PhRMA

By Messenger

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Jane Axelrad, Associate Director for Policy
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike - Room 6027
Rockville, Maryland 20852

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Lana Ogram, Director
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North One
7520 Standish Place, Room 229
Rockville, Maryland 20855

RE: PhRMA Initial Comments on the Compounding Provision of FDAMA – § 127

Dear Jane and Lana:

We are writing on behalf of the Pharmaceutical Research and Manufacturers of America to provide industry input on compounding provisions of the FDA Modernization Act of 1997 (Section 127). The enclosed memorandum discusses issues of unique concern to the pharmaceutical manufacturing industry as the FDA implements Section 127. These issues include the compounding of commercially available products, limitations on inventories of compounded products, products that present demonstrable difficulties for compounding, bulk drug substances without USP or National Formulary monographs or FDA approval, advertising and promotion restrictions, and the memorandum of understanding with the states. The enclosed memorandum was prepared by the PhRMA Compounding Work Group.

In addition, PhRMA will be submitting comments on the FDA's notice requesting nominations for bulk drug substances that are neither contained in a USP or National Formulary monograph nor ingredients in approved drugs.

The PhRMA Compounding Work Group would be pleased to meet with you or others in the Agency who are working on the implementation of Section 127, or provide any other assistance that might be helpful.

Sincerely,

Douglas Mendenhall

Douglas W. Mendenhall, Ph.D.
Glaxo Wellcome Inc.

Marjorie Powell

Marjorie E. Powell
PhRMA

Enclosure
Implementation of the Pharmacy Compounding
Provisions, FDA Modernization Act of 1997 (Sec.127)

98D-0272

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April 24, 1998

IMPLEMENTATION OF THE PHARMACY COMPOUNDING PROVISIONS OF THE FDA MODERNIZATION ACT OF 1997 (§ 127)

Section 127 of the Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997), adds a new section 503A to the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. § 353a) to clarify the application of the FFDCA to the compounding of drug products by pharmacists and physicians. In particular, Section 127 specifies the circumstances under which pharmacy compounding will be permitted under federal law and exempt from the adulteration, misbranding, and new drug provisions of the FFDCA. Section 127 is carefully crafted to preserve the appropriate practice of compounding based on individual medical needs identified by the physician and pharmacist, while ensuring that compounding is not used to evade the important federal requirements that exist to regulate drug manufacturing and protect the public health. As Congress stated when enacting Section 127, "It is the intent of the conferees to ensure continued availability of compounded drug products as a component of individualized therapy, while limiting the scope of compounding so as to prevent manufacturing under the guise of compounding." Joint Explanatory Statement of the Committee on Conference at 4.

When FDA promulgates regulations to implement Section 127, as required by the FDA Modernization Act, it must take special care to enforce the boundaries between legitimate and illegitimate pharmacy compounding embodied in the Act. Key implementation issues will include (1) enforcing the prohibition against compounding copies of commercially available drug product regularly or in inordinate amounts; (2)

ensuring that only limited quantities of product are compounded before receipt of a valid prescription order for an individual patient; (3) dealing with products that present demonstrable difficulties for compounding; (4) developing a list of products that can be compounded using bulk drug substances that are neither the subject of a United States Pharmacopoeia (USP) or National Formulary monograph nor components of already approved drugs; (5) enforcing the advertising and promotion restrictions provided for in the statute; and (6) developing memoranda of understanding with states.

1. Prohibition on Compounding Commercially Available Drug Products

Section 127 prohibits pharmacists and physicians from compounding regularly or in inordinate amounts any drug product that is "essentially a copy of a commercially available drug product." FFDCA § 503A(b)(1)(D); 21 U.S.C. § 353a(b)(1)(D). As Congress indicated when enacting Section 127, compounding should only occur for an individual patient based on the medical need of the patient for the compounded drug. S. Rep. No. 105-43 at 67-68 (1997). The need for a medical justification for compounding is reflected in Section 127's basic requirement that compounding only occur based on the unsolicited receipt of a valid prescription or a notation approved by the prescribing practitioner on the prescription that a compounded product is necessary for the identified patient. FFDCA § 503A(a); 21 U.S.C. § 353a(a). Where an appropriate commercially available product exists, there is no medical need for a compounded product. As such, in accordance with the text of Section 127 and congressional intent, compounding of a copy of a commercially available drug should only be permitted in rare circumstances.

