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Dear Ms. Axelrod and Ms. Ogram:

The following comments are submitted by the International Academy of Compounding Pharmacists (IACP) in response to a letter from the Pharmaceutical Research and Manufacturers of America (PhRMA) dated April 24, 1998 (PhRMA letter). PhRMA's recommendations would place unreasonable limits on the practice of compounding, and, if adopted by the Food and Drug Administration (FDA), would compromise the quality of care that physicians could provide to their patients. Moreover, in several

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instances PhRMA urges FDA to exceed the authority granted to it by Congress to regulate the practice of compounding. In general, PhRMA's letter is little more than a thinly veiled attempt to place additional obstacles in the way of pharmacy compounding.[1]

1. Prohibition on Compounding Commercially Available Drug Products

PhRMA suggests that the compounding of a copy of a commercially available drug should be "rare." Specifically, PhRMA recommends that compounding of commercially available drugs be restricted to "an emergency situation as a one-time event," and that FDA should "prohibit the compounding of copies of commercially available products in all other circumstances." PhRMA letter at 4. There is no support for such a restrictive interpretation of § 503A.

If Congress had intended to restrict the practice of compounding copies of commercially available drugs to emergency situations, it could have done so with explicit language to that effect. It did not. There is nothing in the language of the statute, or the legislative history, to suggest that Congress sought to impose this restriction on pharmacy compounding. While

[1] For Reasons that it never explains, PhRMA targets pharmacy compounding, not compounding by physicians.

Congress did limit the scope of compounding of commercially available drugs; it did not establish the extraordinary restrictions now suggested by PhRMA.

Significantly, at the same time Congress added § 503A to the Federal Food, Drug, and Cosmetic Act (FDC Act), it amended § 520(m) to address emergency situations relating to the use of devices. Thus, when Congress wanted to cover emergency situations in the legislation, it did so directly. If Congress had chosen to limit compounding to emergency use, it would have said so.

PhRMA goes on to suggest that "[i]n 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 manufacture [sic] a product." PhRMA letter at 4. By this statement PhRMA is urging FDA to impose greater restrictions than Congress did. There is no basis for confining compounding of commercially available products to "emergency" settings. Congress did say that the exemption would not apply if a pharmacy compounds "regularly or in inordinate amounts." While this does limit the compounding of commercially available products, it is far less limiting than "emergency" situations.

PhRMA also proposes that FDA should require prescribers to identify the clinical justification for compounding and "rigorously examine claimed

differences between a compounded drug and the comparable commercially available drug product to determine whether they are essentially copies." Id. However, it is clear that Congress felt FDA can make better use of its resources. The Committee conferees stated explicitly that they expected that "FDA and the courts will accord great deference to the licensed prescriber's judgement in determining whether the change produces a 'significant difference.'"[2] Additionally, the conferees instructed that drugs should fail to qualify for the compounding exemption only "where it is readily apparent, based on the circumstances, [that] the significant difference' is a mere pretext to allow compounding of products that are essentially copies of commercially available products." Id. (emphasis added). Once again, PhRMA's proposed standard "rigorously examine" is devoid of legislative support and would serve the sole purpose of curbing compounding.

2. Limitations on Inventories of Compounded Products

PhRMA urges FDA to set limits on the quantity of compounded drugs that a pharmacy may store in inventory. Specifically, PhRMA contends that the failure to limit the amount of drug compounded to the compounding history of the pharmacy, encourages "manufacturing" rather than compounding based on individual need. PhRMA letter at 6. However, § 503A

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[2] H.R. Rep. No. 105-399, at 94 (1997).

preserves the practice of anticipatory compounding: compounding prior to the receipt of a valid prescription. Furthermore § 503A does not limit the amount of drug that may be compounded to the amount that has been compounded in the past by that pharmacy. To do so would freeze each pharmacy's compounding practice at its current level. Interpreting the provision in this way would fail to account for fluctuations in the surrounding population, the entrance (or exit) of pharmacies in a specific market area, changes in medical practices, and other variables that change over time.

