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VIA Hand Delivery

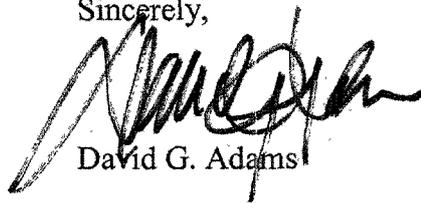
Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, MD 20852

Re: Submission of Citizen Petition on behalf of Members of CHASM

Dear Sir or Madam:

Please accept the attached citizen petition (in four copies) submitted on behalf of members of the Consumer Health Alliance for Safe Medication pursuant to 21 C.F.R. § 10.35.

Sincerely,



David G. Adams

March 24, 2005

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

Re: Citizen Petition re Labeling and Advertisements for Compounded,
Aqueous-Based Drugs for Inhalation

Dear Sir or Madam:

This petition is submitted pursuant to 21 C.F.R. § 10.35 by the following member participants of the Consumer Health Alliance for Safe Medication (the CHASM petitioners):

American Academy of Allergy Asthma & Immunology (AAAAI)

American Association for Respiratory Care (AARC)

American College of Allergy, Asthma & Immunology (ACAAI)

American Latex Allergy Association (A.L.E.R.T., Inc.) (ALAA)

American Partnership For Eosinophilic Disorders (APFED)

Association of Asthma Educators (AAE)

Asthma & Allergy Network Mothers of Asthmatics (AANMA)

Asthma and Allergy Foundation of America (AAFA)

COPD-Alert

A. ACTION REQUESTED

The CHASM petitioners request the Commissioner of Food and Drugs to take the following actions with regard to aqueous-based drugs for inhalation that have been compounded¹ by pharmacy operations:

¹ As used in this petition, the term "compounded" refers to the preparation of an unapproved drug and is not intended to refer to the preparation of an approved drug for administration in accordance with approved labeling.

1. Confirm that all pharmacy or other business entities involved in dispensing such drugs to patients or in promoting such drugs to patients or to health care professionals are required under the Food, Drug, and Cosmetic Act (FDCA) to include material facts in all labeling and advertisements provided to patients and to health care professionals, including the following:
 - The product is not approved by FDA
 - The product is/was compounded [or prepared] in a pharmacy
 - The product does not comply with FDA standards for sterility
 - The product has not been demonstrated safe or effective
2. Take appropriate steps to inform the public of this confirmation of the statutory requirement in order to ensure that pharmacy operations dispensing such products are aware of their obligations and patients and health care professionals are aware of their rights to have the aforementioned material facts disclosed in labeling and advertisements. FDA should specifically advise patients who receive this information to consult with their prescribing health care professional with regard to any concerns they may have over taking such products.
3. Promulgate a regulation to provide specific wording and specifications for prominent display of the aforementioned material facts in labeling and advertisements for health care professionals and patients.
4. In the case of compounding establishments that operate outside of the traditional practice of pharmacy, continue to enforce general requirements of the FDCA as set forth in FDA's compliance policy guide (CPG) on pharmacy compounding.² Where FDA takes or has taken an enforcement action (such as the issuance of a warning letter) based on the statutory requirements and considerations set forth in this CPG, the agency should consider also whether the establishment has failed to provide the material facts set forth above in labeling and in advertisements.
 - Where the establishment has failed to provide the aforementioned material facts in labeling or advertisements to health care professionals, FDA should require the establishment to notify each health care professional who submitted a prescription for a compounded inhalation drug during the previous twelve months that information was not provided.
 - Where the establishment has failed to provide the aforementioned material facts in labeling or advertisements to patients, FDA should require the establishment to notify each patient to whom an illegally manufactured inhalation drug was dispensed during the previous twelve months that the information was not provided .

² FDA, COMPLIANCE POLICY GUIDE FOR FDA STAFF AND INDUSTRY § 460.200 (2002).

B. STATEMENT OF GROUNDS

1. Background

The Supreme Court's Admonition on Labeling for Compounded Drugs

In *Thompson v. Western States Medical Center*, the Supreme Court struck down a provision of the FDCA that had imposed a ban on promotion of compounded drugs.³ The Court found the provision unconstitutional because it resulted in an unwarranted restriction on truthful and nonmisleading speech that might be beneficial.⁴ In so doing, the Court admonished the government to consider that the public could be protected from misleading promotion by requiring more information rather less information. The Court advised that the 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."⁵ This is the heart of the relief requested in this petition.

Aqueous-Based Drugs for Inhalation

This petition seeks relief limited to a unique class of medications -- aqueous-based drugs for inhalation. These medications are intended for patients whose compromised conditions require drugs that are sterile and that are carefully formulated to account for critical patient sensitivities. While there are numerous safe and effective inhalation drugs that have been approved by FDA, large-scale compounding operations are now dispensing substitute formulations containing the same active ingredients. Thousands of patients have been dispensed compounded formulations that have not been demonstrated safe, effective, and sterile.

Although compounding operations promote and dispense these formulations based on claims of special needs of individual patients, health care professionals are concerned over the safety and efficacy of these formulations and question whether the use of such unapproved formulations can be justified on medical grounds. In some instances, health care professionals and patients have been misled about the origin and quality of these compounded formulations. Thus health care professionals and patients need, desire, and are entitled to the basic information necessary to determine whether compounded inhalation drugs are safe and medically appropriate.

³ 535 U.S. 357 (2002) (striking former FDCA § 503A).

⁴ *Id.* at 374-77.

⁵ *Id.* at 376.

The CHASM Petitioners

The petitioners are members of the Consumer Health Alliance for Safe Medication a working group of patient and health care professional organizations⁶ dedicated to ensuring that patients with respiratory conditions have access to safe and effective medications and are protected from products that may pose unwarranted risks. These respiratory conditions include asthma, emphysema, chronic bronchitis, cystic fibrosis, and pneumonia.

The American Academy of Allergy Asthma & Immunology (AAAAI) is the largest professional medical specialty organization in the United States, representing allergists, asthma specialists, clinical immunologists, allied health professionals, and others with a special interest in the research and treatment of allergic disease. Its mission is the advancement of the knowledge and practice of allergy, asthma and immunology for optimal patient care.

The American Association for Respiratory Care (AARC) is a 37,000 membership organization of respiratory therapists and others involved in pulmonary health. Respiratory therapists work in the hospital, the home setting, doctor's offices, and sleep clinics, with patients of all ages to diagnose, treat, and manage lung disease and illness.

The American College of Allergy, Asthma & Immunology (ACAAI) is a professional medical organization comprised of qualified allergists/immunologists and related healthcare professionals dedicated to the clinical practice of allergy, asthma and immunology through education and research to promote the highest quality patient care.

The American Latex Allergy Association (A.L.E.R.T., Inc.) (ALAA) is a lay organization affiliated with AAAAI and ACAAI that provides education and support to individuals with natural rubber latex allergy. ALAA supports the doctor/patient relationship in the treatment of individuals with latex allergy.

The American Partnership For Eosinophilic Disorders (APFED) is a patient-advocacy organization dedicated to families coping with eosinophilic gastrointestinal diseases, eosinophilic esophagitis, hypereosinophilic syndromes, and Churg-Strauss Syndrome. The organization's four point mission includes education, awareness, support and research in both the lay and professional communities.

The Association of Asthma Educators (AAE) is the premier interdisciplinary professional organization praising the competency of individuals who educate patients and families affected by asthma.

⁶ CHASM was organized and is administered by AANMA as a special project to develop strategies and build coalitions for unified action by organizations representing patients and health care professionals. The CHASM petitioners gratefully acknowledge the expert support provided by Sarah Sellers, Pharm.D., Executive Director of the Center for Pharmaceutical Safety.

Asthma & Allergy Network Mothers of Asthmatics (AANMA) is a national membership organization dedicated to eliminating suffering and death due to asthma, allergies, and related conditions through education, advocacy, community outreach, and research.

