

Starting A Compounding Pharmacy Practice

Goal: To describe what one must be willing and able to do upon entering pharmaceutical compounding practice.

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

1. Explain the various factors that must be considered when starting a pharmacy compounding service.
2. Evaluate the requirements and determine if one is willing to make the commitments for pharmacy compounding.
3. Determine whether or not the resources required are available for the type of compounding practice being considered.
4. Discuss the various activities involved in compounding a prescription for an individual patient.

INTRODUCTION

The purpose of this issue of *Secundum Artem* is to discuss the factors to be considered when deciding upon whether or not to establish a compounding pharmacy practice. This discussion is not all-inclusive because the factors that need to be considered are quite numerous.

Pharmacists possess knowledge and skills that are not duplicated by any other profession. Their roles in ambulatory care can include dispensing and compounding medications, counseling patients, minimizing medication errors, enhancing patient compliance, monitoring drug therapy, and minimizing drug expenditures. A pharmacist's expertise must be used to adjust dosage quantities, frequencies, and even dosage forms for enhanced compliance. All pharmacists must be aware of the drug therapy options provided by compounding. Pharmacy is united in the belief that pharmacists have a responsibility to serve their patients and compound an appropriately prescribed product in the course of professional practice. It is both the right and the responsibility of pharmacists to compound medications (sterile and nonsterile) to meet the specific needs of patients.

Compounding may hold different meanings for different pharmacists. It may mean the preparation

of suspensions, topicals, and suppositories; the conversion of one dose (e.g., oral to rectal, injection to oral) or dosage form into another; the preparation of select dosage forms from bulk chemicals; the preparation of intravenous admixtures, parenteral nutrition solutions, and pediatric dosage forms from adult dosage forms; the preparation of radioactive isotopes; or the preparation of cassettes, syringes, and other devices with drugs for administration in the home setting. This paper describes what one must be willing and able to do upon entering pharmaceutical compounding.

BACKGROUND

Compounding pharmacy is unique because it allows pharmacists to use more of their scientific, math, and technology background. Compounding pharmacists develop a unique relationship with the patients they serve and the prescribers with whom they work. They work hand in hand with physicians to solve clinical problems not addressed by manufactured dosage forms. It almost seems unbelievable that, as we in health care become more aware that patients are individuals, respond as individuals, and must be treated as individuals, some health care providers appear to be grouping

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patients into categories for treatment and categories for reimbursement from third-party payers or for determining levels of care in managed care organizations. Along the same lines, the trend toward using pharmaceutical manufacturers' fixed-dose products, which are available just because the marketing demand is sufficiently high to justify their manufacture and production, seems not quite appropriate. Since when must the availability, or lack of availability, of a specific commercially available product dictate the therapy of a patient?

REQUIREMENTS-PERSONAL

A question often posed is, "Should Every Pharmacist Compound?" The answer is "Definitely not!" Only properly trained pharmacists should be involved in pharmaceutical compounding. Graduation from a school/college of pharmacy does not necessarily qualify one for compounding because of the limited training offered in most schools. If pharmacists wish to compound but do not possess the required techniques and skills, they must participate in continuing-education programs that have been designed to provide the proper training, including the scientific basis and practical skills necessary for sound, contemporary compounding.

Today, any pharmacist can legally compound, but to be capable of meeting the special or advanced needs of today's patients, whether human or animal, a compounding pharmacist must:

- Have access to the most recent information available,
- Maintain an inventory and provide for proper storage of drugs and flavoring agents and be capable of obtaining any chemical within a reasonable time,
- Be dedicated to pharmacy and willing to put forth the necessary financial and time investment,
- Have the appropriate physical facilities and equipment to do the job right (the extent and type of compounding may be determined or limited by the facility),
- Be committed to lifelong learning and continuing education, since a major advantage of compounded prescriptions is that they provide treatments that are new, undeveloped, and often not commercially available, and
- Have a willingness to tear down walls and build bridges to share experiences with others for the good of all.

When considering whether or not to compound, pharmacists must consider the technical aspects and economic impact of the service.

