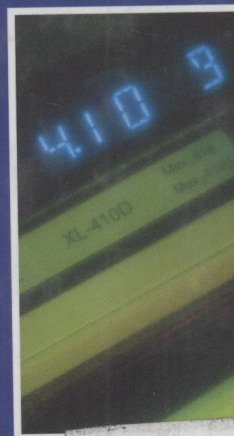


Second Edition

The Art, Science, and Technology of Pharmaceutical Compounding

Loyd V. Allen Jr., PhD



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and Technology of
Pharmaceutical Compounding**

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Preface to the Second Edition

The phenomenal growth of pharmaceutical compounding in recent years has been spurred by several simultaneous events. First, the number of discontinued drug products continues to increase. A number of reasons contribute to this increase, including low profits on certain products that are ultimately discontinued, difficulty in manufacturing and formulation processes that lead to a decision to discontinue the product, and the difficulty in obtaining—including importing—certain raw materials used in some commercial products. Despite the reason for discontinuing a product, patients still need the medication; fortunately, in most cases, pharmacists can compound these preparations.

Second, physicians are becoming more aware of use in other parts of the world of various drugs and dosage forms that are not produced and marketed here in the United States. To obtain these preparations, U.S. physicians turn to pharmacists in many cases.

Third, many physicians have patients who can benefit from new drugs or new drug applications. The physicians work with compounding pharmacists to formulate the preparations.

Fourth, the incidence of drug shortages has been increasing in recent years. This increase may be caused by several factors, including just-in-time manufacturing, miscalculations of actual drug usage rates, and difficulty in obtaining some imported raw materials.

We are now in an era of increased emphasis on quality and documentation of compounded formulations. Therefore, it is incumbent on all pharmacists who compound to be intimately familiar with General Chapter <795>, "Pharmacy Compounding," of the *United States Pharmacopeia 25/National Formulary 20*. Pharmacists—as well as all personnel involved in compounding—should be trained in the principles outlined in this chapter and should practice within its guidelines.

Colleges and schools of pharmacy are beginning to reinstate laboratory classes in the curriculum; these classes are important as pharmacy compounding requires a strong scientific base in inorganic and organic chemistry, physical pharmacy, pharmaceuticals, natural products chemistry, biochemistry, and other physical and life sciences. Approximately 75% of the colleges and schools of pharmacy now have some students who receive specialized training from the compounding support industry.

Compounding of sterile products also continues to grow and should be done only by pharmacists who have been properly trained and validated in aseptic processing. Some states already require specific annual training by pharmacists involved in compounding sterile preparations.

Recent activities related to the Food and Drug Modernization Act of 1997 have served to document the importance of pharmacy compounding and the need for it. The Food and Drug Administration (FDA) recognizes the importance of and supports the ability of pharmacists to compound specific preparations for individual patients. FDA is working closely with the United States Pharmacopeia in continuing to enhance the quality of compounded preparations.

In summary, as this second edition is prepared, pharmacy compounding has regained a place of prominence and importance in the overall provision of pharmaceutical products, patient services, and pharmaceutical care. After all, individualization of individual prescriptions through pharmacy compounding is the actualization of providing total pharmaceutical care.

May 2002

Preface to the First Edition

Historically, compounding has been an integral part of pharmacy practice, as shown by the following definitions and references to pharmacy.

- Pharmacy is the art or practice of preparing and preserving drugs, and of compounding and dispensing medicines according to the prescriptions of physicians.¹
- Pharmacy is (1) the art, practice, or profession of preparing, preserving, compounding, and dispensing medical drugs and (2) a place where medicines are compounded or dispensed.²
- Pharmacy is the science, art, and practice of preparing, preserving, compounding, and dispensing medicinal drugs and of giving instructions for their use.³

Compounding is a professional prerogative that pharmacists have performed since the beginning of the profession. Even today, definitions of pharmacy include the “preparation of drugs.”^{4,5}

The heritage of pharmacy, spanning some 5000 years, has centered on providing pharmaceutical products 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.

