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Regulatory and Clinical Aspects of the Resurgence of Compounding by Pharmacists

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ABSTRACT

During the past decade there has been a significant increase in the number of pharmacists in the United States who devote a substantial part of their professional activities to compounding prescription, in some instances for a wide variety of drugs and drug delivery systems. There is dispute about the legal status of some of these activities. Also, the clinical safety and efficacy of some of these products may be open to question. The present paper explores issues involved in the present debate.

INTRODUCTION

For pharmacists who entered the profession some decades ago, compounding of mixtures, emulsions powders, suppositories, injections, eye drops, ointments, creams, tablets, linaments, lotions, and cachets was a central and essential element of their professional training and education. Many pharmacists looked forward to professional careers in which compounding would be a major focus of their activities.

The winds of change have blown strongly through the profession of pharmacy during the past 20 years or so and there have been radical changes in many areas, especially in community pharmacy. The growth of chain drugstores places the very existence of the individually owned pharmacy in considerable jeopardy. The burden-some paperwork and bureaucratic control over reimbursement by government agencies or other entities for prescription costs has added to the sense of frustration experienced by many pharmacists. An abhorrence of a professional life which might be described as "lick, stick, pour, and fill" must surely have been one of the factors which led to the growth of clinical pharmacy, the area that some practitioners see as the salvation of their profession.

In many pharmacies the relative importance of compounding has continued to decrease in recent years. At the same time the level of expertise required for the commercial manufacture of drug delivery systems by the pharmaceutical industry has dramatically increased. Food and Drug Administration (FDA) requirements for Good Manufacturing Practices (cGMPs) have evolved

and the agency has on a number of cases, most notably perhaps in the Barr case (1), insisted that the "c" in cGMP does indeed stand for "current" and clearly implies to the agency a continuing process of improvement. Such concepts as validation of process which were generally unheard of in the pharmaceutical industry even as late as 1970 are now routinely applied for all drug delivery systems for which the pharmaceutical industry gains marketing approval from FDA. Possibly the most important development, in terms of control over clinical response, has been the recognition that apparently very similar versions of the same pharmaceutical product can exhibit substantial differences in the rate and extent at which the drug enters the patient's bloodstream (bioavailability). As a result both the United States Pharmacopeia (USP) and FDA now devote considerable attention to dissolution and other tests (including tests in human subjects) which are of relevance to bioavailability. Much of the lively debate on the topic of "generic equivalence" has revolved around the question of relative bioavailability of brand name and generic products.

This paper is divided into three sections. Part one reviews legal and regulatory issues, part two clinical and other quality assurance aspects, and part three examines some professional points.

LEGAL AND REGULATORY ISSUES

Traditionally, compounding by pharmacists of a prescription issued by a medical practitioner (or other qualified person) for a patient has been under the control of the relevant State Board of Pharmacy and in fact 41 of the 50 state laws which define the practice of pharmacy specifically including "compounding" per se in their definition (2). The National Association of Board of Pharmacy (NABP) drafted the Model State Pharmacy Act (3) which includes in the description of the practice of pharmacy:

> the responsibility for compounding . . . of drugs and devices.

The Federal Food and Drug Administration has been given by the Congress very broad powers under the Federal Food, Drug, and Cosmetics Act (the Act) and other laws which allow it to regulate many aspects of the manufacture, marketing, and distribution of drug products not produced by a retail pharmacy. Further, the courts have held that the pharmaceutical industry is a "pervasively regulated" industry and that FDA regulations have the force of law. The agency has, therefore, been able to impose a quite substantial body of regulation concerning standards for drug products on the industry.

The Act provides criteria for the definition of retail pharmacy. If an operation meets with the definition provided in the Act then it is exempted from FDA requirements such as preparation of pharmaceutical products in compliance with cGMP regulations. However, if a retail pharmacy were to become involved in nontraditional compounding or manufacturing operations, it would then lose its immunity from FDA control and be expected to comply fully with all the requirements which the agency applies to pharmaceutical manufacturers. Thus, there is considerable interest in delineating precisely the border between "compounding" and "manufacturing."