Legal and Regulatory

As a result of new USP standards related to compounding, many states are rewriting their laws and regulations. Additional quality initiatives and standards are likely to be developed for several years to come in response to new USP standards. Also, H.R. 3204, the Drug Quality and Security Act, passed in 2013 describes two types of compounding entities; (1) 503a facilities which include traditional compounding, and (2) 503b facilities which are "Outsourcing Facilities" that are required to follow Good Manufacturing Practices, register with the FDA and have numerous requirements. This paper discusses only the 503a facilities for traditional compounding.

Financial Considerations

Several economic factors must be considered when making the decision to start a compounding program. The financial investment to begin a compounding service is dependent upon the scope of compounding to be considered. It can range from tens of thousands of dollars if a facility is available to hundreds of thousand of dollars if new construction is required or if significant alteration to a current facility is needed. Much of the costs involved relate to equipment, ingredients and supplies and possibly some remodeling expenses.

REQUIREMENTS-PROFESSIONAL

The Compounding Process

Before the first step in the compounding process of a prescription is taken, the following questions must be considered:

- What are the physical and chemical properties and medicinal and pharmaceutical uses of the drug substance?
- Are the quantity and quality of each active ingredient identifiable?
- Given the purpose of the prescription, will the preparation and route of administration provide adequate absorption, either locally or systemically?

- Are excipients present from any source (manufactured products) that may be expected to cause an allergic reaction, irritation, toxicity, or an undesirable organoleptic response by the patient?
- For preparations that are to be administered orally, are the active ingredients stable in the normal gastric pH range, or are they subject to extensive hepatic first-pass metabolism?

Stability, Expiration, and Beyond-Use Dating

The USP defines *stability* as the “extent to which a dosage form retains, within specified limits and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of its preparation.” The compounding pharmacist must avoid formulation ingredients and conditions that could result in a subpotent preparation that leads to poor clinical results. Knowledge of the chemical reactions by which drugs degrade can enable the pharmacist to establish conditions that minimize the rate of degradation. At all steps in the compounding, dispensing, and storage processes, the pharmacist must observe the compounded drug preparation for signs of instability.

In determining a beyond-use date, the pharmacist may consider the following: (1) The nature of the drug and its degradation kinetics, (2) The use of preservatives or stabilizers, (3) The container in which the drug is packaged, (4) The storage conditions to which the preparation is expected to be exposed, (5) The expected length of therapy, (6) The expiration date of similar commercial products, (7) Published literature, and (8) Information obtained from the manufacturer.

Personnel Requirements

Only personnel authorized by the responsible pharmacist must be in the immediate vicinity of the drug-compounding operation. Any person with an apparent illness or open lesion that may adversely affect the safety or quality of a drug preparation being compounded must be excluded from direct contact with components, drug preparation containers, closures, in-process materials, and drug preparations until the condition is corrected or determined by competent medical personnel to not jeopardize the safety or quality of the preparations being compounded.

All personnel who assist in compounding procedures must be instructed to report to the responsible pharmacist any health condition that may have an adverse effect on drug preparations.

Pharmacists must possess the education, training, and proficiency necessary to properly and safely perform compounding duties at the level in which they are involved. All pharmacists who engage in the compounding of drugs must be proficient in the art and science of compounding and must maintain that proficiency through current awareness and training.

Compounding pharmacists must be proficient in:

- The proper use of compounding equipment such as balances and measuring devices, including guidelines for selecting proper measuring devices, limitations of weighing equipment and measuring apparatus, and the importance of accuracy in measurements,
- Pharmaceutical techniques needed to prepare compounded dosage forms (i.e., comminution, trituration, levigation, pulverization by intervention, and geometric dilution),
- Properties of dosage forms to be compounded and related factors, such as stability, storage considerations, and handling procedures,
- Literature regarding stability, solubility, and other physicochemical properties of the ingredients,
- Handling of nonhazardous and hazardous materials in the work area, including protective measures for avoiding exposure, emergency procedures to follow in the event of exposure, and the location of material safety data sheets (MSDSs) in the facility,
- Use and interpretation of chemical and pharmaceutical symbols and abbreviations in medication orders and in formulation directions, and
- Review of pharmaceutical calculations.

Personnel engaged in the compounding of drugs must wear clean clothing appropriate to the operation being performed. Protective apparel, such as coats or jackets, aprons, or hand or arm coverings, must be worn as necessary to protect drug preparations from contamination. A clean laboratory jacket usually is considered appropriate attire for nonsterile compounding procedures.

