September 16, 2005

BY FACSIMILE AND ELECTRONIC SUBMISSION
Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, Maryland 20852

RE: Docket No. 2005P-0116—Comments in support of broader agency response to CHASM Citizens' Petition re Labeling and Advertisements for Compounded, Aqueous-Based Drugs for Inhalation

Dear Sir or Madam:

On March 24, 2005, the Consumer Health Alliance for Safe Medications (CHASM) filed the above referenced citizens' petition asking the FDA to clarify and enforce regulations that provide basic consumer and prescriber protections when compounded aqueous-based drugs for inhalation are marketed, mixed and dispensed to patients.

The agency should grant the relief requested in petition. Rather than limit the relief to aqueous-based drugs for inhalation, however, the agency should broaden the relief to include all medications for human use formulated through "compounding" as this term is used in Section 503A of the Food, Drug, and Cosmetic Act. This is especially important for difficult to compound medications including injectable and other dosage forms that must be sterile.

Background

As a result of the Supreme Court ruling in Western States[3], compounding pharmacies now broadly advertise the availability of specific compounded products, solicit prescriptions for unapproved drugs, make unsubstantiated statements regarding their benefits, and fail to provide balanced information on potential risks. The pervasive advertising of compounded drugs over the Internet has further transformed the traditional practice of compounding (a historical professional pharmacy service) into a marketing-driven industry where prescribers no longer sit in the driver's seat.

Historically, pharmacy compounding was driven by medical necessity. Where no FDA-approved medication existed to treat a patient's condition, doctors exercised their prescriptive authority, writing prescriptions that included specific ingredients and quantities to be formulated into a final drug product by qualified pharmacists. Medical students are educated in the practice of compounding; lectures distinguish compounded medications from generic and branded drugs and students are instructed how to write prescriptions for compounded medications[4]. Contemporary compounding branched out of this traditional practice and has grown to such proportions that multiple businesses now exist in support of a supplier-driven, unapproved drug manufacturing industry operating under the "cloak" of traditional compounding. Today, chemical suppliers that lack

prescriptive authority write formulas which are not tested for safety and efficacy and often protected as "trade secret"[5]; these formulas are sold in a franchise-like manner with training and tools to expand individual pharmacies' markets for unapproved products.

Appropriate pharmacy compounding is required for a small fraction of total prescriptions and can be distinguished from inappropriate compounding through careful and deliberate consideration of medical necessity and risk-benefit criteria. This requires both prescribers and patients know that a medication is or will be compounded and that it differs from an FDA-approved product; compounded drugs are not labeled for safe use, they are not proven safe and effective and they are not manufactured in accordance with federal Good Manufacturing Practices (GMPs). This basic information is critical to initiate thoughtful consideration of potential treatment options.

FDA should consider:

I. Physicians require basic information.

Physicians require information regarding the regulatory status and potential hazards of compounded medications to effectively treat patients, to protect them from unnecessary health risks and to fulfill their role as learned intermediaries.

In a 2004 survey conducted by Galderma, eighty-five percent of 165 dermatologists surveyed wrongly assumed that all prescription drugs are FDA-approved. Eighty-five percent also stated that doctors should be able to determine if FDA has approved a drug product and seventy-five percent stated it would be helpful for this information to be disclosed in labeling[6].

The International Association of Compounding Pharmacists (IACP) has noted the need for physicians to have sufficient information to ensure pharmacy compounding quality and compliance and to refer patients to qualified pharmacists[7]. In a letter to the editor appearing in the Journal of the Academy of Child and Adolescent Psychiatry, former IACP Executive Director Shelly Capps notes:

> …it is the clinician's responsibility to ensure that he or she refers patients to pharmacists who practice within the parameters of the law. In addition, before referring patients to a compounding pharmacist, the clinician should meet the pharmacist in his or her compounding laboratory, tour the facility, and ask questions about procedures and how quality is ensured. The clinician should specifically ask the pharmacist whether he or she is knowledgeable about the law and how compliance is ensured[7].

Without the basic facts that an advertised drug is not FDA-approved and will be compounded, physicians are not alerted to fulfill their responsibility to assess the safety of a marketed drug and/or solicited prescription and the conditions under which it will be compounded. *In the past, doctors explicitly dictated the practice of compounding*. Now,

they may not even recognize the regulatory status of medications proposed for or dispensed to their patients[6,8,9].

II. Consumers require basic information.

Consumers require information regarding the regulatory status and potential hazards of using compounded prescription medications in order to make informed decisions regarding their health and safety. Patients must weigh critical information regarding the risks and benefits of using unapproved drugs in order to select what therapies they may be willing to try (given the circumstances of their condition) and to evaluate, compare and select a supplier for their medication.

In a recent, national survey conducted by MenopauseRx.com, eighty-six percent of women were unaware that pharmacy compounded hormone therapies are not FDA-approved; seventy-five percent of those women stated that FDA-approval was very important when considering hormone therapy treatment options[10].