The controversy is not whether pharmacists have a right to compound, but what defines the act of compounding. The NABP Model State Pharmacy Act defines compounding as:

> The Preparation, mixing, assembling, packaging, or labeling of a drug or device (1) as the result of a Practitioner's Prescription Drug Order or initiative based on the Practitioner/patient/pharmacist relationship in the course of professional practice, or (ii) for the purpose of, or as an incident to research, teaching, or chemical analysis and not for sale or Dispensing. Compounding also includes the preparation of Drug or Devices in anticipation of Prescription Drug Orders based on routine, regularly observed prescribing patterns.

An important phrase in this definition relates to filling a compounded prescription in the context of the practitioner–patient–pharmacist relationship. This triad relationship, commonly expressed with a Prescription Drug Order (PDO) must be in existence when a pharmacist prepares a compounded prescription for the act to be considered within the limits of the practice of pharmacy. To minimize potential problems with FDA, pharmacists should keep thorough records of compounded material, including a copy of the prescription for which it was made.

As to whether a pharmacist may make up compounded material prior to receiving the PDO, the NABP definition of compounding, states the condition that drugs can be compounded

> . . . in anticipation of PDO's when they are . . . based on regularly observed prescribing patterns.

This implies that the pharmacist may make up compounded prescriptions prior to the actual PDO being submitted, if the drug and the quantity have an established pattern of request by PDO to that pharmacist. If the pharmacist were ever investigated by the FDA for this activity, the pharmacist should be able to provide the officials with proof that the drug and the quantity produced have previous PDO requests that warranted the pharmacist to be making up the drug in bulk.

What then is the difference between a compounded prescription made up in bulk quantity and a batch of material manufactured for sale? The NABP *Good Compounding Practices Applicable to State Licensed Pharmacies* (4) (GCPs) states that only:

> compounding of inordinate amounts of drugs in anticipation of receiving prescriptions without any historical basis is considered manufacturing.

Although this is not a law, but a guide for pharmacists, the implication of this statement is that only those compounded drugs made up without basis in anticipated PDO's fall under FDA's jurisdiction of manufacturing. This is potentially misleading to pharmacists, since the FDA's position on this condition is more stringent. The FDA contends that evidence of anticipated PDOs does not necessarily exempt the activity from being presumed to be manufacturing; it is strictly one of several requirements necessary for an act to be considered traditional pharmacy practice.

The agency believes that it is acting under the Food, Drug, and Cosmetic Act (the Act), securing the safety and efficacy of prescription drugs when it investigates potential patient harm which might be caused by compounding drug products. The FDA drafted the Compliance Policy Guide 7132.16 (CPG) (5) in 1992 as a follow-up to multiple warning letters issues by the agency after several instances in which patients allegedly suffered from improperly compounded prescriptions. The policy is introduced by background information which includes the statement:

> FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner. This traditional activity is not the subject of this CPG.

This statement identifies that the existence of the triad relationship (previously mentioned in the NABP definition of compounding) is consistent with accepted compounding practice in FDA's guidelines. The policy refers to anticipated PDOs by stating:

> Pharmacies . . . may prepare drugs in very limited quantities before receiving a valid prescription, provided they can document a history of receiving valid prescriptions.

This, too is consistent with the previously stated NABP definition of compounding.

Thus the basic definition of compounding offered by pharmacists appears to be consistent with what FDA perceives as traditional compounding activity in a retail entity. Agreement on which acts are considered nontraditional practice of pharmacy as compared with traditional practice of pharmacy is not as easily accomplished. There are nine factors listed in CPG 7132.16 which the FDA consider to be nontraditional pharmacy practice which can warrant federal enforcement action FDA's list of factors is not intended to be all inclusive, but merely an outline of circumstances which imply manufacturing, or violation of the new drug, adulteration, or misbranding provisions of the Act. Briefly, these factors include such activity as soliciting business to compound specific drug products, regularly compounding generic copies of commercially available drug products, using non-FDA-approved sources of bulk ingredients, offering compounded drug products at wholesale to other licensed persons for resale, and distributing compounded products out of state.