Work with hazardous materials, such as chemotherapeutic agents, may require the use of goggles, gloves, masks or respirators, double gowns, and foot covers; showers and eyewash stations must be provided. Clean room apparel is required for the compounding of sterile preparations in a controlled environment (clean room).

Facility Requirements

Pharmacies engaged in compounding must have a designated area with adequate space for the orderly placement of the equipment and materials used in compounding activities. The pharmacist is also responsible for the proper maintenance, cleanliness, and use of all equipment involved in the compounding practice.

The compounding facility must be designed, arranged, and maintained to facilitate quality compounding. The area for compounding sterile drug preparations must be separate from the area for compounding or dispensing nonsterile drug preparations. Traffic in the compounding area must be kept to a minimum, with only designated individuals allowed access. The area must be well lighted and have controlled heating, ventilation, and air conditioning to prevent the decomposition of chemicals and to ensure a comfortable workplace without distractions. Humidity must be monitored and controlled as appropriate.

Materials used for the floor, walls, shelving and cabinets, and ceiling must not retain dust, odors, or residues from the compounding activities. The area must be free of dust-collecting overhangs (e.g., ceiling pipes, hanging light fixtures, ledges) as well as from infestation by insects, rodents, and other vermin. The actual work area must be level, smooth, impervious, free of cracks and crevices, and nonshedding. The shelving and cabinets must be easy to clean.

Equipment Requirements

Equipment used in the compounding of drug preparations must be appropriately designed, of adequate size, and suitably located to facilitate compounding operations. The equipment must be of a neutral and impervious composition so that ingredients, in-process materials, and drug preparations do not react with, add to, or become absorbed/adsorbed by it in such a way that the

safety, identity, strength, quality, or purity of the drug preparation is altered beyond the desired composition.

Equipment and utensils used for compounding must be cleaned and sanitized immediately before use to prevent contamination that would alter the drug preparation. To ensure that equipment and utensils are clean, they must be inspected by the pharmacist immediately before compounding operations begin.

The equipment needs of pharmacists vary depending on the type of compounding activities performed. Because the practice of pharmacy is now so diverse, it is doubtful that a single list of equipment will suffice for all practice settings; rather, equipment lists must be tailored to the type of practice.

Ingredient Standards

USP Chapter <795> states that “The pharmacist is responsible for compounding preparations of acceptable strength, quality, and purity with appropriate packaging and labeling in accordance with good pharmacy practices, official standards, and relevant scientific data and information.” A USP or NF grade substance is the preferred source of ingredients for compounding. If that is not available, or when food, cosmetics, or other substances are or must be used, the use of another high quality source, such as analytical reagent (AR), certified American Chemical Society (ACS), or Food Chemicals Codex (FCC) grade, is an option for professional judgment.

The pharmacist has the responsibility and authority to inspect and approve or reject all components, drug preparation containers, closures, in-process materials, and labeling, as well as the authority to prepare and review all compounding records to ensure that no errors have occurred in the compounding process.

Manufactured drug products such as injectables, tablets, or capsules may be sources of active ingredients. If such a product is the source of the active ingredient used in the compounding of a prescription, only a manufactured drug from a container labeled with a batch control number and a future expiration date is acceptable. If a manufactured drug product is used, it is important that

all the ingredients in the drug product be considered relative to the intended use and the potential effect on the overall efficacy (strength, quality, purity, stability, compatibility) of the compounded preparation.

Quality Issues

There is an increased emphasis on quality and documentation of compounded formulations. Therefore, it is incumbent on all pharmacists who compound to be intimately familiar with all the USP chapters related to compounding standards.

Before dispensing the prescription to the patient, the pharmacist must ensure the accuracy and completeness of the compounded preparation by reviewing each step in the preparatory, compounding, final check, and sign-off phases. In the preparatory review, the pharmacist checks that all preparations for the compounding process were handled appropriately.

The pharmacist reviews the compounding steps to ensure that the procedures and techniques used to prepare the formulation were faithfully followed and appropriately documented. This review also ensures that the formulation is reasonably aesthetic and uniform in content.