Compounding Yesterday

The apothecary is listed in the Bible as one of the earliest trades or professions. As one reads through the Bible, it is evident that people experienced pain, disease, and suffering and that they used medicines of various types for healing:

“And thou shalt make it an oil of holy ointment, an ointment compound after *the art of the apothecary*: it shall be an holy anointing oil.” Exodus 30:25 [emphasis added]

“Dead flies cause *the ointment of the apothecary* to send forth a stinking savour: so doth a little folly him that is in reputation for wisdom and honour.” Ecclesiastes 10:1 [emphasis added]

"From the sole of the foot even unto the head there is no soundness in it; *but wounds, and bruises, and putrifying sores*: they have not been closed, neither bound up, neither mollified with ointment." Isaiah 1:6 [emphasis added]

"And by the river upon the bank thereof, on this side and on that side, shall grow all trees for meat, whose leaf shall not fade, neither shall the fruit thereof be consumed: it shall bring forth new fruit according to his months, because their waters they issued out of the sanctuary: and the fruit thereof shall be for meat, and *the leaf thereof for medicine*." Ezekiel 47:12 [emphasis added]

In many cases, the medicines used were either topical ointments or products such as wines and plant extracts that were taken internally. The apothecary was noted for the mixing of perfumes, ointments, and some medicines, and the physician was noted for taking care of the sick. In some cases, the same individual performed both functions. The heritage of the compounding pharmacist is well documented throughout history as one involved in preparing products used for treatment of disease and for cosmetic purposes.

Compounding Today

Prescription compounding is a rapidly growing component of pharmacy practice. This change can be attributed to a number of factors, including individualized patient therapy, lack of commercially available products, home health care, intravenous admixture programs, total parenteral nutrition programs, and problem solving for the physician and patient to enhance compliance with a specific therapeutic regimen. Pharmacists are creative and should have the ability to formulate patient-specific preparations for providing pharmaceutical care.

An article by Angel d'Angelo, RPh, editor of the *U.S. Pharmacist*, explains that compounding is our heritage. There is no other professional license that allows for the extemporaneous compounding of therapeutic agents. Complete pharmaceutical care must involve the dosage form, which might necessitate compounding a patient-specific form not available commercially; possibly the preparation of a product without a preservative or a specific allergy-producing excipient that must be removed from the formulation. With pharmacokinetic services, the need for individualized dosage units will be required more frequently to meet these patient-specific needs. Pharmacists who compound have a desirable and needed skill.⁶

Pharmacy is united in the sense that pharmacists have a responsibility to serve their patients and to compound an appropriately prescribed product in the course of their professional practice. It is the right and responsibility of pharmacists to compound medications to meet the specific needs of patients. Pharmacists are ultimately responsible for the integrity of the finished product prepared by them or under their immediate supervision.

Pharmacists are the only health professionals formally trained in the art and science of compounding medications. Consequently, they are expected to possess the knowledge and skills necessary to compound extemporaneous preparations. In 1995, the percentage of compounded prescriptions represented approximately 11% of all prescriptions dispensed,⁷ which is a five- to tenfold increase in the percentage of such prescriptions dispensed in the 1970s and 1980s. It is evident that the need for individualized drug therapy for patients has been realized and is resulting in patient-specific prescriptions and the compounding of medications that are not commercially available.

The purpose of this book is (1) to provide a basic foundation of knowledge that will enable pharmacists to sharpen their skills in compounding pharmacy, (2) to serve as an educational tool for those pharmacists who did not receive instruction in compounding in colleges or schools of pharmacy, and (3) to become a textbook for current pharmacy students taking courses in pharmaceutical compounding. This first edition of the book serves as a basic text; it will be revised and developed in greater depth with future editions.

The support of Paddock Laboratories in developing some of the materials used in this book is gratefully acknowledged. Some material was originally published or adapted from materials published in the *Secundum Artem* series by Paddock Laboratories, Inc., of Minneapolis, Minnesota. Other material, including the cover design, has been adapted from the *International Journal of Pharmaceutical Compounding (IJPC)*, a bimonthly professional and scientific journal devoted to pharmaceutical compounding and published in Edmond, Oklahoma. Photographs of compounding equipment were graciously supplied by the Professional Compounding Centers of America, Inc. The use of these materials is sincerely appreciated.

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Introduction

Pharmacists are unique professionals, who are well trained in the natural, physical, and medical sciences and aware that a single mistake in the daily practice of their profession may result in potential tragedy. However, because of their demonstrated expertise, their demeanor, and the manner in which they have practiced their profession over the years, pharmacists continue to be ranked among the most respected individuals in our society. In general, pharmacists have the reputation of being available to residents of the local community in times of need, interacting with and providing needed medications for patients, and working with patients to regain or maintain a certain standard of health or quality of life.

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.

