February 3, 2014

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs
Division of Dockets Management (HFA - 305) Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852


Docket Number: FDA-2013-1444

Dear Commissioner Hamburg:


PCCA provides its more than 3,600 independent community compounding pharmacy members across the United States and worldwide with drug compounding ingredients, equipment, extensive education, and consulting expertise and assistance. We appreciate this opportunity to comment on the Draft Guidance
concerning 503A, including, but not limited to, appropriate and fair implementation of Section 503A and federal implementation of the new Compounding Quality Act (Pub. L. No. 113-54, 127 Stat. 587 (2013)). Keeping in mind the goal of patient access to safe and necessary compounded medications, the issues set forth in the draft guidance and in FDA’s implementation of the legislation are of critical importance to our members and PCCA’s entire organization. Set forth for your consideration are PCCA’s comments concerning various provisions of the Draft Guidance.

(1) **FDA’s List of Bulk Substances Developed Through Regulation**

FDA’s Draft Guidance at page 4 (section A.3 at lines 110-116) and page 5 (B.2 at lines 170-186):

Addresses FDA’s development of a final regulation setting forth a list of substances that may be used in compounding under Section 503A.

FDA’s Draft Guidance at page 5 (section B.2, lines 184-186) states:

> Until a bulk drug substances list is published in the Federal Register as a final rule, human drug products should be compounded only using bulk drug substances that are components of approved drug products . . . or are the subject of USP or NF monographs

**Comment**

Under FDCA Section 503A(b)(1)(A)(i)(III), if a drug is not compounded in compliance with a USP/NF monograph, or from a component of an approved drug
product, then it must appear on a “list developed by the Secretary through regulations….”
in order to be used by a compounding pharmacy to fill a prescription. Paragraph 3 of the
of FDA’s Draft Guidance confirms that bulk substances must comply with the standards
of an applicable USP or NF monograph, if one exists. If such a monograph does not
exist, then the substance must be a component of an approved drug product. If the
substance used is neither of the above, then the bulk substance must be included on a
“positive list” developed through regulation to be used in compounding.

FDA first published a proposed positive list of such substances in 1999. That list
contained 20 substances that FDA initially recommended, and another 10 then still under
consideration by FDA. See 64 Fed. Reg. 996 (Jan. 7, 1999). FDA did not issue a final
rule adopting the 30 substances or otherwise finalize the list. On December 4, 2013,
FDA withdrew its proposed rule and bulk substances list stating it would reconsider the
substances on the original list, and requesting nominations for specific bulk substances to
be included on a new list. 78 Fed. Reg. 72841 (Dec. 4, 2013). The FDA also requested
specific information from interested groups and individuals when nominating substances
for the new list. Id. at 72843.

PCCA urges FDA to continue to exercise enforcement discretion pending FDA’s
publication of a final rule addressing substances to be included on the bulk drug list. In
the period since FDA published its 1999 list, many of these substances were prescribed
by numerous physicians, and continue to be prescribed today. To now preclude their use,
after this prolonged period of permissible use, until finalization of a new list would mean disruption for the physicians who prescribe these therapies and the untold number of patients who have come to rely upon them. Such disruption of therapy will lead to negative outcomes for patients who have come to rely on personalized compounded medications for their specific medical needs. In addition, PCCA recommends discontinuance of compounding bulk substances that are not included on FDA’s positive list only after expiration of a grace period of 90 days after publication of the final regulation. Use of enforcement discretion will permit continued use of substances necessary for compounding needed medications. Bulk substances that illustrate the importance of continued access include: betahistine,\(^1\) cantharidin,\(^2\) diphenylcyclopropenone,\(^3\) piracetam,\(^4\) and quinacrine HCl.\(^5\) Such long-used products compounded from bulk substances are critical to patient access to needed medications, and allowing them to remain available until finalization of the positive list is consistent with FDA’s risk-based enforcement approach with respect to compounded drugs. See Draft Guidance at 8 (description of FDA’s exercise of enforcement discretion).