The Asthma and Allergy Foundation of America (AAFA) is dedicated to improving the quality of life for people with asthma and allergic diseases through education, advocacy and research.

COPD-Alert is a nationwide, online, support and advocacy group for COPD patients, caregivers, and medical professionals.

Knowledge and Information for Health Care Providers and their Patients

One of the primary goals of CHASM is promoting knowledge and information for the professionals who provide health care to patients with respiratory disease. The members of CHASM are particularly concerned that health care professionals who prescribe inhalation drugs have an armamentarium of FDA-approved safe and effective medications that are supported by full disclosure labeling, as provided in the FDA-approved package insert. CHASM seeks to ensure that these health care providers are always fully informed of the source, identity, and important characteristics of the medications presented to them for prescribing to patients.

An equally important goal of CHASM is to help ensure that patients and their families are able to understand the nature of their prescribed medications and the risks and benefits of such medications relative to other available therapies. This is vital to the ability of patients and their families to have an informed dialog with their health care providers and to protect themselves from potentially unsafe or ineffective formulations that might be substituted for approved medications without their knowledge.

2. Patients Are Being Exposed to Illegally Manufactured Inhalation Drugs on a Massive Scale.

Compounded inhalation drugs are being substituted for approved inhalation drugs on an extraordinary scale. This is part of a general trend known as “substitution compounding,” which involves compounding and promoting drugs to replace commercial products.⁷ In the case of inhalation drugs, federal policies related to reimbursement under Medicare have enabled durable medical equipment suppliers to secure reimbursement for compounded inhalation drugs based on levels of reimbursement established for approved medications with the same active ingredient(s). This policy has provided a considerable inducement to replace approved medications with compounded medications with the same active ingredient(s), which can be prepared by pharmacists at a far lower cost than the acquisition cost of the approved medications.

⁷ Philip E. Johnson, M.S., R.Ph., *Legal and Practice Concerns with Extemporaneously Compounded Medications*, 5 J. OF PHARM. CARE IN PAIN SYMPTOM CONTROL 47, 48 (1997).

As FDA has noted in recent warning letters, some compounding sources for inhalation drugs have essentially become drug manufacturers that operate outside the strict requirements of the FDCA.

In a December 9, 2004, warning letter to Lincare, Inc., and Reliant Pharmacy Services (Lincare), the agency determined that the compounding operation for inhalation drugs “produces *enormous amounts* of what are essentially copies of commercially available drugs,” and “goes well beyond the scope of traditional pharmacy compounding and instead more closely resembles a drug manufacturing operation.”⁸ More significantly, the agency noted that Lincare had “no documentation that physicians were told of and/or approved the use of [Lincare’s] compounded products in lieu of the commercially available, FDA-approved products.”⁹

In a December 20, 2004, warning letter to Respi Care Group of Puerto Rico (Respi Care), the agency found that the “*production volume is [not] consistent with that of a pharmacy* that is engaged in the traditional practice of extemporaneous pharmacy compounding” and that “most of the drugs . . . produced in these volumes are essentially copies of commercially available, FDA-approved drugs.”¹⁰ Again the agency found that the company “fail[ed] to document a patient-specific need for the compounded solution.”¹¹ The agency also noted extensive violations of standards for good manufacturing practice related to controls to prevent contamination of the inhalation drugs.¹² Although the company had indicated to FDA a commitment to comply with USP standards for prevention of contamination, the agency pointed out that FDA regulations require all aqueous-based solutions for oral inhalation to be manufactured to be sterile.¹³

FDA has found it necessary to issue numerous letters to compounding pharmacies over the years, including a 2002 warning letter to Med-Mart Pulmonary Services (Med-Mart) in which the agency stated that it remained “seriously concerned . . . about the public health risks associated with the *large-scale production of massive quantities* of inhalation solutions without these products being required to meet all the laws and

⁸ Letter from H. Tyler Thornberg, Director, New Orleans District, FDA, to John P. Byrnes, President, Lincare (Dec. 9, 2004) available at http://www.fda.gov/foi/warning_letters/g5123d.htm (Lincare Warning Letter) (emphasis added).

⁹ *Id.*

¹⁰ Letter from Donald J. Voeller, District Director, FDA, to Severo Pina, Chief Executive Officer, Respi Care 2 (Dec. 20, 2004) available at http://www.fda.gov/foi/warning_letters/g5139d.htm (Respi Care Warning Letter) (emphasis added).

¹¹ *Id.*

¹² *Id.* at 3-9.

¹³ *Id.* at 4 (citing 21 C.F.R. 200.51).

regulations applicable to a drug manufacturer.”¹⁴ Of particular concern, Med-Mart had been required to conduct a class I recall of five lots of various albuterol solutions due to contamination with *Serratia liquefaciens*, and the agency found *Bacillus megaterium* in the first lot manufactured after the previously contaminated lots.¹⁵ The agency also documented extensive violations of good manufacturing practice related to, *inter alia*, controls for prevention of contamination.¹⁶

In a state enforcement action indicating the scale of the problem, the Missouri State Board of Pharmacy obtained an injunction against Med 4 Home Pharmacy, which was forced to recall two contaminated batches of compounded albuterol/ipratropium solution that involved contacting over 19,000 patients.¹⁷

3. These Compounded Formulations Pose Special Risks to Patients.

(a) Sterility

(i) *Aqueous-Based Drugs for Inhalation Must Be Sterile*

All of the inhalation drugs approved by FDA are formulated in aqueous-based liquids.¹⁸ Compounded inhalation drugs, such as those prepared by Lincare, Respi Care, and Med-Mart, are also formulated in aqueous-based liquids.

FDA has determined that all aqueous-based drugs for inhalation must be sterile and has imposed this requirement by regulation.¹⁹ In proposing the regulation in 1997, the agency described the risks posed by non-sterile products:

Contaminated inhalation solutions for nebulization are likely to cause lung infections because the drug product is introduced directly into the lungs in a manner which at least partially bypasses the patient's natural defense mechanisms. Many patients using inhalation solution products for nebulization have chronic obstructive airway disease or cystic fibrosis, or are immunocompromised. Microbial contamination of these products may result in serious health

¹⁴ Letter from Dennis Linsley, Director, San Francisco District, to Peter B. Kelly, President and Chief Executive Officer, Med-Mart, 1-2 (Sept. 30, 2002) *available at* http://www.fda.gov/foi/warning_letters/g3527d.pdf (Med-Mart Warning Letter) (emphasis added).

¹⁵ *Id.* at 2.

¹⁶ *Id.* at 3-5.

¹⁷ Press Release, Missouri State Board of Pharmacy, Missouri Board Takes Action Against Kansas City Company (Mar. 10, 2003) *available at* <http://pr.mo.gov/boards/pharmacy/press/2003-10-03.pdf> (Tab 1).

¹⁸ The aqueous-based drugs for inhalation approved by FDA are limited to the following active ingredients: albuterol sulfate, cromolyn sodium, levalbuterol hydrochloride, ipratropium bromide, albuterol/ipratropium, terbutaline sulfate, acetylcysteine, budesonide, metaproterenol sulfate, and, tobramycin sulfate.

¹⁹ 21 C.F.R. 200.51 (2004).

consequences due to opportunistic pathogens entering the lungs or to the possible inactivation of the drug product by these microorganisms.²⁰

In the preamble to the final regulation, the agency further explained that a sterility standard was necessary over and above the strict requirements of the agency's good manufacturing practice regulations:

A sterility requirement for all inhalation solutions for nebulization will provide the necessary assurance that these solutions will not be contaminated. The sterility requirement is necessary for several reasons.

First, there is a high risk of contamination of inhalation solutions. Microbial contaminants identified in two of the recalls were *Pseudomonas* species (spp.), which are ubiquitous and are commonly found in pharmaceutical water supplies and nonsterile manufacturing environments.