Some pharmacy practitioners are not in agreement with FDA that the above factors are representative of nontraditional pharmacy practice. These practitioners contend that the agency is trying to oversimplify the separation between compounding and nontraditional pharmacy practice. Demands on pharmacies with regard to their demographics determine the frequency and quantity of compounded prescriptions presented to individual pharmacies. What is common compounding activity for one pharmacy may be more or less activity for another.

The contents of CPG 7132.16 were directly argued in a correspondence addressed to Mr. Ronald Chesemore (Associate Commissioner for Regulatory Affairs, FDA) on behalf of the Joint Commission of Pharmacy Practitioners (6). The correspondence presents eight hypothetical situations in which one or more of the factors previously mentioned is argued, followed by statements which purport to explain why the cases represent compounding within the practice of pharmacy, and not manufacturing.

The correspondence concludes with a summary of the similarities and differences between compounding and manufacturing. The first difference mentioned is:

> compounding has at its core, a physician, pharmacist, patient relationship. Manufacturing does not have Good Compounding Practice.

This reiterates the opinion of the NABP as stated in their CPG guide. The implication of this point is that manufacturing, as defined by FDA's list of nontraditional pharmacy practice, is not based on the triad relationship. This may not necessarily be true, since all nine of the factors listed in the CPG could be conducted within a patient–physician–pharmacist relationship. Alternatively, the implication may be that all activity which is based on the triad relationship should be considered to be within the practice of pharmacy, not manufacturing. Although the triad relationship is a necessary component of compounding, it may be difficult to use it as the only factor which separates traditional pharmacy practice from nontraditional pharmacy practice.

The second difference mentioned in the correspondence is:

> A difference of scale and emphasis.

Scale cannot be used as a universal tool for distinguishing between compounding and manufacturing, since certain acts of compounding which the FDA deems within the traditional practice of pharmacy may result in an introduction of a nontypical amount of compounded drug produced. Manufacturing activity cannot be identified merely on a quantitative scale; it is a qualitative and safety issue which potentiates federal enforcement.

Although the topic of extemporaneous compounding versus manufacturing has become a recent subject for debate; regulating alleged manufacturing activity of pharmacies is not a new role for the FDA. More than 25 years ago, in *Cedars North Tower Pharmacy, Inc. v U.S.* (7), the FDA contended that the pharmacy's activity with regard to specific acne drugs was considered manufacturing, and therefore the pharmacy was required to register as a manufacturer and submit a New Drug Application. Cedars argued that the act was compounding, and thus they were exempt as a retail pharmacy from the manufacturing provisions of the Act. The court decided that Cedars activities were violative of the intent of the statute. In the decision, the court listed six factors which pharmacists can use as a guideline to determine if their activity is considered traditional pharmacy practice. These guidelines are similar to the nine factors of nontraditional pharmacy practice listed in CPG 7132.16.

More recently, in 1994, an organization titled Professionals and Patients for Customized Care (P2C2) brought action against FDA and others challenging the CPG 7132.16 in *P2C2 v Donna Shalala et al.* (8) The P2C2 group consists of pharmacists, patients, and physicians supportive of the practice of compounding, and whose purpose is to promote increased awareness of the benefits of pharmacy compounding. The P2C2 group argued that CPG 7132.16 is a change of enforcement policy regarding compounding medications, and those impacted were not given the right of notice and comment. The defendants contended that the CPG is a policy statement, not a substantive rule, and therefore not subject to the rule requirements of the Administrative Procedures Act (APA). The court concluded the CPGs are general statements of policy, and not subject to APA requirements. The results was that the court refused to grant the plaintiff a permanent injunction preventing enforcement of CPG 7132.16.