Specifically, FDA should restrict the compounding of a commercially available product to an emergency situation as a one-time event (for example, when a patient needs a prescription filled immediately and the pharmacist has no way to fill the prescription in a timely manner without compounding the commercially available product). The allowable quantity to be compounded in an emergency situation should be limited to a 30-day supply or less for the patient, depending on the patient's therapy. FDA should prohibit the compounding of copies of commercially available products in all other circumstances. In the absence of an identified medical need to compound a product that is not commercially available, or an emergency which justifies compounding a limited amount of a commercial product, there is no longer a public health justification for a pharmacy to manufacture a product. A pharmacy cannot provide the same assurances offered by the regulatory and scientific framework which surrounds the commercial production of drug products.

In addition to limiting the circumstances under which compounding commercially available products is permissible, FDA must rigorously examine claimed differences between a compounded drug and the comparable commercially available drug product to determine whether they are essentially copies. Compounding should not be allowed based on minor differences between products that do not have clinical significance or a medical justification, or else the protections of Section 127 would be completely undermined. As Section 127 provides, to avoid being a copy of a commercially available drug product, the compounded product must include "a change, made for an identified individual patient, which produces for that patient a *significant difference*." FFDCA § 503A(b)(2); 21 U.S.C. § 353a(b)(2) (emphasis added).

Medical justifications supporting the need to compound a modified product could include a patient's allergy to some component of the commercial product (*e.g.*, a color additive), or inability to use the commercially provided dosage forms (*e.g.*, capsule vs. liquid). Compounded products with only minor changes in dosage strength from the commercial product or clinically insignificant differences in the shape or size of a tablet lack medical justification for compounding and should be considered mere copies of the commercial product.

FDA should require by regulation that compounding only be permitted where the prescriber identifies the clinical justification for compounding, so that FDA or a state inspector will be able to determine whether the compounded product is different from the commercial product in a medically significant way or is just a copy. Section 127 contemplates that the prescriber will provide some indication of the need for the compounded product, *see* FFDCA § 503A(a); 21 U.S.C. § 353a(a), and the legislative history indicates that the medical need for compounding must be documented either on the prescription order or elsewhere, *see* S. Rep. No. 105-43 at 68 (1997). FDA should elaborate on this requirement when it promulgates implementing regulations.

2. <u>Limitations on Inventories of Compounded Products</u>

For compounded products that are not copies of commercial products, pharmacists and physicians can only compound after receiving a prescription requesting compounding for an individual patient or in *limited quantities* prior to receipt of a prescription if the quantity is supported by the compounding history of the pharmacy. FFDCA § 503A(a)(1); 21 U.S.C. § 353a(a)(1). Significant concerns arise when a pharmacist or physician compounds more than a limited quantity of a product before

receiving a valid prescription calling for a compounded drug. First, when compounding is not based on an individual prescription order or an anticipated individual prescription order, the compounding becomes simply manufacturing product for sale rather than compounding a product based on an individual therapeutic need. Second, the greater the amount of compounded product a pharmacy stores, the greater the concern about product stability. Unlike commercial product, stability data often does not exist to support the proper storage of compounded product. In the absence of stability data, limits need to be stipulated for the different types of compounded formulations/dosage forms, such as the beyond-use dates in the USP's good pharmacy compounding practices.