Second, most species of *Pseudomonas* associated with the contamination of inhalation solutions have the potential to be human pathogens. Of special concern is the fact that many of the patients using these products have compromised pulmonary defense mechanisms and are therefore at a particularly high risk of serious infection.

Third, adherence to current good manufacturing practice (CGMP) regulations without appropriate sterilization procedures does not provide an adequate level of assurance that inhalation solutions for nebulization will not be contaminated. Even if antimicrobial preservatives are used in a product, they may not be effective because many bacteria, including *Pseudomonas* spp., may develop resistance to these preservatives. The albuterol sulfate product recalled in January 1994, for example, contained benzalkonium chloride, an antimicrobial preservative, yet the preservative failed to prevent microbial contamination of the product. Resistance to preservatives is not species specific; strains of many species are resistant. Furthermore, use of a single preservative in the manufacture of a nonsterile inhalation solution for an extended period may actually select for preservative-resistant strains of *Pseudomonas* spp. or other bacteria. Also, the microbial limits test does not ensure against contamination. End-product microbial limits tests performed prior to distribution may not be capable of detecting sufficiently low levels of contamination; a product that initially passes the microbial limits test may support the growth of contaminating organisms, which could later grow to unacceptable levels.²¹

In this rulemaking, the agency made clear its expectation that compounding pharmacies would be subject to the sterility requirement under section 503(A) of the

²⁰ 62 Fed. Reg. 49,368, 49,369 (1997).

²¹ *Id.* The agency takes the sterility requirement for aqueous-based inhalation drugs quite seriously and has refused to allow an exception for a manufacturer that argued its patients had a special need for its nonsterile inhalation drug. Letter from Peter Cooney, FDA, to David Watton, Vice President, Pascal Co. Inc. (June 21, 2000) available at <http://www.fda.gov/foi/warning.htm> (Tab 2).

FDCA,²² which imposed such drug manufacturing requirements to pharmacies that compounded inordinate amounts of products that were essentially copies of commercially available drug products or promoted their compounded formulations to physicians.²³ In the case of compounding pharmacies that avoided this requirement because of their lesser scale of operation, the agency indicated that it would exercise its authority under section 503A to require adherence to USP requirements for compounding sterile preparations.²⁴ As discussed above, however, section 503A was subsequently struck by the Supreme Court in the *Western States* decision²⁵ and compounding pharmacies continue to expose patients to nonsterile inhalation drugs.

(ii) *Compounded Inhalation Formulations Do Not Meet FDA Standards for Sterility.*

While the scope of violations of good manufacturing practice described by FDA in the warning letters issued to Respi Care and Med-Mart were alarming, the failure of such operations to ensure sterility came as no surprise. FDA has noted in the past that “few pharmacies perform environmental sampling, end-product testing, and process validations, and often sterile products are prepared in uncontrolled environments,”²⁶ and has acknowledged that “[t]he risks of having a non-sterile product are greater when the manufacturing controls employed by manufacturers are not in place.”²⁷

Moreover, compounding pharmacists have themselves generally acknowledged that they cannot or will not meet FDA’s sterility requirement for their compounded medications. In fact, the International Academy of Compounding Pharmacists (IACP) has opposed less stringent sterility requirements proposed by the United States Pharmacopoeia (USP) and by individual states. The organization has opposed requirements related to validation of sterilization, aseptic processing, environmental quality controls, processing, and finished product release checks as being unnecessary, unrealistic, or incomprehensible.²⁸

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

²³ FDCA § 505A(b)(1)(D), (c).

²⁴ The agency proposed promulgating a regulation under FDCA § 503A that would have prohibited the compounding of sterile drugs under procedures other than those set forth in Chapter 1206 of the USP. FDA, CONCEPT PAPER: DRUG PRODUCTS THAT PRESENT DEMONSTRABLE DIFFICULTIES FOR COMPOUNDING BECAUSE OF REASONS OF SAFETY OR EFFECTIVENESS (2000) (FDA CONCEPT PAPER).

²⁵ See note 3, *supra*.

²⁶ FDA CONCEPT PAPER at 9.

²⁷ *Id.* at 5-6. The agency emphasized that “aqueous-based inhalation solutions, must be sterile (i.e., free from all living microorganisms)” and that “[s]terility is absolute and should never be considered in a relative manner - a product cannot be partially or almost sterile.” *Id.* at 4

²⁸ See Letter to Missouri State Board of Pharmacy from L.D. King, Executive Director, IACP (Jan. 31, 2003) (Tab 3); Letter to Revisions Committee from L.D. King, Executive Director, IACP (Dec. 2, 2002) (Tab 4); Letter to Arizona Board of Pharmacy from L.D. King, Executive Director, IACP (Nov. 26, 2002) (Tab 5); New Requirements for Sterile Compounding; Request for Comments (IACP 2002) (Sterility testing proposed by the USP “is currently not performed in pharmacy practice(Tab 6); INT’L ACAD. OF

(b) Manufacturing Practices Generally

(i) The Broader Problem

Compounding pharmacies acknowledge that they do not prepare their inhalation drugs in conformity with good manufacturing practice. This raises concerns going well beyond sterility. In the warning letter to Respi Care, the agency found that the inhalation drugs were being prepared “with virtually no regard to the current good manufacturing practice (cGMP) requirements of the Act and the cGMP regulations”²⁹ The violations included controls related to final product testing, reliability of drug components, stability testing, product identity, strength, quality, and purity, and batch production and recordkeeping.³⁰ The agency analyzed samples of the Respi Care inhalation drugs and found that products failed to contain the quantity of the drug substance claimed in the labeling.³¹ The warning letter to Med-Mart documented similar problems.³²

Good manufacturing practice concerns have also been documented by state enforcement personnel. Personnel from the Florida Department of Health testified before FDA that inhalation drugs were prepared by compounding pharmacies without lot numbers, expiration dates, identification of strength, and identification of quantity.³³ The state official noted shocking conditions for handling and storing ingredients and formulated products, including storage of bulk solutions in a common refrigerator with food items, storage of container/closure systems in a restroom, and storage of finished product in a restroom.³⁴

The risks posed by failure to adhere to good manufacturing standards are well documented. A 2002 FDA survey of compounded drugs found a 34% failure rate for drugs analyzed for potency and/or purity and further found that, with regard to the drugs failing potency, most contained less than 70% of their labeled content.³⁵ Approximately 1.4 million doses of pharmacy-compounded respiratory drug products distributed

COMPOUNDING PHARMS., DRAFT COMMENTS TO USP PROPOSED CHAPTER 797: PHARMACEUTICAL COMPOUNDING- STERILE PREPARATIONS (Jul. 23, 2002) (Tab 7) (final comments submitted to the USP by IACP are not publicly available).

²⁹ Respi Care Warning Letter at 2.

³⁰ *Id.* at 3-9.

³¹ *Id.* at 9.

³² Med-Mart Warning Letter at 2-3.

³³ Greg Jones, State of Florida Department of Health, Testimony before FDA Pharmacy Compounding Advisory Committee Meeting 33-35 (Jul. 14, 2000) (Jones Testimony) (Tab 8).

³⁴ *Id.*

³⁵ Subramaniam V, Sokol G, and Zenger V et al. Survey of drug products compounded by a group of community pharmacies: Findings from an Food and Drug Administration Study (Tab 9).

throughout the United States have been recalled for bacterial or fungal contamination.³⁶ Moreover, according to one study, pharmacy compounding errors have significantly more serious outcomes compared to other errors by pharmacists and warned that children are “particularly at risk because of the increased potential for error in the preparation and use of liquids.”³⁷ As discussed above, risks of pathologic contamination are particularly disturbing in the case of inhalation drugs for respiratory conditions.

