to the rigor of the accreditation process and the absence of “drivers” that would compel pharmacies to seek accreditation, e.g., reimbursement and insurance. Nevertheless, PCAB in recent months has seen an upswing in applications with over 140 pharmacies awaiting survey. Emerging “drivers” include professional organizational endorsements of PCAB (beyond PCAB’s governing board institutions), including the American Medical Association, American Veterinary Medical Association, American Animal Hospital Association, American Association of Equine Practitioners, and others, as well as incentives offered by liability insurers.

In 2008, PCAB established a separate Accreditation Committee that now oversees the accreditation process, and more recently began the first formal review of PCAB standards since their adoption in 2004. The revised standards are expected to be available before the end of 2009.

3. CONFORMITY ASSESSMENTS FOR PRACTITIONERS

There are several organizations and accreditation activities that speak to conformity assessments for practitioners. The Accreditation Council for Pharmacy Education (ACPE) is the national agency responsible for the accreditation of professional degree programs in pharmacy. ACPE sets accreditation standards and guidelines for pharmacy education and conducts conformity assessment of institutions. Standardized assessment of practitioner competence also occurs through the North American Pharmacists Licensure Examination (NAPLEX) developed by the National Association of Boards of Pharmacy (NABP). NAPLEX is used by boards of pharmacy as part of their assessment of pharmacy practitioners’ competence prior to licensure. Certification through the Board of Pharmaceutical Specialties (BPS) is one additional conformity assessment for practitioners. BPS certification is a voluntary process by which a pharmacist’s education, experience, knowledge, and skills in a particular practice area are confirmed as well beyond what is required for licensure; however, there is currently no BPS specialty in compounding.

² Pharmacy Compounding Accreditation Board, www.pcab.info 2009.



UNITED STATES GOVERNMENT APPROACHES

1. FEDERAL

The role of federal law and regulatory oversight of compounding has proven to be one of the most problematic for FDA, particularly in recent years. As a general rule, FDA has tended to avoid involvement with activities that relate to the practice of medicine and pharmacy, both of which traditionally are regulated at the level of the states in the U.S. However, FDA pays close attention to the quality of products regardless of whether they are manufactured products or compounded preparations. Sorting out the scope of state versus federal authority, and the demarcation between compounding and drug manufacturing, has proven elusive. Congressional efforts to resolve the issue have so far failed. For now, there is a legal and regulatory stalemate, leaving compounding practitioners and regulatory authorities in a state of uncertainty.

The federal legal history leading up to this point helps illuminate the current situation. In FDA's view, compounded drugs in interstate commerce are "drugs" under the Federal Food, Drug, and Cosmetic Act (FDCA), and are potentially subject to the full panoply of requirements (including pre-approval prior to marketing, such as a New Drug Application (NDA), good manufacturing practices (GMPs) required for manufacturing, and compliant labeling). In recognition of the role of compounding, FDA has generally, in the exercise of its enforcement discretion, excused such compounded drugs from most requirements otherwise applicable to "drugs." In particular, under FDA Compliance Policy Guidance (CPG) 460.200, eligible compounding has been exempted from: the adulteration provisions of the FDCA with respect to GMPs; the misbranding provisions regarding labeling with adequate directions for use; and the new drug requirements, that is, approval of an NDA or Abbreviated New Drug Application (ANDA).

In 1997, Congress sought to codify many aspects of FDA's compounding policy and generally provide a limited regulatory exemption from certain requirements of the FDCA for compounding. Section 127 of the FDA Modernization Act (FDAMA), which added §503A to the FDCA, in large part reflected CPG 460.200, and, among other things, provided that bulk drug substances used for compounding must comply with *USP* or *NF* requirements. To identify the compounding eligible for the less stringent regulatory requirements of 503A, Congress stipulated that such eligible compounders could not "advertise or promote the compounding of any particular drug, class of drug, or type of drug," although the "compounding service" itself could be advertised and promoted. These limits on advertising were found by the 9th Circuit U.S. Court of Appeals in the *Western States* decision to be unconstitutional; moreover, the 9th Circuit held that the advertising restriction was not severable from the rest of FDCA 503A, thereby leaving at least the 9th Circuit in a pre-FDAMA condition (in terms of the application of the overall FDCA). The Supreme Court later affirmed *Western States*, but declined to consider the severability issue. More recently, the 5th Circuit declined the request of pharmacists to find that compounded drugs are exempt from the "new drug" provisions of the FDCA, but also found that the unconstitutional advertising restrictions of FDCA 503A are severable (leaving what some now call a "503A safe harbor").



