

December 13, 2005

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, MD 20852

0117 '05 DEC 13 P2:35

Re: Docket No. 2005P-0116; Comments in Support of CHASM Petition re
Compounded Drugs for Inhalation and in Opposition to Comments
Submitted by the International Academy of Compounding Pharmacies

Dear Sir or Madam:

Sepracor Inc. ("Sepracor") submits these comments in support of the petition filed by members of the Consumer Health Alliance for Safe Medication ("CHASM") related to labeling and advertising for compounded drugs for inhalation. In these comments we also respond to comments submitted by the International Academy of Compounding Pharmacies ("IACP").¹

I. FDA Should Grant the CHASM Petition in All Respects

Sepracor supports the CHASM Petition because it requests that FDA enforce basic labeling and advertising requirements in the Food, Drug, and Cosmetic Act ("FDCA") for prescription drugs. Entities that promote and dispense compounded formulations of liquid inhalation drugs should provide patients and physicians with basic material facts regarding their products, which must include at a minimum the following information:

- The product is not approved by FDA
- The product is compounded in a pharmacy
- The product does not comply with FDA standards for sterility
- The product has not been demonstrated safe or effective

FDA should promulgate a regulation and take all of the other steps requested in the CHASM Petition to ensure that physicians and patients receive vital information on these drugs and are not misled as to the nature and quality of such products.

II. FDA Should Expand the Relief to Include All Liquid Inhalation Drugs

The CHASM petition requests that FDA take the aforementioned actions with regard to *aqueous-based* drugs for inhalation. It is important to recognize that some liquid drugs formulated for use in nebulizers may not be aqueous-based, but may

¹ Comments in Opposition to CHASM Citizen Petition re Labeling and Advertisements for Compounded, Aqueous-Based Drugs for Inhalation, No. 2005P-0116:C2 (dated August 15, 2005) ("IACP Comments").

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nevertheless present the same issues. An example of such a drug is cyclosporine inhalation solution, that was addressed by the Pulmonary-Allergy Drugs Advisory Committee in June of this year. Although the solution contains no water, FDA still required that it be sterile.² The development of other liquid, nonaqueous drugs for inhalation will present similar issues. FDA should thus grant the relief requested in the CHASM Petition with regard to all liquid inhalation drugs.

III. FDA Should Reject the Comments Submitted by IACP.

IACP's comments advance numerous propositions and arguments in opposition to the relief requested in the CHASM Petition. Some of these propositions are erroneous and none of the arguments provides any basis for permitting compounding pharmacies to avoid compliance with the basic labeling and advertising provisions of the FDCA.

1. CHASM Is Not Required to Generate Data on Prescribing Patterns.

IACP argues that the CHASM Petition relies heavily on "anecdotal evidence" (referring to FDA Warning Letters as "anecdotal evidence"), and suggests that CHASM should be required to demonstrate that the misleading promotion has affected prescribing patterns of physicians.³ The suggestion is a red herring that ignores the basic legal requirements of the FDCA.

The FDCA requires that compounding pharmacies provide material facts in their labeling and advertisements. Materiality is demonstrated if the absence of the information renders the labeling or advertising misleading. Neither FDA nor the courts have required that materiality be demonstrated through a study of prescribing patterns on the part of physicians, or through any other empirical evidence.⁴ The question is not what prescribers have done, but what prescribers need to know. The CHASM Petition presents abundant evidence from health-care professionals themselves expressing concerns over compounded drugs and the differences between compounded drugs and approved drugs.⁵

² Chiron Corporation Pulmonary-Allergy Drugs Advisory Committee Briefing Document, 46 (June 6, 2005).

³ IACP Comments at 3.

⁴ See, e.g., *Pharmaceutical Manufacturers Association v. FDA*, 634 F.2d 106 (3rd Cir. 1980); *Research Labs v. United States*, 167 F.2d 410 (9th Cir. 1948); *United States v. Vitamin Industries, Inc.*, 130 F. Supp. 755 (D. Neb. 1955).