(ii) Risks from Impurities

One of the key concerns in formulating inhalation drugs is the possibility that chemical impurities may be introduced through source materials. Patients who are prescribed inhalation drugs for a bronchial disease or condition are especially susceptible to such chemical impurities, which may cause heightened bronchial responsiveness and inflammation.³⁸ Moreover, these reactions may appear similar to the symptoms of their disease, leaving the patient and their health care professional unable to determine whether the patient’s reaction is caused by the product or the disease itself.

³⁶ See FDA Recall Notice No. D-207-2: Med-Mart Pulmonary Services (Mar. 27, 2002) available at <http://www.fda.gov/bbs/topics/enforce/2002/ENF00736.html>; Kris Hundley, *Lincare Pharmacy Runs Afoul of Missouri Regulators*, ST. PETERSBURG TIMES, Apr. 18, 2003, at 1E. (Tab 10).

³⁷ S.A. Seifert, *Pharmacy prescription errors reported to a regional poison control center*, 40 J. OF TOXICOLOGY 919, 922 (Tab 11).

³⁸ See Eugene Sullivan, Ph.D., FDA, Testimony before FDA Drug Safety and Risk Management Advisory Committee 20-21 (May 5, 2004) (“Chemical components in inhalation drug products may be associated with a variety of adverse effects, including irritant and immunologic effects, leading to acute bronchospasm and airway inflammation and hyperresponsiveness, other toxicologic injury, or even potentially carcinogenicity”) (Tab 12). See also the following abstracts: T. Kawajiri et al. *Pathology and mechanism of lung toxicity following inhalation of hair spray in rats*, 16 INHAL. TOXICOL. 147 (2004); Ronald D. Reynolds, MD & Richard M. Smith, MD, *Nebulized bacteriostatic saline as a cause of bronchitis*, 40 J. FAM. PRACT. 35 (1995); J. Pauluhn, *Comparative analysis of pulmonary irritation by measurements of Pehn and protein in bronchoalveolar lavage fluid in brown Norway rats and Wistar rats exposed to irritant aerosols*, 16 INHAL. TOXICOL. 159 (2004); Neil E. Alexis, PhD. et al., *Effect of inhaled endotoxin on airway and circulating inflammatory cell phagocytosis and CD11b expression in atopic asthma subjects*, 112 J. ALLERGY AND CLIN. IMMUNOL. 353 (2003); (Tab 13).

⁴³ See, e.g., THE LETCO COMPANIES, RESPIRATORY PHARMACY PRODUCTS (2004) available at www.letcoinc.com (last visited Feb. 11, 2004). (listing USP grade chemicals as well as non-USP chemicals) (Tab 14); REDBOOK DATABASE SERVICES, REDBOOK 243, 357, 400 (2004) (Tab 15).

Risks from impurities may arise where pharmacists use bulk chemicals from questionable sources or use non-pharmaceutical grade drug substances.⁴³ These concerns are heightened by findings that compounding pharmacies have become a primary route of entry for counterfeit bulk drugs.⁴⁴ Former Commerce Committee Chair Tom Bliley noted in a letter to FDA that counterfeit bulk drugs “pose a real or potential health hazard because their manufacturer is often unknown” and that the “impurity profile is [also] unknown, and the age, the storage, the manufacturing environment, or the synthesis of the product cannot be determined.”⁴⁵ This, according to the committee chair, created a situation where “no amount of finished product testing can build quality into the product.”⁴⁶

The potential exposure of patients to compounded drugs made from substandard bulk drug substances is documented in FDA’s own recall notices. Although surveillance is limited, large quantities of chemicals for use in compounding have been recalled because bulk drug packages contained the wrong chemical ingredient, and for potential contamination or failed purity tests.⁴⁷

Pharmacies cannot rely on certificates of analysis or on their own analyses to ensure the quality of their bulk drug supplies. Compounding pharmacists admit that they “are generally not equipped with the equipment or skill necessary to test bulk drugs for

⁴⁴ *Counterfeit Bulk Drugs: Hearing Before the Subcomm. on Oversight and Investigations of the House Comm. on Energy and Commerce*, 106th Cong. (Jun. 8, 2000) (prepared statement of The Honorable Fred Upton) (“Lured by high prices and potential profits in the U.S., counterfeit bulks can get into our prescription drugs in several ways: (1) as imported ingredients to U.S. manufacturers; (2) as imported ingredients to pharmaceutical compounders; and (3) as source ingredients for internet pharmacies marketing to the U.S. The counterfeiters use sophisticated methods such as preparing false labeling, containers, seals and certificates of analysis, or using a manufacturing process that differs from the filed manufacturing process.”) (Tab 16).

⁴⁵ Letter from The Honorable Tom Bliley, Chairman, The Committee on Energy and Commerce, United States House of Representatives, to Jane Henney, M.D., Commissioner, FDA (May 8, 2000).

⁴⁶ *Id.*

⁴⁷ *See, e.g.* the following FDA Recall Notices: Medisca Pharmaceutique (2003) *at* <http://www.fda.gov/bbs/topics/enforce/2003/ENF00792.html>; Meridian Pharmaceutical (2003) *at* <http://www.fda.gov/bbs/topics/enforce/2003/ENF00803.html>; Chem. Source (2003) *at* <http://www.fda.gov/bbs/topics/enforce/2003/ENF00803.html>; Medisca (2003) *at* <http://www.fda.gov/bbs/topics/enforce/2003/ENF00794.html>; Hawkins Chemical (2000-2001) *at* <http://www.fda.gov/bbs/topics/ENFORCE/2001/ENF00709.html>, <http://www.fda.gov/bbs/topics/enforce/2003/ENF00792.html> and <http://www.fda.gov/bbs/topics/ENFORCE/2001/ENF00706.html>; Spectrum Laboratory (2000) *at* <http://www.fda.gov/bbs/topics/ENFORCE/ENF00625.html>; Paddock Labs (2000) *at* <http://www.fda.gov/bbs/topics/ENFORCE/ENF00633.html>; Gallipot (1999) *at* <http://www.fda.gov/bbs/topics/ENFORCE/ENF00594.html>; Medisca (1999) *at* <http://www.fda.gov/bbs/topics/ENFORCE/ENF00584.html>; Paddock Labs (1998) *at* <http://www.fda.gov/bbs/topics/ENFORCE/ENF00521.html>; Eudaemonic Corporation (1996) *at* <http://www.fda.gov/bbs/topics/ENFORCE/ENF00447.html>; Paddock Labs (1995) *at* <http://www.fda.gov/bbs/topics/ENFORCE/ENF00386.html>; Professional Compounding Centers of America (1992) *at* <http://www.fda.gov/bbs/topics/ENFORCE/ENF00166.html>; Professional Compounding Centers of America (1992) *at* <http://www.fda.gov/bbs/topics/ENFORCE/ENF00166.html>.

identity, potency, or sterility,” and take the position that “the cost of this testing would be prohibitive.”⁴⁸ One expert has described the problem in the following terms:

Reliance on USP specifications and Certificates of Analysis as quality indicators for bulk APIs used in compounding may be insufficient. USP specifications are normally confirmed through extensive testing by the pharmaceutical industry prior to drug manufacturing; neither pharmaceutical repackagers nor pharmacies have the equipment, resources or capacity to accomplish such analysis prior to compounding. Certificates of Analysis vary substantially in content and lack standard requirements. And, in the absence of pedigree requirements for bulks used in compounding, the ability to trace ingredients back to original manufacturers becomes difficult. In addition, bulk substances and diluents not specifically manufactured for use in sterile dosage forms may contain unacceptable levels of contaminants including bacteria, mold, endotoxin, and/or solvents that represent significant concerns for drugs intended to be sterile⁴⁹

(iii) Risks from Packaging

Other aspects of good manufacturing practice, such as selection of packaging materials, may also be an issue. Compounded respiratory solutions are typically packaged in low density polyethylene plastic vials with paper labeling that is glued onto the container. This is not the case for sterile inhalation drugs products manufactured by pharmaceutical companies because, as FDA has stated in a 2002 Draft Guidance, paper labels applied directly to the primary container of the medication contain components with significant potential to leach and enter the drug product.⁵⁰ Compounded inhalation drugs generally fail to adhere to the standards of the Draft Guidance in numerous respects, posing risks from chemical contaminants that may raise significant health concerns for patients with airway hyper-responsiveness and an underlying propensity for allergic responses.⁵¹ Moreover, as noted above, these reactions may appear similar to the symptoms of their disease, leaving the patient and their health care professional unable to determine the source of the reaction.