An interesting conclusion generated from this case is that:

> drugs compounded in pharmacies are not exempt from the adulteration, misbranding, and new drug provisions of The Act.

This implies that even compounded material produced under traditional pharmacy practice may fall under the regulation of the Act, 21 U.S.C. 351-52,355, because it can be considered a new drug.

This conclusion is believed to be the first time a court has ruled that a pharmacy practice may not be exempt from the "new drug" provision of the Act. Previously, the new drug provision in the context of compounding had only been decided for organizations other than pharmacies. In *U.S. v Sene X Elemosynary Corp., Inc.* (9) the defendants, Roger L. Sabastier and Seven Freedom Pharmacy, claimed exemption from sanctions of the Act (specifically the new drug provisions) by stating their activities constituted the practice of pharmacy. The court's answer was that the defendants' activities of compounding, promoting, and distribution of the drug GH-3 were not normal pharmacy practice, and thus:

> The question of whether the customary or usual practice of pharmacy is exempt from the Act's new drug provisions need not be resolved in this case.

In this case, the court determined the alleged activity by the defendants was atypical of pharmacy practice; thus

the Act applied to them as manufacturers without any exemptions, allowing the new drug provisions of the Act to apply without debate.

Under the Act, any drug is a "new drug" unless its element is:

> Such that such drug is . . . generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended or suggested in the labeling thereof. . . . [21 U.S.C. s321(p)(1)]

Thus, the decision from the P2C2 case could be interpreted as a means for FDA to regulate all compounding activity, whether or not the activity is alleged to be manufacturing. This ruling has caused distress to those who believe that all compounding practice by pharmacists is being challenged.

In an effort for pharmacists to retain the ability to compound, and to maintain all pharmacy regulation by the State Boards of Pharmacy, a bill has been introduced to Congress. The bill, H.R. 598, introduced by Mr. Bill Brewster (R-TX), and Mr. Tom DeLay (R-TX), is cited as the "Pharmacy Compounding Preservation Act of 1994." This bill, if passed by the Congress, would:

> guarantee the ability of licensed pharmacists to conduct the practice of pharmacy compounding and to ensure their rights to the necessary supply of bulk drug products, subject to applicable State and Federal laws.

It is claimed that there is much public support for this bill.

Also of note in the regulatory area is the publication by USP of a proposed general chapter on compounding. The chapter entitled <1161> Pharmacy Compounding Practices was drafted by the USP Drug Standards Division Compounding Advisory Panel, composed of representatives from both academia and the pharmacy profession. The intention of the new chapter, as stated in the summary paragraph is:

> to enhance the pharmacist's ability to compound extemporaneously safe, effective drug preparations in pharmacies.

Since USP is recognized by the Congress as providing official standards for drugs and dosage forms, the possible entry of the compendium into the discussions on compounding is certainly an important factor. The Packaging, Storage, and Distribution subcommittee of the USP Committee of Revision is presently considering draft compounding monographs for a number of specific pharmaceutical products and, since some of the preparations which are being considered for USP compounding monographs are orally administered products for which bioavailability consideration may be of critical importance in clinical practice, it is to be hoped that the USP subcommittee on Bioavailability and Dissolution will be given an opportunity to evaluate these monographs before they become official. Similarly, since one of the draft compounding monographs is for an opthalmic solution, it is hope that any USP monograph will adequately address the evaluation of the microbiological status of such products.

CLINICAL AND QUALITY ASSURANCE ASPECTS

Apart from purely legal and regulatory aspects, there will be many of us for whom the critical issues in any return by pharmacists to a substantial involvement in compounding will be the clinical properties of the products so produced and the level of adequacy of the quality assurance procedures used in the fabrication of compounded products. Safety and efficacy matters are of paramount importance for these products.