The pharmacist's review of the final check phase must be comprehensive. It is intended to verify the following:

- The calculated yield is consistent with the actual yield.
- The tolerance for individual dose weight variation has been met by a sampling technique when appropriate (e.g., capsule weight).
- The physical characteristics (clarity, color, odor) of the preparation are consistent with those predicted for the preparation.
- Physical tests have been performed when appropriate, and the preparation meets the test limits.
- The preparation is suitably labeled, and the contents have been verified with the prescription order. All legal requirements have been imprinted on the label and in the compounding record.
- The preparation is suitably packaged for patient use, and the container that is selected will protect

the preparation from undue environmental exposure until at least the discard-after or beyond-use date.

- Documentation as appropriate.
- The patient or caregiver has been adequately informed about ways to identify obvious evidence of instability in the compounded preparation.
- The preparation is labeled with explicit storage and administration instructions.

The pharmacist may also decide to submit samples of compounded preparations to an analytical testing laboratory or test it within the pharmacy. Such analytical testing could include strength/potency testing, stability, pH, sterility, nonpyrogenicity, viscosity, dissolution rates and others. The pharmacist may use an analytical testing laboratory to perform some of the testing; this would involve testing samples of a compounded preparation.

Record and Report Requirements

Compounding pharmacists must keep the records required by the states in which they practice, as well as those characteristic of a well-operated compounding pharmacy. Pharmacists must maintain at least four sets of records for compounding: (1) formulation records, (2) compounding records, (3) Standard Operating Procedures (SOPs), including equipment maintenance records, and (4) ingredient records, including certificates of analysis and MSDSs. Records and reports must be retained for the period of time required by state laws and regulations for the retention of prescription files. All records and reports must be readily available in the pharmacy for authorized inspection during the retention period.

Formulation Record

The formulation record provides a consistent source document for preparation of the formulation, considered the "recipe," whereas the compounding record documents the actual ingredients in the preparation and the person responsible for the compounding activity. Formulation records must be maintained in sufficient detail that the preparations can be duplicated; computerized records are appropriate.

Individual formulation records for compounds are obtained from a variety of sources, including journals, books, other pharmacists, organizations, and even individual development. The formulation record must include the following information:

- Name, strength, and dosage form of the preparation,
- All ingredients and their quantities,
- Equipment required to produce the preparation,
- Pertinent calculations,
- Mixing instructions,
- Quality control procedures,
- Source of the recipe,
- Beyond-use date,
- Container used, and
- Storage requirements.

Compounding Record

The compounding record must contain the name, strength, and dosage form as they appear in the formulation record. The compounding record is the worksheet for preparing an individual formulation. The following information must be recorded for both types of compounded formulations (individual prescriptions and preparations compounded in anticipation of orders):

- Formulation record used for the preparation,
- Individual ingredients, their lot numbers, and the actual quantities measured or weighed,
- Quantity of preparation prepared (i.e., weight, volume, or number of units prepared),
- Signature of pharmacist or technician compounding the preparation,
- Signature or initials of the pharmacist responsible for supervising the preparation and conducting in-process and final checks of the compounded preparation if a technician performed the compounding function,
- Date of preparation,
- Assigned internal identification number, if applicable,

- Prescription number,
- Assigned beyond-use date, and
- Results of the quality control procedures (e.g., the weight range of filled capsules).

The compounding records are maintained for easy retrieval according to individual state requirements.

Standard Operating Procedures

All significant procedures performed in the compounding area must be covered by standard operating procedures (SOPs) and documentation, as appropriate. Procedures must be developed for the facility, equipment, personnel, preparation, packaging, and storage of compounded preparations to ensure accountability, accuracy, quality, safety, and uniformity in a compounding practice. More important, the implementation of SOPs establishes procedural consistency and provides a reference for the orientation and training of personnel. Documentation enables a pharmacy to systematically trace, evaluate, and replicate the steps throughout the preparation process of a compounded preparation whenever necessary.

SOPs provide assurance that (1) equipment is maintained in good working order, calibrated, and documented; (2) supplies are received, logged in, stored properly, disposed of correctly, and maintained fresh and within compendial requirements; and (3) all manipulations and procedures are performed uniformly and then documented.

Material Safety Data Sheets

Material Safety Data Sheets (MSDSs) must also be maintained for any drug substance or bulk chemical located in the pharmacy. The ingredient information consists mainly of physicochemical, toxicity, and handling information. Precautions, information about potential hazards, and shipping instructions are also included. This information must be reviewed for the protection of the pharmacist as well as for that of the patient.