⁴⁸ Letter to California State Board of Pharmacy from L.D. King, Executive Director, International Academy of Compounding Pharmacists 3 (Oct. 21, 2002) (Tab 17).

⁴⁹ Sarah Sellers, Pharm.D., Comments on Pharmacy Compounding Compliance Policy Guide, FDA Docket No. 02D-0242 (Dec. 27, 2002) available at <http://www.fda.gov/ohrms/dockets/default.htm>. Ms. Sellers was formerly a member of FDA’s Advisory Committee on Pharmacy Compounding.

⁵⁰ FDA, DRAFT GUIDANCE FOR INDUSTRY: INHALATION DRUG PRODUCTS PACKAGED IN SEMIPERMEABLE CONTAINER CLOSURE SYSTEMS 4 (2002) (2002 DRAFT GUIDANCE).

⁵¹ *E.g.*, compounded nebulizer medications (1) are routinely packaged with paper labels, (2) do not have secondary packaging, (3) lack adequate controls to prevent the entry of volatile environmental contaminants and volatile chemical constituents from packaging components into the drug product, and (4) lack adequate controls to prevent water loss. *Id.* at 3-4. See also Vibhakar Shah PH.D., FDA, Presentation before the Drug Safety and Risk Management Advisory Committee, *Inhalation drug products in LPDE Containers: A Quality (CMC) Perspective*, at slide no. 7, 8, 10-13, 19-23 (May 5, 2004) (Tab 18).

(iv) The Response from Compounding Pharmacists

In response to oft stated concerns over their manufacturing processes and controls, compounding pharmacies have argued that they cannot realistically comply with FDA standards, or even with USP standards for pharmacy compounding. The International Academy of Compounding Pharmacists (IACP) has submitted comments to numerous state rulemaking proceedings challenging the application of USP standards and arguing that pharmacists are incapable of complying due to costs or required expertise.⁵²

(d) New Untested Formulations

Although compounded inhalation drugs may be similar to approved medications in terms of the identity and labeled strength of the active ingredient, they are different formulations that have not been demonstrated to be safe and effective based on clinical data. Safety and efficacy of inhalation drugs can be compromised by numerous characteristics of the product.⁵⁴

Compounded inhalation drugs are often formulated as combinations of two or more active ingredients found in separately approved drug products. The combination of these active ingredients may result in accelerated chemical degradation and/or inactivation with the potential to reduce therapeutic efficacy.⁵⁵ In addition, compounded solutions containing multiple active ingredients are likely not to be isotonic, which may induce bronchoconstriction and mucosal irritation.⁵⁷

⁵² See n. 28, *supra*. In further comments, the IACP argued that a proposed state requirement to keep a log of refrigerator and freezer temperatures "is overly burdensome to pharmacists and contributes little to the purpose of increasing quality control. This requirement should be removed." Letter to Revisions Committee from L.D. King, Executive Director, IACP, 1 (Dec. 2, 2002) (Tab 4). IACP also argued that a proposed requirement for end-product testing for every product "would be prohibitive to both pharmacy and patient," And that a proposed requirement for end-product testing "would be financially devastating to pharmacies and patients and would undermine the purpose of this regulation." *Id.* at 2.

⁵⁴ See, e.g., FDA, GUIDANCE FOR INDUSTRY: NASAL SPRAY AND INHALATION SOLUTION, SUSPENSION, AND SPRAY DRUG PRODUCTS – CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION (2002).

⁵⁵ John H. Perrin, *Comments on drugs difficult to compound and the quality of chemicals used in compounding*, 25 DRUG DEV. AND INDUS. PHARM. 553, (1999) (Tab 19); Myrna A. Dolovich, P. Eng, et al., *Consensus Statement: Aerosols and Delivery Devices*, 45 RESPIR. CARE 589, 589-90 (2000). (Tab 20).

⁵⁷ R. Beasley, *Adverse reactions to the non-drug constituents of nebulizer solutions*, 25 BR. J. CLIN. PHARMACOL. 283 (1988) ("Both hypotonic and hypertonic nebulizer solutions produce bronchoconstriction through a combination of mast cell and reflex-mediated mechanisms") (Tab 21); R.J. Kuhn, *Formulation of Aerosolized Therapeutics*, 120 CHEST 97s (2001) ("If large amounts of hypotonic or hypertonic solutions or solutions with altered pH are introduced into the airways, mucosal irritation may result") (Tab 22).

Inactive ingredients used in compounded inhalation drugs are also a significant concern. Preservatives, stabilizing agents, solvents and other additives may cause coughing, mucosal irritation, or bronchospasm in patients. Thus, as a general proposition, inhalation drugs must be free of preservatives and toxic materials.⁵⁸ Some compounded inhalation drugs may contain solvents or other inactive ingredients that have not been tested and may be harmful to patients with respiratory disease. Compounded solutions may be acidic due to such additives, which may increase the risk of bronchoconstriction.⁵⁹ Patients who have received compounded solutions of budesonide have reported to AANMA that their medication smelled of alcohol and caused airway irritation. Ethanol has also been shown to cause airway inflammation in animal models.⁶¹ Similarly benzyl alcohol used as a preservative causes bronchitis.⁶² Patients and health care professionals concerned over the presence of alcohol or other solvents in compounded inhalation drugs cannot readily determine whether such solvents are in the product because the product labeling does not list inactive ingredients.

Inactive ingredients may also affect distribution and deposition of the drug in the lungs, which may pose issues of safety as well as efficacy.⁶³ The use of ethanol as a cosolvent in MDIs has been shown to affect the deposition of drug particles; with higher concentrations resulting in decreased respirable deposition.⁶⁴

The nebulizer used with the inhalation drug can also affect its performance. The choice of nebulizer can affect particle size and thus distribution to the lungs.⁶⁵ This may pose issues of toxicity as well as efficacy.⁶⁶ The FDA-approved inhalation drugs are commonly combination products that are approved for use only with a specific nebulizer. In the case of approved drugs, the drugs are demonstrated safe and effective based on studies conducted using specific nebulizers, which are often referred to in the approved

⁵⁸ *Id.*

⁵⁹ Beasley, *supra* note 57, at 284.

⁶¹ Marcello Trevisani et al., *Ethanol Causes Inflammation in the Airways by a Neurogenic and TRPV1-Dependent Mechanism*, 309 J. OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS 1167, 1169 (2004) (Tab 23).

⁶² Ronald D. Reynolds, MD & Richard M. Smith, MD, *Nebulized Bacteriostatic Saline as a Cause of Bronchitis*, 40 J. OF FAM. PRAC. 35, 38-9 (1995) (Tab 24).

⁶³ Declaration of Robert J. Kuhn, Pharm.D. ¶ 8 (Sept. 30, 2004) (Tab 25).

⁶⁴ Abhishek Gupta, B.S. et al., *Balancing Ethanol Cosolvent Concentration with Product Performance in 134a-Based Pressurized Metered Dose Inhalers*, 16 J. OF AEROSOL MED. 167, 171-73 (2003) (Tab 26).

⁶⁵ Kuhn Declaration, *supra* note 63 ¶¶ 5-6.

⁶⁶ *Id.* at 6; Declaration of Dr. Richard Moss, M.D., F.C.C.P. ¶¶ 9, 11 (Sept. 24, 2004) (Tab 27);

labeling. There are no such studies demonstrating compounded medications safe and effective in any nebulizer.