⁵ CHASM Petition at 16-18, (citing Declaration of Robert J. Kuhn, Pharm.D. (Sept. 30, 2004) (Petition Tab 25); Declaration of Dr. Richard Moss, M.D., F.C.C.P. (Sept. 24, 2004) (Petition Tab 27); Dear Colleague Letter from Michael Schatz, MD, MS, FAAAAI, President, AAAA, and Michael Blaiss, MD, President, ACAAI, (Aug. 31, 2004) (Petition Tab 28); Patrick J. Coyne, APRN, BC et al., *Compounded*, 103 Am. J. Nurs. 76, 85 (2003) (Petition Tab 29); Lawrence Trissel, B.S., FASHP, *Editorial: Compounding Our Problems -- Again*, 60 Am. J. Health-Syst. Pharm., 432 (2003) (emphasis added) (Petition Tab 30) American Society of Health-System Pharmacists, *Helping Members respond to Problems with the Supply of Quality Pharmaceuticals* (2004) (Petition Tab 31); *Compounding Sterile Preparations Raises Informed-Consent Issues* AJHP News (Jun. 15, 2003) (statements of Robert E. Rapp, Chair of the University of

There is, moreover, strong evidence that physicians are being misled on a significant scale and that compounded drugs are being prescribed in the absence of a determination that the compounded formulation is necessary to meet the needs of an individual patient that cannot be met with an approved drug. In its Warning Letters to Lincare and Respi Care, FDA described the manufacture on a massive scale of compounded products that were essentially the same as approved drugs with no documentation of medical necessity and no evidence that the prescribers were even aware that the drugs were compounded.⁶

2. The CHASM Petition Requests Full Disclosure Rather than a Restriction on Speech.

IACP asserts that “CHASM’s attack on the right of pharmacists to advertise their compounding services” is foreclosed by the First Amendment.⁷ In fact, the CHASM Petition does not challenge the right of compounders to advertise compounding services. CHASM rather requests that, when the compounders advertise their services, the compounders be forthright and truthful, and that they advise prescribers and patients of material facts as required by FDCA § 201(n). The CHASM Petition requests more information rather than a restriction on information – a course specifically suggested by the Supreme Court in *Thompson v. Western States Medical Center*, where the Court noted that government’s interest in preventing misleading information “could be satisfied by the far less restrictive alternative of requiring each compounded drug to be labeled with a warning that the drug had not undergone FDA testing and that its risks were unknown.”⁸

3. The Incentive to Dispense Compounded Drugs in the Place of Approved Drugs Has Not Been Eliminated.

IACP suggests that FDA need not require compounders to provide material facts in labeling and advertisements because “the economic inducements referred to in the citizen petition no longer exist.”⁹ IACP suggests that the economic incentive has been

Kentucky, Human Investigations Committee, Kevin Kinkade, Missouri Board of Pharmacy Executive Director, Jesse C. Vivian, Professor, Wayne State University College of Pharmacy, Jane J. McCaffrey, President, American Society of Healthcare Risk Assessment) (Petition Tab 32); Thomas Kaye, R.Ph., MBA, *The Quandary of Compounding for MCOs: Administrative Costs, Risks, and Waste*, 2003 Managed Care 42, 46 (Petition Tab 33).

⁶ Letter from H. Tyler Thornberg, Director, New Orleans District, FDA, to John P. Byrnes, President, Lincare (Dec. 9, 2004); Letter from Donald J. Voeller, District Director, FDA, to Severo Pina, Chief Executive Officer, Respi Care (Dec. 20, 2004).

⁷ IACP Comments at 4.

⁸ 535 U.S. 357, 376 (2002).

⁹ IACP Comments at 4.

removed because Medicare reimbursement is now based on Average Sales Price (ASP) rather than on Average Wholesale Price (AWP), which was higher.¹⁰ IACP knows better.

The economic incentive to compound a formulation from bulk chemicals rather than dispense an approved drug is not a function of the overall level of reimbursement. It is rather a function of the difference between the cost to the pharmacist of stocking an approved drug and the cost of compounding a similar drug from bulk chemicals. Because both compounded drugs and approved drugs are reimbursed based under Medicare on the same ASP (which is based on the sales price of the manufacturer of the approved drug), the pharmacist will still make a greater profit by compounding a formulation from bulk chemicals than by purchasing an approved drug at wholesale. While the overall level of reimbursement for dispensing a drug may be reduced, the pharmacist always makes more by dispensing the drug that costs the pharmacist less. The continued profitability from compounding is acknowledged by distributors of approved and compounded respiratory drugs.¹¹

Moreover, even if the economic incentive to compound inhalation drugs were removed, that would not affect the legal and ethical obligation of compounding pharmacies to provide material facts in their labeling and advertising for compounded drugs.