Some of the questions which arise in any evaluation of drug delivery systems compounded by pharmacists will include: the adequacy of in-process and final product testing, the nature of the facilities and equipment used in the compounding, and level of training and experience of those pharmacists or technicians who perform the product preparation and evaluation.

At present it appears that the in-process and final product testing used by many compounding pharmacists is, to say the least, rudimentary in nature. The three areas which may be of greatest concern in this regard are: absence of specific stability data for the product as compounded by the individual pharmacist or technician such as to allow a shelf life to be justifiably assigned to the product, lack of data on biological availability, and paucity of pertinent data on the microbiological status for products such as eye drops or injections.

Since some of the drugs presently being compounded by pharmacists are notorious for stability problems (nifedipine is a good example), there are good reasons for concern about the stability of some products. Assigning a shelf life based on generic knowledge of the drug substance and dosage form rather than laboratory data obtained from a study of the individual product compounded in a particular pharmacy may well be a highly

imprecise exercise. There may therefore be justifiable concern that in some cases patients may receive subtherapeutic doses.

Bioavailability and bioequivalence concerns are likely to be substantial, especially for extended-release products. It is noted that some compounding pharmacists are preparing an extended-release product of phenytoin (time release) using a general-purpose extended-release formula. It is understood that no bioavailability studies in human subjects nor even dissolution tests are performed on these products despite the fact that phenytoin is a drug with a relatively narrow therapeutic ratio one for which pharmacokinetic titration at the start of treatment is relatively common, and a drug which—because it exhibits nonlinear pharmacokinetics—requires very precise dosage control. Of course, for any extended-release product there is always a potential danger of dose dumping and the propensity of any product to exhibit this problem does require careful evaluation of release rates.

The techniques in quantifying bioequivalence have become increasingly sophisticated in recent years and improved methods are under review. For example, at the meeting of the FDA Expert Advisory Committee on Generic Drugs held on September 6 and 7, 1995, the possibility of requiring the assessment of *individual* subject bioequivalence, rather than simply *average* bioequivalence, was discussed. It would seem very strange to consider imposing such requirements for generic versions of given drug product—especially an extended-release system—if compounded versions without any bioavailability data were also being used by patients.

Since some of the products being produced by compounding pharmacists are parenterals (e.g., injection of morphine sulfate) or eye drops (e.g., cefazolin sodium) absence of pyrogens and viable pathogenic organisms is obviously a matter which for some compounded products may be of critical importance. Unfortunately, it appears that in many, if not all instances, compounding pharmacists are preparing injections and opthalmics without any data whatsoever on the microbiological status of the raw materials (total bioburden and nature of the bioburden) at the time of manufacture nor any product testing for sterility and absence of pyrogens. Since serious toxic hazard, including blindness or even death, could result from use of a product with an inappropriate microbiological status, this lack of data may well be a cause of grave concern.

Of course, there may also be some other very basic quality assurance aspects that would concern some pharmaceutical scientists such as the absence of identity or potency tests.

Even a cursory evaluation of a few pharmacies involved in extensive compounding activities suggests that there is presently considerable variation in the nature of such facilities.

What about the level of education and training of pharmacists with respect to compounding activities? Thirty years ago an unequivocal endorsement of the adequacy of virtually any U.S. registered pharmacist to engage in compounding a wide variety of drug delivery systems was probably possible. Nowadays there may well be less certainty in this area. Many U.S. University bachelor-degree or Pharm.D. programs in pharmacy now provide considerably less in terms of required course work in compounding, and indeed it is now possible for a student to graduate from an ACPE-accredited program who has, for example, never prepared an ophthalmic or parenteral product.