Without adequate testing and labeling, risks posed to patients by new compounded formulations cannot be known by health care professionals and their patients.⁶⁷

4. Health Care Professionals and Patients Have Significant Concerns over the Dispensing of Compounded Inhalation Drugs.

Health care professionals are properly concerned over the risks posed to patients by substituting compounded inhalation formulations for approved drugs. This concern is one of the key reasons that CHASM was formed. The American Academy of Allergy Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI), both members of CHASM, have cautioned their members regarding the use of such compounded inhalation drugs:

We're aware of pharmacies making budesonide and albuterol combinations, budesonide and ipratropium combinations, and combinations of all three for nebulization. There are no data to support the efficacy of these combinations in outpatient settings nor to assure their chemical compatibility in solution. Poorly manufactured respiratory agents could result in increased drug-related morbidity and mortality for our asthma patients. This could occur from:

- Toxicity from super-potency
- Failed responses to therapy due to sub-potency
- Infection from bacterial or fungal contamination
- Respiratory complications from intolerable levels of endotoxin or other adulterants⁶⁸

Nurses have raised similar concerns. An article in the *American Journal of Nursing* advises nurses to be cautious in approaching compounded formulations and to insist in written materials from compounding pharmacies on formulations, including ingredients, potential side effects, and rationale for use.⁶⁹ Nurses are also advised to discuss the advantages and drawbacks of the drug with the patient before treatment:

Nurses have the responsibility to teach and patients have a right to know about these products. Written materials for them should be accessible and patients and families should be aware of the amount of research published on them.⁷⁰

⁶⁷ Kuhn Declaration, *supra* note 63, ¶ 9; Moss Declaration, *supra* note 66, ¶ 13.

⁶⁸ Dear Colleague Letter from Michael Schatz, MD, MS, FAAAAI, President, AAAAA, and Michael Blaiss, MD, President, ACAAI, (Aug. 31, 2004) (Tab 28).

⁶⁹ Patrick J. Coyne, APRN, BC et al., *Compounded*, 103 AM. J. NURS. 76, 85 (2003) (Tab 29).

⁷⁰ *Id.*

Health-system pharmacists have also raised concerns. A 2003 editorial in the *American Journal of Health-System Pharmacists* states:

Sterile preparations made from nonsterile components are termed “high risk” by ASHP [the American Society of Health-System Pharmacists] and USP because of the risk of inadvertent contamination and harming patients is especially high for this type of compounding. High-risk compounding should not be treated casually. It should be performed only in qualified pharmacies with outstanding quality assurance and reserved for those occasions when the medical need can be met on no other way. *Convenience and financial incentives are inappropriate reasons for compounding or purchasing preparations compounded from nonsterile substances.*⁷¹

In line with these concerns, ASHP has cautioned that, in considering the use of a compounded formulation from a compounding pharmacy, the institutional pharmacy should “inform health care professionals (e.g., prescribers, nurses) that a compounded preparation from an outside source will be used, including the possible risks associated with its use.”⁷² ASHP also reports that experts generally believe that patients should be informed about the risks involved in using compounded formulations compounded from nonsterile ingredients.⁷³

Managed care professionals have also expressed concern over the substitution of compounded inhalation formulations for approved drugs. One expert notes that “[c]ommercial manufacturers offer robust and varied selections of products” and that “[h]ighly sophisticated manufacturing processes evaluated by the FDA provide the patient, prescriber and payer with a degree of assurance that the medication and the delivery device are effective and safe.”⁷⁴ The author questions the substitution of formulations from compounding pharmacy centers, which “do not offer evidence-based outcomes for the products they manufacture, other than anecdotal articles and self-reported testimonials on actions or results of these medications” and “pose a greater risk of harm.”⁷⁵

⁷¹ Lawrence Trissel, B.S., FASHP, *Editorial: Compounding Our Problems – Again*, 60 AM. J. HEALTH-SYST. PHARM., 432 (2003) (emphasis added) (Tab 30).

⁷² AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS, *HELPING MEMBERS RESPOND TO PROBLEMS WITH THE SUPPLY OF QUALITY PHARMACEUTICALS* (2004) (Tab 31).

⁷³ *Compounding Sterile Preparations Raises Informed-Consent Issues* AJHP News (Jun. 15, 2003) (statements of Robert E. Rapp, Chair of the University of 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) (Tab 32).

⁷⁴ Thomas Kaye, R.Ph., MBA, *The Quandary of Compounding for MCOs: Administrative Costs, Risks, and Waste*, 2003 MANAGED CARE 42, 46 (Tab 33).

⁷⁵ *Id.* The commentator discussed budesonide as an example:

In fact, health care practitioners have questioned whether, under a well-informed risk/benefit assessment, compounded inhalation formulations can *ever* be medically justified.⁷⁶

5. Compounded Inhalation Drugs Are Promoted in a Misleading Manner.

(a) Compounding Operations Have an Economic Incentive to Promote Compounded Formulations over Approved Drugs

The availability of approved inhalation drugs and the known risks posed by compounded alternatives beg the question of why health-care professionals prescribe compounded formulations for their patients. The answer lies in the manner in which the products are promoted.

Compounded inhalation drugs are not prescribed based on determinations by health care professionals that their patients' individual needs preclude the use of an approved drug and require the use of an unapproved compounded drug of questionable safety and efficacy. These drugs are prescribed based on promotional activities by compounding pharmacies that have an economic incentive to switch patients from approved drugs to compounded drugs.

In a recent Medicare fraud case involving the mass compounding of inhalation drugs, one of the defendants explained that "it is cheaper to make a compound solution and sell this medication than to buy an industrial product from an authorized supplier, it is much more expensive, so the profit you are going to obtain with a brand is much less than the one you are going to obtain with compounding. That is the reason for compounding, it is only profit."⁷⁷ In an article examining the acquisition cost of respiratory drugs which appeared in a homecare trade journal, a compounding supplier noted that "providers, especially small ones, will risk compounding before losing that

The compounded budesonide solution is prepared as a substitute to the commercially available form (Pulmicort Respules). Pulmicort Respules is a suspension product that offers optimized pharmacological effects when used for respiratory nebulization in the treatment of airway disease. Compounding by pharmacists results in an inferior product, with poor drug delivery to the small airways of the lungs and the possibility of bacterial contamination.[footnote] Nebulization is affected by device, viscosity, temperature, and composition of the liquid. The commercially available product, however, has been formulated to provide optimized particle-size distribution to allow for drug delivery into the airway sacs.

Id. at 45 (citing T.B. Fausnight, et al., *Case report of the efficacy of pharmacy compounded vs. FDA approved budesonide inhalation solution*, 79 ANN. ALLERGY ASTHMA IMMUNOL. 1081 (2001).

⁷⁶ Perrin *supra* note 55.

⁷⁷ Testimony of Carlos Gomez, M.S., Ph.D., at 1017-1018, U.S. v. Arias., No. 00-683-CR-LENARD (S.D. Fla. 2002) (Tab 34).

kind of money” and further acknowledged that “it’s illegal, but profitability often overrules what’s legal and illegal”⁷⁸

Thus compounding operations began to promote their compounded products to health care professionals with the goal of switching patients from approved drugs to the more lucrative compounded drugs. The Florida state official referred to above testified that “[b]ecause of the tremendous amount of profit in compounding these products,”⁷⁹ home medical equipment companies began detailing physicians and instructing their sales forces on how to obtain prescriptions permitting compounded products.⁸⁰ Where a prescription specified a commercially available product, the instructions indicated that “they would have to go through the extra step of contacting the physician to change the order.”⁸¹

(b) Physicians and Patients Are Being Misled.