These records are retained as original hard copy; true copies, such as photocopies, microfilm, or microfiche; or other accurate reproduction of the original records. Computerized records are also acceptable. Employees must be instructed as to the location of the files and their format.

REFERENCE LIBRARY

The compounding of quality preparations requires access to up-to-date, reliable drug information as well as pharmacy compounding information. Compounding pharmacists must have ready access to reference materials and electronic data bases.

The contents of a reference library at a particular practice site will depend in part on the type of compounded formulations being prepared. The following references should be a part of every pharmacy reference library:

- Allen LV Jr., Editor-in-Chief. *Remington: The Science and Practice of Pharmacy*. 22nd ed. Chicago: Pharmaceutical Press; 2012.
- Allen LV and Ansel HC, *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*. 10th ed. Baltimore: Lippincott Williams & Wilkins; 2014.
- Ansel HC. *Pharmaceutical Calculations*. 13th ed. Baltimore: Lippincott Williams & Wilkins; 2010.
- McEvoy GK, Editor-in-Chief. *AHFS Drug Information 2014*. Bethesda, Md: American Society of Health-System Pharmacists; 2014.
- *The Merck Index*. 14th ed. Rahway, NJ: Merck & Co; 2006.
- Reynolds JEF. *Martindale: The Extra Pharmacopoeia*. 38th ed. London: The Pharmaceutical Press; 2014.
- Rowe RC, Sheskey PJ, Cook WG, Fenton ME. *Handbook of Pharmaceutical Excipients*. 7th ed. Washington, DC: American Pharmacists Association; 2012.
- *Secundum Artem*. Minneapolis, Minn: Perrigo Pharmaceuticals [semi-annual journal].
- Shrewsbury R. *Applied Pharmaceutics in Contemporary Compounding*. 2nd ed. Englewood, Colo: Morton; 2008.
- *United States Pharmacopeia 37/National Formulary 32*. Rockville, Md: United States Pharmacopeial Convention; 2014.

Some editions of these references must be retained in a “previous editions” section of the reference library because they contain valuable information that was not carried forward to new editions; examples include *Remington: The Science and Practice of Pharmacy* and *Martindale: The Extra Pharmacopoeia*. Older editions of some references must be discarded, however, if new research has shown that previously published information is no longer appropriate; examples include the *United States Pharmacopeia/National Formulary*, *Handbook on Injectable Drugs*, and *King Guide to Parenteral Admixtures*.

THE FUTURE

Compounding is a professional responsibility that pharmacists have performed since the beginning of the profession. The heritage of pharmacy, spanning some 5,000 years, has centered on providing pharmaceuticals for patients. Pharmacists are the only health professionals who possess the knowledge and skill required to compound and prepare medications to meet the unique needs of patients.

The practice of pharmacy compounding continues to grow. Factors contributing to the current and future growth of compounding pharmacy in health care include drug shortages, discontinuation of drug products, lack of pediatric formulations, specialty compounding, veterinary compounding, the need for alternative drug delivery, dosage adjustment, the use of short-dated (unstable) drugs, and others.

The technological, pharmaceutical, medical, and social aspects of pharmaceutical compounding will continue to change. As pharmacogenomics becomes a more important part of medical practice, compounding pharmacists must be able to meet the specific needs of individual patients—a longtime goal of pharmacy and medicine.

SUMMARY

Many pharmacists intimately involved in pharmaceutical care have come to realize the importance of providing individualized patient care through the compounding of patient-specific preparations. As compounding pharmacy continues to grow, it will provide an opportunity for more pharmacists to use their innovative skills to solve individual patients' drug problems.

The question often is asked, "Where can I get free information on compounding?" The answer is generally that very little "free information" is available. *Secundum Artem* has been published for years and it is available for free online. Other than that, most training, education, journals, databases, etc. require an investment of both time and money. Providers of the information are businesses and charge for their products and services in order to be able to continue offering them.

Pharmaceutical compounding provides pharmacists with a unique opportunity to practice their time-honored profession. It will become an even more important part of pharmacy practice in the future, particularly for those involved in community, hospital, long-term care, home health care, veterinary care, and specialty practices.

Although pharmacists must not hesitate to become involved in pharmacy compounding, they must be aware of the requirements for and uniqueness of formulating a specific drug product for a specific patient. This service is an important component in providing pharmaceutical care. After all, without the pharmaceutical product, there is no pharmaceutical care.