The "history" which Congress intended a pharmacy to use for anticipatory compounding is, rather, the track record of the pharmacy in receiving orders for the drug compounded, with the recognition that the prescribing history would evolve. That is, if physicians prescribe a greater amount of a medication or the pharmacist compounds for additional patients, then the level of anticipatory compounding may increase to keep pace. Anticipatory compounding facilitates patient care by allowing the prompt dispensing of prescribed medication. PhRMA's interpretation would impede the timely dispensing of compounded medications to patients to fill their prescriptions.

PhRMA also cites its concerns regarding the stability of compounded products as a rationale for setting predetermined limits on the amount of

compounded drug that should be stored. PhRMA argues that "the greater the amount of compounded product a pharmacy stores, the greater the concern about product stability." Id. As a result, PhRMA suggests that no product should be held beyond a period established by stability data. Such a restriction would significantly limit the practice of compounding beyond what Congress intended.

Section 503A explicitly provides that compounding should be conducted consistent with the United States Pharmacopoeia (USP) chapter on pharmacy compounding. FDC Act § 503A(b)(1)(B). The USP emphasizes that stability data will not always be available and provides the pharmacist with factors that should be considered in determining the stability of formulations. The USP does not suggest that the amount of drug stored has any bearing on stability. Rather, the pharmacist is instructed to consider "the nature of the drug and its degradation mechanism, the container in which it is packaged, the expected storage conditions and the intended duration of therapy when assigning end use dates."[3] The USP also provides suggested maximum beyond use dates for various formulations, including those for which stability data is not available. But, most significantly, the USP recommends that in addition to using all available information, the pharmacist should use his or her pharmaceutical education and experience. By incorporating the

[3] USP, Drug Information Volume III: Approved Drug Products and Legal

USP standard, Congress rejected the imposition of federally mandated stability limits.

3. Products that Present Demonstrable Difficulties for Compounding

PhRMA recommends that FDA prohibit compounding for specific "products." PhRMA specifically cites four categories of "products" which it claims have "demonstrable difficulty" in being compounded: modified release products, complex sterile dosage forms (suspensions and lyophilizates), narrow therapeutic index drugs and dosage forms which contain small amounts of potent drugs. PhRMA letter at 6-7. Such sweeping limitations on the practice of compounding are unacceptable. In some instances, compounded versions of these products represent the only option between treatment and non-treatment for an individual patient. Moreover, the USP chapter on compounding provides guidance on the process for compounding many of these formulations. While Congress left open the possibility that some drugs may present demonstrable difficulties in compounding, PhRMA's recommendation is too broad and is inconsistent with Congress' specific intent to rely on the standards established by the USP.

Furthermore, the "demonstrable difficulty" designation is to be made for a specific compounded "drug product." A drug product is narrowly defined

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Requirements, v/102 (18th ed. 1998).

by FDA's regulations. 21 C.F.R. § 210.3(b)(4). PhRMA goes much further. Its list extends beyond drug substances into ill-defined, broad-ranging categories that are not drug product specific. Finally, as a factual matter, PhRMA is simply wrong. Pharmacists successfully compound medications that fall into these broad categories.

PhRMA makes specific recommendations concerning the breadth of good compounding practices that should be used in compounding, and on the use of dedicated facilities and equipment for compounding. Congress has determined that the USP represents the professional standard that should be applied to the practice of compounding. FDA should refrain from adopting PhRMA's specific recommendations and rely, rather, on the standards established by USP. This will allow greater flexibility and will promote the early adoption of advances in the practice of compounding. In addition, PhRMA's specific recommendation concerning the validation of sterilization procedures suggests that FDA apply Good Manufacturing Practices to compounding, when Congress has specifically exempted compounded drugs from the GMP regulations. Never the less, pharmacists maintain specific policy and procedure manuals with regards to validation of sterility. These measures are perhaps state mandated or simply a part of compounding protocol.