The financial incentive to switch patients to compounded formulations rather than dispense approved medications has led some compounding operations to engage in promotional practices that have been misleading to prescribers. A common practice in seeking a change in the prescriber’s order is to send a refill authorization form filled out for a specific formulation that is available only in a compounded medication supplied by the pharmacy.⁸² In other instances, the prescriber is provided initially with an order form that lists numerous formulations that are available only as compounded medications. The materials do not inform prescribers of any of the risks associated with switching a patient from an approved drug to an unapproved compounded drug and, in many instances the materials do not even indicate that the formulations being promoted are compounded.⁸³ Indeed, FDA noted in its Warning Letter to Lincare that the company had “no documentation that physicians were told of and/or approved the use of [Lincare’s] compounded products in lieu of the commercially available, FDA-approved products.”⁸⁴ In other instances, pharmacies have suggested that their compounded formulations are

⁷⁸ E. Beaulieu, *DuoNeb pricing spells trouble for HMEs*, HME NEWS, Jul. 2001, available at <http://www.hmenews.com/july2001/news/topstory4.htm> (Tab 35).

⁷⁹ Jones Testimony at 35 (Tab 8).

⁸⁰ Describing an example of these instructions that he provided to the Committee, Mr. Jones stated that “[a] good prescription is written for compounded inhalation solutions. A bad prescription would indicate the name of the product.” *Id.*

⁸¹ *Id.* at 36.

⁸² See RRT Group, Inc., Refill Authorization Request Form (addressed to A. Schechter).

⁸³ See various prescription forms: Prescription Form from Concern Care Pharmacy (A); Prescription Form from NationsHealth (B); Order Form from Respiratory Services (C); Confidential Patient Information Form from Bright Medical Technologies [referring to professional sterile lab on premises] (D); Doctor Order Form Better Living Now, Inc. (E); Rx – Respiratory Medications and Supplies form from Jefferson Medical (F); Doctor order Form from Liberty Home Pharmacy Corporation (G); Handwritten Price List from Reliant Pharmacy (H); Prescription Form from Lincare (I); Form from American Homepatient (J); Form from Home Medical Pharmacy (K); (Tab 36).

⁸⁴ Lincare Warning Letter at 2

approved by the agency,⁸⁵ are clinically substantiated,⁸⁶ are therapeutically equivalent to FDA-approved products,⁸⁷ or are superior to FDA-approved products.⁸⁸

It is thus not surprising that health care professionals are being misled and often are not even aware that the products they are authorizing are compounded formulations rather than approved drugs.⁹⁰

Compounded inhalation drugs are sometimes also promoted directly to patients. Some promotions fail to inform patients that the products are not approved by FDA, are not prepared in conformity with FDA's standards for good manufacturing practice, are not prepared sterile, and have not been demonstrated safe and effective.⁹² Some compounding operations even promote their formulations as being superior and free of risk.⁹³

Although compounded formulations are sometimes promoted directly to patients, patients have generally been left in the dark with regard to the substitution of compounded inhalation formulations for approved drugs. Patients generally assume that the drugs dispensed to them by pharmacists are regulated by FDA and demonstrated to be

⁸⁵ See Letter to physician from Rotech ("Rotech is now able to offer Budesonide Budesonide is the first FDA approved aerosolized steroid offered in a .4 mg dose") (Tab 37)

⁸⁶ See Budesonide/Formoterol Nebulizer Medications from Rotech ("Several studies comparing the response of budesonide/formoterol with currently available steroid/long-acting beta agonist in asthma and COPD are very favorable") (Tab 38); Fact Sheet from Med Link America, Inc. (Budesonide . . . gives you a powerful, safe and effective tool") (Tab 39); Order Form from Morgan Drugs (Budesonide . . . Is a safe and effective steroid nasal spray") (Tab 40); Promotional materials from Pulmodose including report of clinical study on Symbicort® product approved in Europe (Tab 41).

⁸⁷ See Dear Doctor Letter from RRT Group, Inc.(Sept. 8, 2004) (Tab 42); Product label from Gino's Pharmacy ("Equivalent to ATROVEN") (Tab 43); Order Form from Morgan Drugs ("It is comparable to other prescription steroid Nasal sprays. Such as RhinoCort . . . Flonase . . . NasaCort AQ . . .") (Tab 44); Prescription Form from Prescriptions Plus Pharmacy ("Budesonide (Generic for Pulmicort)") (Tab 45).

⁸⁸ New Compounded Product Announcement from BMS Company, Inc. ("Many physicians feel this combination of drugs (budesonide/formoterol) is a very good therapeutic substitute for Advair Diskus. . . . Budesonide + Formoterol may be a better choice for your COPD patients for the following reasons . . .") (Tab 46).

⁹⁰ Jones Testimony (Tab 8) at 45.

⁹² See, e.g., Ward Drug Company, Website, available at www.warddrug.com (last accessed Feb. 11, 2005) (Tab 47).

⁹³ See Broncho Dose, Website, available at <http://broncho-dose.com/patients.htm> (last accessed Mar. 22, 2005) ("Spend less time on your nebulizer. Avoid mis-dosing. No Risk!") (Tab 48); Med-Equip, Website, available at <http://www.med-equip.com/Resp%20Meds.htm> (last accessed Mar. 22, 2005) ("Respiratory Medications are compounded under sterile conditions . . . which prevents contamination. . . . [M]edications are placed in a very small volume of liquid, , , and you get greater benefits from the medicine in a shorter amount of time.") (Tab 49).

safe and effective.⁹⁴ Compounding pharmacies generally dispense compounded inhalation drugs to patients with no information about the substitution of a compounded formulation for an approved drug, and AANMA has received numerous complaints from patients and family members with regard to newly dispensed drugs that appear similar but not quite identical to the approved medications they had previously received. AANMA professional staff recognized these drugs to be unapproved compounded drugs. The patients received no information on the safety and efficacy concerns posed by substituting compounded formulations for approved drugs, and were not even aware that the products had been compounded.

6. Labeling and Advertisements for Compounded Inhalation Drugs Must Provide Material Facts Regarding Substitution for FDA-Approved Drugs.

(a) The Material Facts

As discussed above, health care professionals are often uninformed as to the compounded formulations they are prescribing. They are sometimes even unaware that they are authorizing prescriptions for compounded drugs that are not approved by FDA.⁹⁵ They are not informed that the products are not subjected to the same manufacturing standards as FDA-approved drugs and do not meet FDA standards for sterility. They are not informed that the risks and benefits of the compounded formulations have not been established. These are facts that every prescriber must know to assess whether it is medically necessary for an individual respiratory patient to receive a compounded formulation in the place of an approved drug .

Patients are entitled to the same facts. Like health care professionals, patients are generally uninformed about compounded inhalation drugs. Patients must be informed about compounded inhalation formulations they receive from the pharmacist to evaluate whether to accept the unknown risks posed by the substitution of compounded formulations for approved medications. As discussed above, health care experts agree that patients should receive this information prior to administration of the drug. At a

⁹⁴ See, e.g., Phil Johnson, M.S., R.Ph. & Gregg Jones, R.Ph., *Editorial: Pharmacist Compounding of Analgesic Medication: The Risk of a Little-Known Practice*, 84 J. FLA. M.A. 13 (1997) (“Quality, safety, and effectiveness of our U.S. Drug Supply are comfortable assumptions made by the trusting American public and the physicians who prescribe those drugs”) (Tab 50); Carrie Teegardin, *Druggists Disciplined for Mixing Overdoses*, THE ATLANTA J. CONST., Feb. 21, 2002, at 1A (John Perrin, Professor of Medicinal Chemistry, University of Florida, stated: “We’d like to see a situation where the compounding pharmacist is made to tell the public this is being compounded and has not been tested for quality and performance.”) (Tab 51); Patricia Simms & Deborah Kades, *Debate Rages over Designer Hormones*, WISCONSIN STATE J., Jun. 22, 2002, available at <http://www.madison.com/wsj/index.php>. (Larry Sasich, Public Citizen’s Research Group stated: “[p]atients are often in the dark . . . I don’t believe the average patients who gets these products has any understanding of what’s going on, that none of these products (is) FDA-approved) (Tab 52); Carrie Teegardin, *Probe Questions Safety of Pharmacy-Made Drugs*, THE ATLANTA J. – CONST., Mar. 30, 2001, at 3C (Tab 53);

⁹⁵ See, e.g., Declaration of Dr. Christopher Landon, M.D., F.A.A.P., F.C.C.P. ¶ 12 (Sept. 30, 2004) (Tab 54).

minimum, patients must have this information in order to engage in an intelligent discussion with their prescriber about substitution of the compounded product.