Pharmacy activities that individualize patient therapy include clinical and compounding functions. The functions are related and equally important to the success of such activities. A pharmacist's expertise must be used to adjust dosage quantities, frequencies, and even dosage forms for enhanced compliance. All pharmacists should 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 responsibility of pharmacists to compound medications (sterile and nonsterile) to meet the specific needs of patients.

What Is Compounding?

The definition of compounding has been the subject of much discussion and has been addressed by the National Association of Boards of Pharmacy.

Compounding means the preparation, mixing, assembling, packaging, or labeling of a drug or device (i) as the result of a practitioner's Prescription

Drug Order or initiative based on the pharmacist/patient/prescriber relationship in the course of professional practice, or (ii) for the purpose of, as an incident to research, teaching, or chemical analysis and not for sale or dispensing. Compounding also includes the preparation of drugs and devices in anticipation of Prescription Drug Orders based on routine, regularly observed patterns.¹

Still, 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.

The pharmacist plays an important role on the hospice team and can greatly enhance quality of life for hospice patients. Pediatric patient compliance is a challenge as children either don't want to, or can't, take tablets or capsules and manufacturers don't provide liquid dosage forms for many medications; this is where the pharmacist steps in. Compounding for the geriatric patient can be a much greater challenge than for almost any other group of patients. Oftentimes there are physical, emotional and social difficulties affecting compliance and many geriatric health problems are chronic rather than acute. Pharmacists have also become intimately involved in working with veterinarians in the treatment of animals (companion, recreational, food and exotic).

Compounding has always been a basic part of pharmacy practice, but today it is one of the most rapidly growing areas, and many pharmacists in all types of practice are becoming involved in compounding sterile and nonsterile products. The dramatic growth of pharmaceutical compounding is attributed to the impact of home health care, unavailable drug products, orphan drugs, veterinary compounding, and biotechnology-derived drug products. Newly evolving dosage forms and therapeutic approaches suggest that compounding of pharmaceuticals and related products specifically for individual patients will become more common in pharmacy practice in the years ahead.

Compounding pharmacy is unique because it allows pharmacists to use more of their scientific, mathematical, and technology background than some other types of practices. Compounding pharmacists develop a unique relationship with the patients they serve. They work hand in hand with physicians to solve clinical problems not addressed by commercially available 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 patients into "categories" for treatment and "categories" for reimbursement from third-party payers or "categories" for determining levels of care in managed care organizations. Along the same lines, the trend to use "fixed-dose products" provided by pharmaceutical manufacturers that are available just because the marketing demand is sufficiently high to justify their manufacture and production seems not quite appropriate. Since when should the availability, or lack of availability, of a specific commercially available product dictate the therapy of a patient?

Should Every Pharmacist Compound?

Only properly trained pharmacists should be involved in pharmaceutical compounding. If pharmacists wish to compound but do not possess the required techniques and skills, they should 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 is legally qualified to compound, but who is a technically qualified, trained, compounding pharmacist? 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.
- have a willingness to tear down walls and build bridges to share experiences with others for the good of all.

Should You Compound?

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

Technical Considerations

There are three types of compounded prescriptions: isolated, routine, and batch prepared. An isolated prescription is one that the pharmacist is not expecting to receive nor will expect to receive again. A routine prescription is one that the pharmacist may expect to receive on a routine basis in the future; there may be some benefit to "standardize" such preparations to ensure product quality, that is, maintain preparation protocols on file. A batch-prepared prescription is one that is prepared in multiple identical units as a single operation "in anticipation" of the receipt of future prescriptions.

Pharmacists must consider not only their technical qualifications to compound a product, but also the technical validity of the prescription. The box "Technical Considerations for Compounding a Prescription" presents a series of questions designed to aid in evaluating the technical considerations for compounding.

The "batch production" of sterile products, especially in the hospital and home health care environments, has increased noticeably. There are a number of reasons for this increase, including the following:

- The changing patterns of drug therapy, such as home parenteral therapy and patient-controlled parenteral administration.