Individual pharmacies highlight the need for consumers to distinguish compounding pharmacies based on safety and quality measures; this requires patients have the essential information called for in the CHASM petition. O'Brien pharmacy's website notes:

> From natural hormones to sterile injectables, O'Brien Pharmacy has garnered a reputation as one of the nation's top compounding pharmacies. In fact, with our commitment to quality and excellence in compounding, O'Brien Pharmacy has few peers[11].

O'Brien states further:

> Because state and federal compounding regulations are largely inexact and undefined, a compounded medication will have significant variation from one pharmacy to the next. Factors like education, equipment, experience, formula, techniques and sourcing of ingredients determine the ultimate safety and effectiveness of the medication. Unbelievably, most pharmacies that compound do not even use pharmacists to make your medication—they rely on technicians. And pharmacy schools do not prepare the pharmacist for the level of difficulty and complexity in compounding that we encounter everyday[11].

In the absence of information provided to both the physician and the patient that a proposed or prescribed medication is not FDA-approved and will be compounded, patients will be denied critical information necessary to first determine if they are willing to use an unapproved product and, if so, what pharmacy they should select to have the product compounded.

III. Sentinel events associated with compounded medications heighten the need for prescribers and patients to be fully informed.

Recent sentinel events involving recalls, alleged fraud, deaths and disease outbreaks associated with compounded medications heighten the need for prescribers and patients to be provided with the material facts called for the CHASM petition.

2002: The Centers for Disease Control (CDC) reported 5 cases of infection including one death from fungal meningitis associated with methylprednisolone acetate injections compounded at an independent pharmacy in Spartanburg, SC[8]. FDA alerted consumers and health professionals after the pharmacy refused to voluntarily recall other injectable medications compounded by the pharmacy that were distributed to physicians, hospitals, clinics and consumers in Connecticut, Illinois, Indiana, Kentucky, Louisiana, Massachusetts, Mississippi, New Hampshire, North Carolina, South Carolina and Virginia[12]. *In connection with the outbreak investigation, physicians and health systems were warned that compounded injectable drug products may be getting into distribution chains without their direct knowledge*[8].

2004: 22-year old college student Shiri Berg died after applying a pharmacy-compounded topical anesthetic gel prior to a laser hair removal procedure; other deaths and adverse events associated with similar creams were uncovered after Berg's case was extensively covered in the press[13,14]. Studying the Berg case, emeritus professor and expert in pharmaceutics John Perrin noted: "The physical pharmacy of the compounders' formulation is excellent; however**,** its conception is poor in that the drugs' biopharmaceutical properties and their clinical implications have been ignored". Perrin further notes that this case is "a classic example of why clinical trials are necessary…"[15].

2005: CDC reported 11 cases of *Serratia marcescens* bacteremia occurring in patients who received compounded magnesium sulfate solutions manufactured by a "hybrid" pharmacy that was operating in compliance with *United States Pharmacopoeia* Chapter 797[16]. The bacteremia outbreaks occurred in California and New Jersey and included patients undergoing cardiac surgery[20].

2005: A pharmacy in Richfield, Minnesota, initiated "a nationwide recall of Trypan Blue 0.06% Ophthalmic Solution because it may be contaminated with *Pseudomonas aeruginosa,* a bacteria that, if applied to the eyes, might lead to serious injury, including possible blindness"[18]. Two cases of loss of vision have been reported by the CDC, medication has tested positive for the bacteria and an investigation by the FDA is ongoing[18].

2005: In a scheme to defraud Medicaid, two individuals were arrested and sued for making a "rudimentary homemade mixture of chemicals" found in FDA-approved medications and using their pharmacy to sell counterfeit drugs to patients with serious medical conditions including cystic fibrosis[19]. On chemical analysis, FDA found one of the chemicals used in compounding was contaminated with bacteria and did not conform with standards that apply to starting materials used in FDA-approved products[19].

2005: The CDC reported an outbreak of *Pseudomonas fluorescens* blood stream infections occurring in four states throughout the country[20]. In Missouri, 9 cases were diagnosed (8 of which were cancer patients)[20]. In Michigan, a single patient with an indwelling catheter was diagnosed after a surgical procedure[20]. In New York, 12 cases were diagnosed in children with central venous catheters, and in Texas, 14 cases were diagnosed in hospital patients diagnosed with serious conditions including pneumonia, colon cancer and sepsis[20]. CDC determined that all cases of *P. fluorescens* infections were administered heparin/saline flush solution devices compounded by IV Flush[20]. CDC noted that sterility testing of finished products, mandated for FDA-approved products, was reportedly not performed in this case and concluded "Companies that manufacture products intended for injection should follow FDA regulations for ensuring the sterility of these products"[20].

IV. Compounding medications introduces additional risks and uncertainties to medications that may be unknown to prescribers, patients and pharmacists.