PROFESSIONAL ASPECTS

An organization, Professional Compounding Centers of America (PCCA), is active in promoting compounding by pharmacists. PCCA is a company which provides pharmacists and technicians with training. It also supplies bulk chemicals, equipment, and model formulations for the practice of extemporaneous compounding. The company has grown to include over 90 employees from its establishment in 1981 by a pharmacist. The company is a strong proponent of the Compounding Preservation Act and was instrumental in bringing the compounding issue to public attention.

With proponents in the private and public sector, and the judicial activity currently occurring on the topic, the debate over compounding practices of pharmacists has resulted in a flurry of correspondences, policy issuances, and legislative drafts that may not always have been helpful.

It is believed that CPG 7132.16 was published to inform pharmacists that they did not have carte blanche to compound without obligation to the safety and health of the patient, and to inform the pharmacists that their exemptions from the Act were conditional, and thus the FDA could inspect them if nontraditional pharmacy practice had allegedly occurred. The FDA's commitment to maintaining safety and efficacy of prescription medication appeared to be the sole source of its intent as seen in their cooperation in developing communica-

tions between state and federal officials for pharmacy inspections in the fall of 1992. Seven months after the drafting of the CPG, FDA officials met with the NABP to discuss the improvement of cooperation and communication between federal and state officials relating to enforcement of the CPG.

Outlined in a correspondence from Ronald Chesemore and Carmen A. Catizone (Executive Director, NABP) to various state and federal officials involved with this topic, is a three-step outline to enhance cooperation agreed upon during this meeting (10). The first step is to establish federal and state contact points on pharmacy inspection and compounding and manufacturing issues. The second step is to improve the dissemination of information regarding compounding pharmacies between federal and state officials. Therefore, if FDA receives a complaint of manufacturing by a pharmacy, FDA should inform the state contact, which would then investigate the complaint. The third step is to make available reference material for both state and federal officials as to the differences between compounding and manufacturing.

It would be highly desirable if this policy on federal and state cooperation could become a functional compromise for the two sides involved in the extemporaneous compounding debate. While both sides of this debate have significant points to make, the underlying focus should be on the safety and efficacy of the products. Compounding is an innate component of traditional pharmacy practice, and a significant percentage of the population use compounded products. However, problems have occurred as a result of poorly compounded material. Some regulation of compounding standards needs to be established to prevent further problems.

The proposed USP/NF chapter may well be a good start in establishing guidelines for practicing safe and effective compounding. A source of reference for compounding would perhaps standardize what appears to be a nonstandardized practice. USP, FDA, and other interested bodies might perhaps cooperate in preparing a "Current Good Compounding Practice" guide to serve as a source for method defining the concept of traditional compounding practice, and a method for standardizing the equipment, materials, and formulations commonly used for compounding. Also it might well be useful for the state boards of pharmacy to take a more active role in establishing safe compounding criteria for pharmacists to follow. It may also be appropriate to establish some testing scheme for the analysis of randomly selected compounded products.

An examination of information from PCAA indicates that some pharmacists who are strongly promoting their compounding activities are generating substantial income from this work. It is to be hoped that financial factors will not cloud professional vision so that judgment becomes distorted. Given the advances in required quality assurance techniques for manufactured drug delivery systems, there are probably some types of product which compounding pharmacists should never attempt to prepare. Extended-release products, particularly those for drugs of a low therapeutic ratio for which manufactured products are available, may well fall into this category. On the other hand, there is a strong case for a pharmacist compounding a special "one of" topical ointment for a dermatologist who requires a special product for a particular patient when such a product is not available from the pharmaceutical industry.

If indeed the present resurgence in compounding by pharmacists continues, it may also be appropriate for ACPE to reconsider its accreditation requirements for Pharm.D. programs so as to assure that all those graduating with that degree have a strong background in contemporary methods of compounding and evaluating all the products which they might be called upon to prepare.

It will be to the benefit of the community in general, and patients in particular, if FDA, USP, state boards of pharmacy, and all other interested parties can work together so as to assure that harmonious relationships promote safe and effective compounding without excessive bureaucratic control.

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