4. State Regulation Is Inadequate And Does Not Relieve Compounders from the Basic Requirements of the FDCA.

IACP argues that FDA should not expend scarce resources in regulating compounded drugs because state laws forbid dispensing of compounded drugs without the prescriber's prior consent.¹² Of course, as the CHASM Petition demonstrates, the prescriber's "consent" is meaningless unless the compounding pharmacy presents the prescriber with all of the material facts about its product and refrains from making material misrepresentations as to the safety, efficacy, and regulatory status of the product. Moreover, the mere existence of state laws and regulations governing compounding is not enough. The CHASM Petition amply demonstrates that the states have largely failed to regulate large-scale, substitution compounding. FDA's enforcement actions also make this clear.

Finally, it is worth noting that there are state laws and regulations governing the manufacture and marketing of drugs by drug companies just as there are state laws and regulations governing pharmacy compounding. State laws generally require that labeling and advertisements of *FDA-approved drugs* include material facts and not be

¹⁰ *Id.*

¹¹ The Full Dose, Respiratory Distributors, Inc., Issue 24 (Dec. 19, 2004); Issue 26 (Jan. 10, 2005) (attached collectively as Exhibit A).

¹² *Id.* at 5.

misleading.¹³ This does not mean that FDA should preserve its resources by refusing to enforce the FDCA labeling and advertising requirements with regard to the manufacture and marketing of approved drugs. FDA should enforce the FDCA requirements for labeling and advertisements with regard to both approved drugs and compounded drugs so that, with respect to *all* drugs, prescribers and patients will have the information they need and to which they are legally entitled.

5. Compliance with Sterility Requirements Is a Material Fact.

It cannot be responsibly questioned that liquid medications used in nebulizers must be sterile,¹⁴ and IACP acknowledges these drugs must be sterile.¹⁵ IACP nevertheless suggests that compounders need not inform physicians and patients that their products fail to meet FDA sterility requirements because FDA had suggested in 2000 rulemaking that certain compounded drugs that in compliance with FDCA § 503A would not have to meet the agency's sterility regulation if they met USP sterility standards.¹⁶

It is important to note several points at the outset. First, FDA suggested in the 2000 rulemaking that the only compounded drugs that were to be exempted from the regulation were those that complied with all of the requirements of section 503A.¹⁷ FDCA § 503A is no longer in effect.¹⁸ Moreover, the requirements of section 503A were similar to the criteria found in FDA's current Compliance Policy Guide and few, if any, of the compounded inhalation drugs currently on the market would satisfy the FDAMA standards.¹⁹ Second, the USP requirements to which FDA referred in the 2000 rulemaking were significantly more stringent than the current requirements to which

¹³ See, e.g., Cal. Health & Safety Code § 110290; Ky. Revised Stat. § 217.015(48); Nev. Rev. Stat. § 585.170.

¹⁴ See, e.g., CDC Guidelines for Preventing Health-Care-Associated Pneumonia 2003, IA, 40-42, 58, 60-62 (attached as Exhibit B).

¹⁵ IACP Comments at 7.

¹⁶ *Id.*

¹⁷ 65 Fed. Reg. 34,082, 34,083 (2000).

¹⁸ Section 503A was struck down by the Supreme Court in *Thompson v. Western States Medical Center*, *supra*.

¹⁹ Section 503A exempted compounded drugs from certain provisions of the FDCA based on various criteria, including the following:

- Dispensing based on an unsolicited prescription for a drug that is medically necessary [§ 503A(a)]
- Limitations on compounding prior to receipt of prescription [§ 503A(a)(2)(A)]
- Standards for active ingredients [§ 503A(b)(1)(A)]
- Standards for inactive ingredients [§ 503A(b)(1)(B)]
- Restrictions regarding products removed from the market based on safety or efficacy [§ 503A(b)(1)(C)]
- Restrictions on compounding copies of commercially available drugs [§ 503A(b)(1)(D), (b)(2)]
- Restrictions related to drugs that are demonstrably difficult to compound [§ 503A(b)(3)(A)]
- Limitations on interstate sales [§ 503A(b)(3)(B)]
- A ban on advertising and promotion [§ 503A(c)]