The FDA is aware of over 200 adverse events involving over 70 compounded medications including deaths and cases of serious injury due to contamination and toxicity[21]. Because compounded drugs have not met federal surveillance requirements, these reported cases are believed to greatly underestimate true adverse event rates. Potential risks are significant and may include:

- Use of unproven formulas
- Use of suspect chemicals lacking pedigrees
- Lack of assurance of potency
- Potential super-potency
- Lack of assurance of purity
- Lack of assurance of sterility
- Lack of assurance of stability
- Use of flawed delivery systems

Conclusion

The potential hazards associated with compounded medications compared to regulated products in unquestionable. This is a critical concern for medications that are difficult to compound in pharmacy settings, including medications made from non-sterile starting materials that must be administered in a final dosage form guaranteed to be sterile. Sterility failure is one of the most serious and also one of the most frequently reported problems with compounded drugs. The provision of material facts called for in the CHASM petition will alert prescribers and health systems that compounded products marketed to their medical facilities, clinics and hospitals are not FDA-approved and may pose unacceptable health risks, including the fact that they are not manufactured in accordance with federal Good Manufacturing Practices and *do not meet FDA sterility requirements.*

Patients and prescribers have a right to know the hazards posed by *all* compounded drugs in order to make an informed decision about risks, benefits and medical necessity. This determination requires accurate and complete information, as called for in the CHASM petition, for *all* compounded drugs. In the present environment, patients and prescribers sit in as surrogates for the FDA for the purposes of making safety and efficacy determinations about the use of unapproved, pharmacy compounded drugs—at the very least, they need to know they have been called to the table.

Respectfully,

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Notes:

1. CHASM Citizen Petition.

2. FDC Act § 503A, 21 U.S.C.

3. Thompson v. Western States Med. Ctr., 535 U.S. 357 (2002).

4. Popovich NG. Principles of Prescription Writing. University of Illinois College of Medicine 2005 [online]. Accessed 9-14-05 from <www.uic.edu/classes/pcol/pcol425/restricted/Popovich/rxwrting2005.pdf>.

5. Alesiani R. HP Operations update, Compounding. ExcelleRx Highlights Hospice Pharmacia Newsletter [online]; accessed 9-9-05 from <www.hospicepharmacia.com/images/pdfs/Novnewsletter.pdf>.

6. Inside Washington Publishers, FDA Week. Galderma: Unapproved drug makers must tell doctors drug's status; January 1, 2005.

7. Capps S. Letter to the Editor. J Acad Child Adolesc Psychiatry 2001; 40: 261.

8. The Centers for Disease Control. Exophiala infection from contaminated injectable steroids prepared by a compounding pharmacy—United States, July-November 2002. MMWR 2002; 51(49); 1109-1112.

9. Bouts BA. The misuse of compounding by pharmacists, QuackWatch 2002 [online]. Accessed 9-14-05 from <http://www.quackwatch.org/01QuackeryRelatedTopics/compounding.html>.

10. Business Wire, Inc., Women confused about new trends in hormone therapy treatments; National survey finds menopausal women unaware of potential risks with customized formulations, treatments; April 12, 2005.

11. O'Brien Pharmacy>Rx Compounding [online]; accessed 9/9/05 from <http://www.obrienrx.com/o_brien_pharm/rx/index.html>.

12. Nationwide alert on injectable drugs prepared by urgent care pharmacy. FDA Talk Paper, November 15, 2002 [online]; accessed 9-14-05 from <http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01171.html>.

13. Shimron Y. and Easterbrook M. Berg's case like one in Arizona; Deaths follow use of numbing cream. News Observer February 5, 2005 [online]; accessed 9-14-05 from <http://newsobserver.com/news/story/2091591p-8470349c.html>.

14. Norris M. Death of North Carolina woman raises questions about safety of laser hair removal. All Things Considered National Public Radio; February 18, 2005.

15. Perrin J. Hazard of compounded anesthetic gel. AJHP 2005; 62:1445-1446.11.

16. Thomson CA. Compounded I.V. solution linked to sepsis cases. 21 March 2005 American Society of Health-System Pharmacists, Bethesda MD [online]; accessed 9-9-05 from <http://www.ashp.org/news/ShowArticle.cfm?id=10275>.

17. The Centers for Disease Control. Serratia marcescens blood stream infections associated with contaminated magnesium sulfate solutions—March 2005 CDC Health Advisory[online]; accessed 9-14-05 from <http://www.state.sd.us/doh/Alerts/Alerts/CDC/224.htm>.

18. Custom Rx Compounding Pharmacy Press Release: Custom-Rx Compounding Pharmacy Issues Nationwide Recall of Trypan Blue 0.06% Ophthalmic Solution; August 26, 2005 U.S. Food and Drug Administration Firm Press Release [online]; accessed 9-9-05 from <http://www.fda.gov/oc/po/firmrecalls/customrx08_05.html>.

19. HT Media Ltd., US Fed News. Two arrested for counterfeiting medications, defrauding Medicaid. April 9, 2005.

20. The Centers for Disease Control. Pseudomonas bloodstream infections associated with a heparin/saline flush—Missouri, New York, Texas, and Michigan, 2004-2005. MMWR 2005; 54(11): 269-272.

21. Heinrich J. Prescription Drugs: State and Federal Oversight of Drug Compounding by Pharmacies. GAO Testimony before the Senate Health, Education, Labor and Pensions Committee October 23, 2003.