Thus, to weigh the risks and benefits posed by the substitution of a compounded formulation over an approved drug, health care professionals and patients must have knowledge of at least the following facts:

- The product is not approved by FDA
- The product was/will be compounded [or prepared] in a pharmacy
- The product does/will not meet FDA standards for sterility
- The product has not been demonstrated safe and effective

Because these facts are necessary to evaluate the need for substitution of a compounded formulation for an approved drug, they must be provided in any labeling and advertising provided by compounding pharmacy operations to health care professionals and patients.

(b) The Requirement that Labeling and Advertisements Provide Material Facts

The FDCA requires that labeling and advertisements for prescription drugs provide all material facts related to the drug. Promotional labeling, including the labeling provided to prescribers in the form of proposals to compound specific formulations of inhalation drugs, falls within the FDCA definition of “labeling” in section 201(m).⁹⁶ Under section 502(a) of the FDCA, such labeling cannot be false or misleading in any particular. Section 201(n) of the FDCA provides that labeling and advertisements may be deemed to be misleading if they fail to reveal a fact that is material to the intended recipient of the information.⁹⁷

Labeling provided by pharmacists to patients with their dispensed drugs is also subject to this requirement. Although section 503(b)(2) exempts drugs dispensed by pharmacists from most of the misbranding provisions of the FDCA, that section specifically requires adherence by pharmacists to the prohibition in section 502(a) against false or misleading labeling.⁹⁸

⁹⁶ “Labeling” is defined in section 201(m) to include “any written, printed, or graphic matter (1) upon any article or . . . (2) accompanying such article. Labeling need not physically accompany a product. Information about a product is deemed to “accompany” the product within the meaning of the statute if it “supplements or explains” the product. *Kordel v. United States*. 335 U.S. 345 (1948).

⁹⁷ Section 201(n) of the FDCA provides that “in determining whether the labeling . . . is misleading, there shall be taken into account (among other things) not only the representations made or suggested . . . but the extent to which the labeling . . . fails to reveal facts material in the light of such representations or material with respect to the consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.”

⁹⁸ *See Pharm. Mfrs. Ass’n v. FDA*, 634 F.2d 106, 108 (3rd Cir. 1980). *See also* S. Rep. No. 82-946, at 9-10 (1951) (“Paragraph (2) of the new [FDCA § 503(b)] provides that a drug dispensed on prescription

Constitutional concerns raised by pharmacists in *Thompson v. Western States Medical Center* regarding regulation of promotion of compounded drugs are not applicable here. As noted above, in *Western States* the Supreme Court addressed a total ban against truthful and nonmisleading speech,⁹⁹ which the Court found would prohibit beneficial speech.¹⁰⁰ The Court specifically acknowledged that the government's interest in preventing misleading promotion "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."¹⁰¹ This is the basic relief requested in this petition.

7. FDA Must Act to Ensure Compliance and to Protect Patients.

(a) Confirmation of Material Facts Regarding Compounded Inhalation Drugs

FDA should confirm in response to this petition that the aforementioned facts regarding compounded inhalation drugs are material facts to which patients and health care professionals are entitled under section 201(n) of the FDCA. This confirmation will remove potential questions as to the agency's interpretation of the statute.

(b) Public Notice

FDA should take appropriate steps to inform the public of this confirmation of the statutory requirement in order to ensure that pharmacy operations dispensing such products are aware of their obligations and patients and health care professionals are aware of their rights to have the aforementioned material facts disclosed in labeling and advertisements. Compliance by responsible pharmacies will immediately help to protect patients from uninformed prescribing decisions and from risks that the patients choose not to take. FDA should specifically advise patients who receive this information in labeling to consult with their prescribing health care professional with regard to any concerns they may have over taking such products.

(c) Regulation Setting Forth Specific Requirements

To ensure the broadest and most effective level of compliance, FDA should promulgate a regulation requiring the aforementioned material facts to be displayed in labeling with precise wording and prominence. It is vitally important that compounding

shall be exempt from the provisions of the act relating to misbranding of drugs except those which specify that a drug shall be deemed to be misbranded if its labeling is false or misleading in any particular (Sec. 502(a)). . . . These provisions continue to apply to any drug subject to the act, whether sold over-the-counter or on prescription.")

⁹⁹ *Id.* at 374-375.

¹⁰⁰ *Id.* at 376-77

¹⁰¹ *Id.* at 376.

pharmacies be required to display the information with such a degree of prominence as to ensure that health care professionals and patients will recognize the risks posed by the medications.

In the case of labeling for professionals, there should be a boxed statement at or near the top of the page (or first page) of the labeling that requires the precise wording of the material facts in bolded font of a size that will provide prominence over most or all other textual matter in the labeling.

In the case of patient labeling, the patient should receive a statement of the material facts physically attached to the dispensed medication or provided with the medication in a bag or other container that contains only the medication.

(d) Remedial Actions by Illegal Compounding Operations

In the case of compounding establishments that operate outside of the traditional practice of pharmacy, FDA must continue to enforce general requirements of the FDCA as set forth in FDA's compliance policy guide (CPG) on pharmacy compounding.¹⁰² Where FDA takes or has taken an enforcement action based on the statutory requirements and considerations set forth in this CPG, the agency should consider also whether the compounding establishment failed to provide the material facts set forth above in labeling and in advertisements.

In the recent warning letters issued to Lincare and to Respi Care, it appears that neither establishment provided this information in labeling or advertisements. In the case of Lincare, FDA found that the prescribing health care professionals may not even have been aware that the dispensed products were compounded medications rather than approved drugs. In the matters involving Lincare and Respi Care, and in any other enforcement action against a pharmacy compounding inhalation drugs, the agency should determine whether the aforementioned material facts were provided to health care professionals and to patients. Where the information was not provided, the agency should require as an element of remedial action that the compounding establishment provide notice to all health care professionals who had prescribed the unlawful compounded inhalation drugs, and to all patients who had received the unlawful drugs, that the drugs should have borne labeling with the material facts set forth above. It is important for these health care professionals and their patients to assess the risks posed by these medications, which may still be in the hands of patients or may still be being prescribed.

C. ENVIRONMENTAL IMPACT

As provided in 21 C.F.R. § 15.30 neither an environmental assessment nor an environmental impact statement is required.

¹⁰² FDA, COMPLIANCE POLICY GUIDE FOR FDA STAFF AND INDUSTRY § 460.200 (2002). These statutory provisions include FDCA §§ 501(a)(2)(B), 502(a), 502(f)(1), 502(o), and 505(a). *Id.*

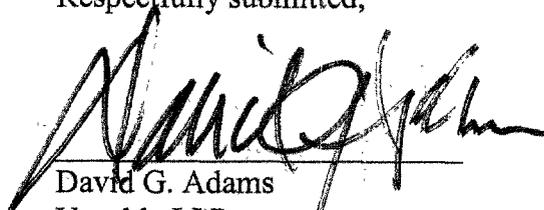
D. ECONOMIC IMPACT

As provided in 21 C.F.R. § 10.30(b) economic impact information is to be submitted only when requested by the Commissioner following review of the petition.

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "David G. Adams", written over a horizontal line.

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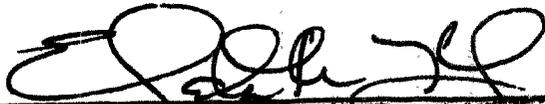
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