IACP refers in its comments. FDA had proposed promulgating a regulation under section 503A that would have required compounders adhere to the sterile compounding standards set forth in Chapter 1206 of the USP.²⁰ The USP has subsequently developed standards for compounding sterile formulations in Chapter 797 that are far less demanding than those of Chapter 1206.²¹

More fundamentally, while compliance with even the watered-down standards in USP Chapter 797 would be a step in the right direction for compounders (few if any compounded drugs comply with USP sterility requirements and compounded drugs do not appear to be labeled as being sterile), this would not relieve compounders from their responsibility to address sterility as a material fact. Even if a compounder were to bring its operation and formulations into compliance with USP sterility standards, it would be important for a prescriber to know that the compounder's products fail to comply with the higher GMP standards set by FDA for drug manufacturers.²²

Moreover, if, as IACP suggests, prescribers should assess compounded drugs based on compliance with the USP sterility standards rather than FDA standards for manufacturers, then IACP should be taking steps to ensure that compounders at least provide prescribers with the facts that IACP acknowledges are material. IACP's position that compounders should meet USP sterility standards thus requires, at a minimum, that compounders disclose whether their products comply with the USP standards.

The facts are (1) although IACP states in its comments that compounders should meet USP sterility requirements, IACP does not require its members to state in labeling and advertisements whether their products meet such requirements and (2) compounders currently fail to disclose such information. The agency may reasonably surmise that compounders generally fail to meet even the minimal USP requirements.

²⁰ FDA, Concept Paper: Drug Products that Present Demonstrable Difficulties for Compounding because of Reasons of Safety or Effectiveness (2000).

²¹ David W. Newton, Ph.D., and Lawrence A. Trissel, R.Ph., FASHP A Primer on USP Chapter , <797> "Pharmaceutical Compounding – Sterile Preparations," and USP Process for Drug and Practice Standards, 8 *IJPC* 251 (July/August 2004) (attached as Exhibit C). Dr. Newton is chairman of the 2000-2005 Sterile Compounding Committee of the Council of Experts of the USP and Mr. Trissel is a member of the committee. The authors provide a table (Table 1) that summarizes the differences between the new standards in Chapter 797 and the previous standards in Chapter 1205 and note that "the more rigorous standards in Chapter <1206> would be more difficult to satisfy." *Id.*

²² See, e.g., Lawrence A. Trissel, R.Ph., FASHP; The New National Standard for Sterile Preparation, 39 *Hospital Pharmacy* 900 (2004) (attached as Exhibit D) ("We are nowhere near talking about GMP in USP <797>, which would clearly be lower on the scale than GMP. . . . we certainly did not want to apply GMP to compounding personnel."). Mr. Trissel notes that FDA had proposed stricter standards for USP Chapter 797: "FDA proposed that if you made even one [drug product], you had to do sterility and pyrogen testing. But, of course, that consumed the vial, which was ridiculous." *Id.* at 904.

6. Compounding Based on Medical Necessity Does Not Negate the Need for Material Facts in Labeling and Advertisements.

IACP lists several examples of what it describes as medically necessary compounding.²³ Although several of the specific examples are questionable in the view of medical experts, the CHASM Petition does not take a position against medically necessary compounding. The petitioners rather point out that prescribers cannot reasonably determine medical necessity if they are denied truthful and accurate information on the formulations that are promoted by compounders. The prescriber cannot determine that the substitution of a compounded drug for an approved drug is medically necessary unless the prescriber understands the risks posed by compounded drugs, the lack of substantiation of safety and efficacy, and the absence of FDA's strict regulatory controls.

7. IACP's Actions and Policies Do Not Negate the Need for Material Facts in Labeling and Advertisements.

IACP describes actions it has taken in support of standards for quality for compounded drugs.²⁴ IACP does not speak for all compounding operations and cannot control the behavior of its members. Moreover, even if IACP controlled the world of compounding, its actions could not negate the two fundamental facts that underlie the CHASM Petition: Compounded drugs are different from approved drugs and prescribers need, and under the FDCA are entitled to, truthful information about those differences in labeling and advertising.