Technical Considerations for Compounding a Prescription

- ▶ Is the product commercially available in the exact dosage form, strength, and packaging?
- ▶ Is the prescription rational concerning the ingredients, intended use, dose, and method of administration?
- ▶ Are the physical, chemical, and therapeutic properties of the individual ingredients consistent with the expected properties of the ordered drug product?
- ▶ Will this compounded product satisfy the intent of the prescribing physician and meet the needs of the patient?
- ▶ Is there an alternative (e.g., different dosage form, different route of administration) by which the patient will receive a benefit?
- ▶ Is there a bona fide prescriber-pharmacist-patient relationship?
- ▶ Can ingredient identity, quality, and purity be assured?
- ▶ Does the pharmacist have the training and expertise required to prepare the prescription?
- ▶ Are the proper equipment, supplies, and chemicals or drugs available?
- ▶ Is there a literature reference that might provide information on use, preparation, stability, administration, and storage of the product?
- ▶ Can the pharmacist perform the necessary calculations to prepare the product?
- ▶ Can the pharmacist project a reasonable and rational "beyond-use" date for the prescription?
- ▶ Is the pharmacist willing to complete the necessary documentation to prepare the product?
- ▶ Can the pharmacist do some basic quality control to check the product prior to dispensing (e.g., capsule weight variation, pH, visual observations)?
- ▶ What procedures are in place for investigating and correcting failures?
- ▶ How long will the patient be using the product and is the expected duration of therapy consistent with an appropriate expiration date? Alternatively, should the product be prepared in small quantities and dispensed to the patient in short intervals?
- ▶ Does the patient have the necessary storage facility, if required, to ensure the potency of the product until its beyond-use date?

- ▶ The use in hospitals of injectable drug products that are not commercially available to meet individual patient needs or the prescriber's clinical investigational protocols.
- ▶ Cost containment, whereby a pharmacy batch produces drug products that are intended to be similar to commercially available products.

Batch compounding can reduce the cost of a medication that must be taken over a long period or continuously for a chronic condition. This process allows the patient to store the product at home and reduce the number of pharmacy visits. Pharmacists who choose to perform batch compounding should be capable and willing to do it properly, particularly when sterile drug products are involved. (See the box "Technical Considerations for Batch Compounding.")

Economic Considerations

Several economic considerations must be weighed when making the decision to compound prescriptions, including the pharmacist's compensation for the service

Technical Considerations for Batch Compounding

- Will the processes, procedures, compounding environment, and equipment used to prepare this batch produce the expected qualities in the finished product?
- Will all the critical processes and procedures be carried out exactly as intended for every batch of the prepared product to produce the same high-quality product in every batch?
- Will the finished product have all the qualities as specified upon completion of the preparation and packaging of each batch?
- Will each batch retain all the qualities within the specified limits until the end of the labeled expiration date?
- Will it be possible to monitor and trace the history of each batch, identify potential sources of problems, and institute appropriate corrective measures to minimize the likelihood of their occurrence?

and the impact of the service on health care costs. Both factors are equally important.

Pharmaceutical compounding is a cognitive service; therefore, appropriate reimbursement is justified. The pricing of a compounded prescription should take into consideration pharmacodynamic/pharmacotherapeutic decision making, formulation expertise, the time involved, and reimbursement for materials. Compounding prescriptions can be attractive for the pharmacist both professionally and financially. Historically, it has been said that compounding is an act whereby the professional and scientific knowledge of a pharmacist can find its expression. For those pharmacists dedicated to performing quality compounding, the professional, psychological, and financial rewards can be substantial.

Compounding prescriptions can be one way of lowering the cost of drug therapy. In some cases it may be less expensive for the pharmacist to prepare a specific prescription for the patient, which may mean that the patient may actually obtain the drug rather than have to do without it. If compounding a prescription will enable a patient to afford the drug therapy, it must be considered.

Another way in which compounding may lower drug costs concerns the economic utilization of very expensive drug products that may have short shelf lives. If a patient does not need the entire contents of a vial or dosage unit, the remaining drug product is often discarded and wasted. In numerous instances, however, the pharmacist can divide the commercial product into smaller usage units, store it properly, and dispense the required quantity on individual prescriptions.

A related economic question involves the commercialization of compounded products. Over the years many compounded products have eventually become commercially available. Examples include fentanyl lozenges, minoxidil topical solution, nystatin lozenges, clindamycin topical solution, tetracaine-adrenalin-cocaine (TAC) solution, erythromycin topical solution, and some premixed intravenous solutions. It is inevitable that a pharmaceutical manufacturer will produce a product when it becomes economically profitable to do so.

Summary

Compounding pharmacists are interested in and excited about their practice. In fact, many pharmacists intimately involved in pharmaceutical care have come to realize the importance of providing individualized patient care through the

preparation of patient-specific products. As compounding pharmacy continues to grow, it will provide an opportunity for more pharmacists to use their innovative skills to solve patient's **drug** problems.

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 should not hesitate to become involved in pharmacy compounding, they should 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.

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