4. Bulk Drugs Without Monographs or FDA Approval

PhRMA urges that "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." PhRMA letter at 7-8. To do so, PhRMA asserts, "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." Id.

PhRMA's approach ignores that Congress specifically exempted compounded drugs from the safety and efficacy standards that govern new drug applications. Congress chose instead to impose other restrictions on the practice of compounding to ensure the safety of compounded drugs.[4] Moreover, Congress considered and rejected the notion that drugs for which no monograph exists or which are not components of drug products approved by the Secretary are not appropriate for compounding. Section 503A(d)(2) specifically directs FDA to develop regulations identifying when these drug substances may be used in compounding. Thus, PhRMA's recommendation directly contradicts the intent of Congress.

In addition, PhRMA's recommendation would be deleterious not only for patient care, but also for drug manufacturers. Ironically, one of the first nominations for a drug substance to be put on the "positive list" was

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[4] 143 Cong. Rec. S9840 (daily ed. Sep. 24, 1997) (comments of Senator

submitted by Abbott Laboratories. Moreover, a number of drug products that ultimately received NDA approval for sale by manufacturers originated with pharmacy compounding, e.g., lithium carbonate capsules, 5-aminosalicylic acid (mesalamine) enemas, and most recently progesterone oil-filled capsules. Thus, PhRMA's recommendation would ultimately impede the introduction of new drug products by drug manufacturers.

5. Advertising and Promotion Restrictions

PhRMA urges FDA to enforce the advertising restrictions imposed by § 503A. IACP assumes that FDA is already aware of the advertising provisions of § 503A. IACP further expects that FDA will appropriately and reasonably use its enforcement resources when it comes to this aspect of the law. IACP is confident that FDA is also cognizant that the advertising by pharmacists is subject to First Amendment protection. See, e.g., Virginia State Bd. of Pharmacy v. Virginia Citizens' Consumer Council, Inc., 425 U.S. 748 (1976).

6. State Memoranda of Understanding

PhRMA recommends that the memorandum of understanding (MOU) with the states, required by § 503A(b)(3)(b)(i), reference the importance of following good compounding practices such as those cited in the USP; require states to have inspection requirements to enforce § 503A; encourage states to consider requiring that accredited pharmacy schools

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Kennedy).

include good compounding practices as part of their curricula; and urges that demonstration of competency in good compounding practices be a prerequisite for engaging in the practice of compounding.[5]

Section 503A(b)(3)(B)(i) requires that the MOU between FDA and the states address the interstate distribution of compounded drug products and provide for appropriate investigation by a state agency of complaints relating to drug products distributed outside such state. It requires nothing more. PhRMA's proposed expansion of the content of the MOU is inappropriate and inconsistent with the law.

The issues PhRMA wishes FDA to address are the dominion of State Boards of Pharmacy. Licensing of health professionals and accreditation of educational institutions is within the powers delegated to the states. To suggest that FDA regulate these practices through the MOU is entirely inappropriate. One of the overriding principles that led to passage of the pharmacy section was Congress' view that states should play the preeminent role in regulating compounding. Through the MOU, PhRMA now seeks to have FDA intrude heavily into areas in which the federal government should play no role.

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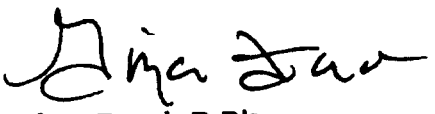
5 Although PhRMA's letter discusses the bulk drug nomination process, it was not put on the public docket. Nor was IACP's letter of May 22, 1998, dealing specifically with that process. In order to ensure that there is full, puplic consideration of the comments tendered to FDA, we believe that both documents need to be put on public display docket No. 98N-0182.

IACP strongly supports efforts to upgrade and enhance the skills of compounding pharmacists. Indeed, IACP has devoted considerable resources to support programs to educate and train pharmacists. Mandating state requirements in the guise of an MOU is not the way to accomplish this objective.

Sincerely,



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