Thus, in the 5th Circuit, 503A, absent the advertising provision, applies to eligible compounders. Elsewhere in the country, FDA’s current compounding policy continues to be reflected in the CPG it issued in the wake of the *Western States* decision.³

While these federal uncertainties are sorted out, USP continues to play an important role: 1) state law may incorporate USP process standards (e.g. General Chapters <797> *Pharmaceutical Compounding – Sterile Preparations* and <795> *Pharmaceutical Compounding – Nonsterile Preparations*) in regulating the practice of compounding, and 2) compounded preparations remain “drugs” under the FDCA and must comply with any applicable USP monographs if they use the name recognized in *USP-NF*.

2. STATE

In the U.S., pharmacy practice, including compounding, is regulated at the state level by state boards of pharmacy. Each state establishes and enforces its own laws and regulations governing the practice of pharmacy and performs routine inspections of pharmacies to ensure compliance. State boards also issue licenses to pharmacists—evaluating their competence to practice—and to pharmacies. When needed, state boards also investigate complaints. There are times when states recognize standards from non-governmental third parties; for example, several states recognize *USP* for sterile and nonsterile compounding and, to a more or lesser degree, other *USP* standards related to compounding, drug product labeling and packaging.

In an effort to maintain a certain level of consistency among the states, NABP offers to boards of pharmacy model language that may be used when developing state laws or board rules. The current set of model regulations also contains the NABP Model Rules for Pharmacy Interns, Institutional Pharmacy, Pharmacist Care, Nuclear/Radiologic Pharmacy, and Sterile Pharmaceuticals.

NON-U.S. APPROACHES

1. ARGENTINA

In Argentina, the Health Department regulates the practice of pharmacy compounding. Legal difficulties abound for compounding practitioners because there are few established regulations to guide compounding practices and the guidelines that do exist are based on outdated legislation. Technical and scientific advances in drug therapy are not considered in the guidelines. Even though the regulatory framework may be lacking in certain respects, some restrictions do exist that ultimately limit patient access to medicines. For example, several dosage forms and therapeutic categories—such as troches, nasal preparations, and ophthalmics—are excluded and hormone replacement therapies, as well as medicines the U.S. would term over-the-counter, are not permitted to be compounded. In addition, Olanzapine (*Zyprexa* for schizophrenia/acute manic episodes) is the only drug that cannot be used in compounding.

³ <http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074398.htm>.



2. BRAZIL

The Brazilian National Health Surveillance Agency (ANVISA) regulates compounded pharmaceuticals. In 2005, ANVISA proposed new rules for compounding pharmacies, including:

- Disallowing compounded drugs of the same formulation as manufactured products;
- Setting limits on the marketing of products to the general public; and
- Requiring the pharmacist to provide the patient with more product information, including the drug formulation, adverse effects, and duration of treatment.

Veterinary pharmaceuticals are regulated by a number of different agencies, including the Ministry of Agriculture and the Ministry of Agriculture, Cattle and Supplying. Brazil appears to be one of the most advanced countries in regards to compounding. Brazil has 306 Schools of Pharmacy and graduates 14,000 pharmacists per year. In contrast the U.S. has slightly over 100 Schools of Pharmacy. There are 7,211 pharmacies in Brazil that are solely engaged in compounding and 16,000 compounding pharmacists. Brazil offers Continuing Education (CE) on compounding over standard TV channels throughout the country. ANFARMAG is Brazil's National Association of Compounding Pharmacies and has a membership of over 4,000 pharmacists.

3. GERMANY

Federal Law, primarily the *Arzneimittelgesetz*, and subordinate federal directives, primarily the *Apothekenbetriebsordnung*, regulates the practice of pharmacy compounding in Germany. Extemporaneous preparation is mandatory when a prescription requiring compounding is presented to a community pharmacy. All dosage forms can be compounded; however, preparations that are difficult to compound (e.g. cytotoxic preps, injectables) can be compounded only after a pharmacist has completed special training. Over-the-counter (OTC) compounding is allowed and occurs frequently. There is a list of preparations that both community pharmacies and hospitals are not allowed to prepare, such as allergens used to trigger an allergic response in a patient. Beyond-use dating for 243 standardized formulas is provided in the *Neues Rezeptur-Formularium (NRF)*. There are 21,570 pharmacies in Germany.