8. The Safety Record of Compounded Inhalation Drugs Is Not Known.

IACP asserts, without any evidence whatsoever, that compounded respiratory medications have an excellent safety record.²⁵ Neither IACP, FDA, nor any other entity can support such an assertion. The risks posed by compounded drugs are well documented and there are no data-collection mechanisms for compounded drugs that can provide the basis for concluding that compounded drugs have an excellent safety record. Unlike FDA-approved drugs, compounded drugs are not subjected to clinical studies, or even to preclinical studies, that might reveal risks to patients. Moreover, while FDA requires that pharmaceutical companies report adverse events, neither FDA nor the states have required compounders to report adverse events. The adverse event profiles of compounded respiratory drugs are thus unknown. The risks, however, are not unknown. They are real, they are documented in the CHASM Petition, and prescribers need to be aware of them.

²³ IACP Comments at 10.

²⁴ *Id.* at 11-12.

²⁵ *Id.* at 12.

9. **Compounded Drugs Are Subject to the New Drug Provisions of the FDCA.**

IACP argues that material facts related to the absence of substantiation for compounded drugs are “entirely inappropriate because compounded drugs are not subject to the FDC Act’s new drug requirements.”²⁶ FDA has determined that the new drug provisions of the FDCA apply to compounded drugs, and its position has been upheld in court.²⁷

10. **Consumers Desire and Are Capable of Handling Truthful Information about Compounded Drugs.**

IACP suggests that patients should not be exposed to material facts regarding compounded drugs because the information will be detrimental to “the patient’s health and well being.”²⁸ IACP claims that patients must be protected from a “nocebo” effect that may result from truthful information about compounded drugs.²⁹

In fact, pharmacists, prescribers, FDA, Congress, and patients generally agree that patients can handle, and are entitled to, the unvarnished truth about their medications. Pharmacists generally believe that patients should be provided with important risk information on their medications³⁰ and generally provide such information to their patients.³¹ Physicians generally agree that patients should be informed of the risks posed by suggested treatments as well as alternative therapies, and state legislatures have imposed such requirements as a matter of law.³² FDA has proposed a draft guidance that would have pharmacists provide patients with detailed information regarding warnings and precautions provided to physicians in the package insert, as well as adverse events associated with their medications.³³ Congress required in section 201(n) of the FDCA that patients as well as physicians be provided with *all* material facts in labeling and advertisements, and clearly does not believe that patients should be shielded from risk

²⁶ IACP Comments at 12.

²⁷ See *United States v. Sene X Eleemosynary Corp., Inc.*, 479 F. Supp. 970 (S.D. Fla. 1979).

²⁸ IACP Comments at 13.

²⁹ *Id.*

³⁰ See Comments submitted by APhA re Docket No. 2005D-0169 (dated July 25, 2005) (attached as Exhibit E); ASHP Guidelines on the Provision of Medication Information by Pharmacists (1996) (attached as Exhibit F).

³¹ Evaluation of Written Prescription Information Provided I Community Pharmacies, 2001, Final Report of the U.S. Department of Health and Human Services and the Food and Drug Administration, 9 (Dec. 21, 2001).

³² See, e.g., AMA Code of Ethics § E-8.08 (attached as Exhibit G); AMA Legal Position on Informed Consent (attached as Exhibit H). It is important to note that the CHASM Petitioners include the American Academy of Allergy Asthma & Immunology and the American College of Allergy, Asthma & Immunology.

³³ Draft Guidance on Useful Written Consumer Medication Information (CMI), 7-9 (2005).

information about their medications. In fact, Congress adopted FDA goals of ensuring that patients receive risk information on the medications dispensed by pharmacists and has required that the Department of Health and Human Services assess the adequacy of patient information provided by pharmacists.³⁴ The importance that patients attach to this type of information is amply demonstrated by the many patient groups who joined in submitting the CHASM Petition, as well as by recent comments submitted to the CHASM Petition docket by the National Women's Health Network.³⁵

CONCLUSION

For all of the foregoing reasons, FDA should (1) grant the CHASM Petition in its entirety and (2) grant the requested relief not only with regard to aqueous-based formulations but with regard to all liquid formulations for inhalation that have to be sterile.

Respectfully submitted,



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³⁴ Public Law 104-180 (1996).

³⁵ No. 2005P-0116:C5.