In light of these concerns, FDA should set limits on the quantity of drug product that a pharmacy or a physician may compound, and require that no product be held beyond a period established by stability data. Requiring that the amount of drug compounded be related to the compounding history of the pharmacy and limiting the quantity stored to an amount which would remain stable within the drugs contemplated storage period (such as the beyond-use dates in the USP's good pharmacy compounding practices) should effectively limit inventory. In addition, no pharmacy or physician should be able to compound in bulk for distribution to other pharmacies or physicians.

3. Products that Present Demonstrable Difficulties for Compounding

Certain products present greater difficulties for compounding than others. The following types of products in particular present technical challenges for proper compounding and should be included on the list FDA is required to promulgate under Section 127 of products that may not be compounded (FFDCA § 503A(b)(3)(A) ; 21 U.S.C. § 353a(b)(3)(A)): (1) modified release products; (2) complex sterile dosage

forms (*e.g.*, suspensions and lyophilizates); (3) narrow therapeutic index drugs for which precision in dosage strength is vital; and (4) dosage forms which contain small amounts of potent drugs and for which a lack of content uniformity could yield subpotency or superpotency.

For other products that may be compounded, good compounding practices such as those issued by the USP should be followed for all compounding. It is especially critical that appropriate good compounding practices be followed for products which by their nature pose an immediate safety risk if compounded without adequate controls (*e.g.*, sterile products including ophthalmics, inhalation solutions, parenterals, and otics). Good compounding practices (*e.g.*, as defined by the USP) should include appropriate in process and/or product controls correlated with biological performance, such as dissolution or blood level profiles. Products that present a risk of microbial contamination (such as sterile products) or cross contamination (such as penicillins, sulfonamides and cytotoxics) should only be compounded in a dedicated work area using dedicated equipment. All products should be compounded with suitable space, facilities, and equipment in accordance with documented processes, including validation of any sterilization process. Using space or facilities that are designed for and normally used for other practice activities is often inappropriate for compounding.

4. <u>Bulk Drug Substances Without Monographs or FDA Approval</u>

As a general principle, there should not be a clinical use of a substance unless the substance has been reviewed and approved by the FDA or the substance is generally recognized as safe and effective. Accordingly, no bulk drug substance that is neither the subject of a USP or National Formulary monograph nor a component of an FDA

approved drug should be used in compounding. Allowance for the use of unapproved drug substances in compounding could effectively create an unregulated mechanism for developing and distributing new drugs that would not be subject to the rigorous review that FDA conducts to ensure that only drugs proven to be safe and effective are given to the public. To avoid this potentially dangerous scenario, FDA should carefully consider whether it should accept any nominations it receives for unapproved bulk drug substances to be used in compounding pursuant to the recent notice FDA published in the Federal Register (63 Fed. Reg. 17011 (Apr. 7, 1998)).

5. Advertising and Promotion Restrictions

Section 127 contains important provisions restricting the advertising and promotion of compounding services. Compounding pharmacies, pharmacists and physicians may only advertise and promote their general compounding services, and may not advertise or promote the compounding of any particular drug, class of drug, or type of drug. FFDCA § 503A(c); 21 U.S.C. § 353a(c). FDA should enforce these restrictions in accordance with the clear provisions of Section 127.

6. State Memoranda of Understanding

Section 127 also directs FDA to enter into memoranda of understanding with the states. In addition to addressing the distribution of compounded drug products interstate, as required by Section 127, these memoranda of understanding should reference the importance of following good compounding practices such as those of cited in the USP, and should ensure that the state will have appropriate inspection requirements to help enforce the provisions of Section 127. As Congress indicated when enacting Section 127, "[t]he conditions set forth in [FFDCA] Section 503A should be used by the state boards

of pharmacy and medicine for proper regulation of pharmacy compounding in addition to existing state-specific regulations." Joint Explanatory Statement of the Committee on Conference at 4. The memoranda of understanding should also encourage states to consider requiring that accredited pharmacy schools include good compounding practices as part of their required curricula, either in the initial degree training or as a post-graduate course, and that demonstration of competency in the principles and application of good compounding practices be a necessary prerequisite for engaging in compounding or a component of pharmacy board license exams.