4. SPAIN

In Spain, regional governments regulate the practice of pharmacy compounding. Four levels of compounding exist: 1) Dispensing; 2) Topical; 3) Oral, rectal and vaginal; 4) Sterile. Beyond-use dates for compounded preparations are based on literature and references, such as *USP-NF*. Health authorities in Spain have a very restrictive attitude toward pharmaceutical compounding. Compounded medicines are generally regarded as the last resource and authorized almost exclusively when all other therapeutic alternatives have failed. Pharmacies that only engage in compounding are not allowed. If a pharmacy only performs Level 1 compounding; i.e., dispensing, it must subcontract with a pharmacy that does other levels of compounding because it is against the law to refuse to serve any patient that enters a pharmacy. "Elaboracion a terceros" (third-party compounding) is the term used when a pharmacy contracts with another pharmacy specializing in higher-level compounding. Spanish patients receive most of their prescription medicines free or at little cost. However, compounded preparations are reimbursed according to a drug list that, according to Spanish practitioners, is currently out of date. Pharmacists are allowed to compound OTCs for sale in their own pharmacies, with the only limitation



being that the medicine must be described in the Formulario Nacional (National Formulary). Additional specialized training is not required to be a compounding pharmacist. AEFF is the Spanish Association of Compounding Pharmacists.

A MODEL SYSTEM

The goal of any model system is to assure access to good quality compounded medicines, assist compounding practitioners—pharmacists and physicians—in delivering such preparations to patients, and ensure patient safety, above all. While a number of standards, including USP's, exist to help ensure that compounded medicines are of good quality, the lack of strong conformity assessments to such standards leaves both practitioners attempting to provide access to good quality compounded medicines as well as patients/consumers who receive them at risk. In this setting, the Council of the Convention Section on Quality of Compounded Medicines offers the following model system of standards and conformity assessments, in which USP would play a primary role in developing monographs and process standards and could play a role in other areas as well.

1. PEOPLE, PROCESS AND PREPARATION STANDARDS

- Ingredient and Preparation Standards (Product)

Optimally, a preparation monograph in *USP* exists for all compounded preparations in the U.S. Compounding monographs are prioritized so that standards for the most frequently compounded articles are developed first. The Compounding Expert Committee, working with compounding practitioners, associations and others, develops a preparation monograph. The Committee takes into account safety and other considerations, such as intended use in target species. This input is obtained through a variety of sources, including FDA (whose views are represented by FDA liaisons to the Committee), NABP, and other practitioner and board associations. As noted above, conformance to such monographs is required under the FDCA.

- Compounding Sites Standards (Practice and Process)

Optimally, practitioner associations and others, including associations representing state practitioner boards such as NABP, develop standards for all compounding sites (both in community and hospital locales where compounding is practiced, as well as practitioner office practices). Practice standards (<795>, <797>, and others) developed by USP for compounding are recognized in state regulations and accreditation standards (similar to the treatment of compounding provided by NABP in its Model Pharmacy Act and Pharmacy Rules).

- Practitioner Training and Accreditation (People)

Adequate professional education and training curricula are adapted in schools of pharmacy to ensure that competencies in compounding are acquired and are supported by assessment through NAPLEX and licensure requirements through the state boards. An independent certifying body, such as BPS, builds an accreditation to define specialty certification of compounding practitioners. Optimally, all practitioners who compound complex or sterile preparations beyond a certain frequency are certified.



2. CONFORMITY ASSESSMENTS

- Site Accreditation

Through Congressional and/or judicial and regulatory determinations, the line between compounding and manufacturing is clarified, with the states retaining responsibility for regulation of compounding and FDA retaining responsibility for regulation of manufacturing. State boards of pharmacy (and other disciplines' boards), working with PCAB or equivalent national practitioner associations, are responsible for conformity assessments of all compounding sites. When appropriate, a state board may deem non-governmental bodies, such as PCAB or equivalent associations, suitable to accredit traditional compounding sites. Optimally, all sites engaging in significant compounding activity require accreditation.

- Adverse Event Reporting

An adverse event reporting system that offers strong Federal confidentiality and privilege protections, as provided by the Patient Safety Act of 2005, is provided and maintained to ensure the capture of adverse events associated with compounded preparations, for deliberation and analysis regarding quality and safety.

SUMMARY

As a general matter, compounding remains both a responsibility for practitioners (those who prescribe compounded medicines as well as those who compound them) and an opportunity for their patients. At the same time, assurance that manufacturing does not occur under the guise of compounding is critically important. This white paper argues for a model system, building on good systems in the U.S. and other countries, that recognizes the interests of all parties in assuring access to good quality compounded preparations.