\(^1\) Used to alleviate vertigo symptoms [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2655085/].
\(^2\) Used in the treatment of warts or of molluscum contagiosum [Pediatric Annals March 2010 - Volume 39 · Issue 3: 124-130].
(2) FDA Recognition of Foreign Compendia

FDA’s Draft Guidance at page 4 (section A.3, lines 105-108) states that compounded drugs may be exempt from certain provisions of the FDCA if:

_The drug product is compounded in compliance with the United States Pharmacopeia (USP) chapters on pharmacy compounding using bulk substances, as defined in 21 C.F.R. § 207.3(a)(4), that comply with the standards of an applicable USP or National Formulary (NF) Monograph, if one exists._

Comment

PCCA believes that FDA should recognize, via publication on the FDA List of bulk drug substances that may be used in pharmacy compounding, the long-standing practice of pharmacy compounding using substances from other internationally recognized compendia. Health care professionals and patients have historically relied on substances listed in internationally recognized compendia in order to provide safe, medically appropriate and clinically necessary treatment to patients. PCCA recommends that substances referenced in specific foreign pharmacopeia – such as the British Pharmacopeia, the European Pharmacopeia, or the Japanese Pharmacopeia, or other official chemical standards by countries identified in Section 802 of the Federal Food, Drug and Cosmetic Act - should be nominated for or otherwise included on FDA’s approved list of substances that may be used in compounding. These identified pharmacopeia are recognized, reliable, valuable and frequently referenced sources. Even USP recognizes the validity of foreign compendia, as evidenced with their ongoing
monograph harmonization projects in conjunction with said foreign pharmacopeia. A description of three drugs – domperidone, methylcobalamin, and nicotinamide adenine dinucleotide – illustrate the importance of inclusion of substances in other recognized compendia on any positive list promulgated by FDA.

a) Domperidone – Domperidone is a valuable therapeutic option for those who suffer from gastroparesis and gastric stasis (the inability of the stomach to digest food quickly enough). This provision would limit access for approximately 110,000 patients. Domperidone is listed in the European Pharmacopeia.

b) Methylcobalamin (Methyl-B12) – Methyl-B12 is widely used by physicians in treating autism and other neurodevelopmental disorders. This provision would limit access for approximately 100,000 patients. Methyl-B-12 is listed in the Japanese Pharmacopeia.

c) Nicotinamide Adenine Dinucleotide (NAD) – NAD is used for improving mental clarity and alertness. Because of its role in energy production, NAD is also used for improving athletic endurance and treating chronic fatigue syndrome (“CFS”). This provision would limit access for approximately 60,000 patients, assuming each patient only received a month’s supply of the drug. NAD is listed in the British Pharmacopeia.

PCCA requests that FDA deem a substance’s inclusion in the British Pharmacopeia, the European Pharmacopeia or the Japanese Pharmacopeia as at least presumptive evidence warranting inclusion of such substances on any list promulgated pursuant to FDA’s request for nominations to that list. FDA already recognizes the

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credibility of certain foreign Pharmacopeia as stated in the Agency’s documentation for request for nominations to the 503A and 503B positive lists.⁷

(3) Office Use Compounding Pursuant to FDCA Section 503A Comment

Although neither Section 503A nor FDA’s Draft Guidance directly address office use compounding under Section 503A, FDA has publicly stated that “Section 503A was not changed by the new law and patient specific prescriptions are required under Section 503A. As you know, as you observe, 503B provides a pathway in which hospitals and health care professionals can purchase compounded drugs without prescriptions.” Pharmacy Compounding Stakeholder Conference Call, Statement of J. Axelrad, FDA (Dec. 3, 2013).

To the extent FDCA Section 503A is considered to restrict office use compounding of sterile and non-sterile drug products, PCCA requests that FDA continue to exercise enforcement discretion concerning certain drugs or categories of sterile and non-sterile compounded drugs that have a history of low-risk use as administered in offices of health professionals. If FDA prohibits all office use compounding under

⁷ FDA states that requests for nominations for the bulk substances lists to be promulgated under Sections 503A and 503B should include: “Information about recognition of the substance in foreign pharmacopeias and the status of its registration(s) in other countries, including whether information has been submitted to USP for consideration of monograph development…. “ Proposed Rule: “List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act,” 78 Fed. Reg. 72841 (Dec. 4, 2013); Notification, Request for Nominations: “Bulk Drug Substances that Maybe be Used to Compound Drug Products in Accordance with Section 503B of the Federal Food, Drug, and Cosmetic Act, Concerning Outsourcing Facilities; 78 Fed. Reg. 72838, 72839 (Dec. 4, 2013).
Section 503A, including those products carrying a low risk to public health and safety, such restrictions do not adequately permit patient and physician access to important compounded products. Continued use of drugs compounded for office use under Section 503A for certain low risk products presents a negligible effect on patient health and safety. Conversely, discontinuance of the long-standing practice unduly restricts patient access and infringes on physicians’ practice of medicine and state regulation of pharmacies. It is precisely what Congress intended to avoid when implementing the Compounding Quality Act. In fact, Senator Coburn expressed clearly the intent of the Act:

There has been a lot of concern that by reaffirming section 503(a) of the Food, Drug and Cosmetic Act, office use of compounded drugs is not recognized as permissible compounding activity. Therefore, I want to make clear that this legislation does not change current State law or authority over the dispensing or distribution of medications by pharmacists, compounded or manufactured for a prescriber's administration to or treatment of a patient within their practice. Currently, the compounding and dispensing of prescription drugs for in-office administration by a prescriber to their patient is governed by State boards of pharmacy, and States have determined what is best for their State regarding office use. In fact, more than 40 States have passed laws over the last 15 years related to current practices of using compounded drugs in the office context.

The issue of office use, indeed all of pharmacy practice regulation, is best left to the States. So the omission of office use from 503(a) should not signal to the FDA that it has the authority to encroach upon State authority to regulate office use.


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Specific examples of low-risk, sterile and non-sterile products that are compounded for office use include, but are not limited to, the following:

- Topical anesthetic gels used by dentists and orthodontists prior to certain procedures
- Topical compounded medications used for the in-office treatment of recalcitrant warts
- Topical sterile antibiotic eye drops used by ophthalmologists for the treatment of corneal abrasions and/or ulcers

Thus, PCCA recommends that any final guidance implementing Section 503A address parameters of FDA’s enforcement discretion for low risk, sterile and non-sterile products for office use compounding.

(4) State/FDA Memorandum of Understanding and 5% limitation on Interstate Dispensing or Distribution.

Comment

Section 503A includes a provision limiting compounding of drug products interstate to 5% of total prescriptions dispensed or distributed unless that state has entered into a Memorandum of Understanding (“MOU”) with FDA addressing the distribution of “inordinate” amounts of compounded drug products. The Draft Guidance states that FDA does not intend to enforce the 5% limit on interstate distribution until 90 days after FDA has finalized a MOU and “made it available to states for consideration and signature.” Draft Guidance at 4 (section 4, lines 196-212). PCCA has several concerns with this part of the Draft Guidance.
First, PCCA requests that FDA exercise enforcement discretion concerning the enforcement of the so-called 5% rule until states have signed the MOU, or another reasonable period of time, such as 90 days after states and FDA determine they cannot reach agreement concerning the terms of a MOU. This is because each state, state board of pharmacy, or other appropriate state entity may require greater than 90 days to review, comment and approve any MOU presented by FDA.

Second, PCCA believes that any MOU (like the attached MOU circulated by FDA in December 1998 and the Colorado draft dated 1998) necessarily would need to be tailored to a particular state. FDA should adopt with states a flexible approach concerning implementation of the MOU provisions of section of 503A. FDA should not hold states (and compounding pharmacies within states) to the 5% limitation on interstate distribution if a particular state, for whatever reason, cannot (or will not) sign FDA’s proposed draft MOU within 90 days after FDA has finalized it in the precise form provided by FDA. PCCA believes that a rigid take-it-or-leave-it approach would implicate thorny issues of federalism. It will also force pharmacies to determine, because of some arbitrary number, which patients should receive their compounded medication and which should not. Doing so will negatively impact patient access to potentially lifesaving medications. As a starting point for any draft MOU that FDA intends to provide to states for review and comment, PCCA refers FDA to the draft dated December 23, 1998 (titled “Memorandum of Understanding on Interstate Distribution of
Compounded Drug Products Between the [State Agency] and the U.S. Food and Drug Administration.”). (FDA Docket 98N-1268).\(^9\) PCCA looks forward to providing separate comments concerning the draft MOU, using this earlier version as a starting point.

Lastly, PCCA believes that any MOU drafted or otherwise negotiated between FDA and states needs to be crafted in such way that it does not violate the interstate commerce provisions of the U.S. Constitution. Although the Compounding Quality Act now includes a “savings clause” that will mitigate the impact of any successful constitutional challenge, FDA should attempt to avoid such a challenge by imposing the least restrictive burden on interstate commerce and to avoid impairing ongoing pharmacy-patient relationships that cross state lines. A rigid limit that unduly burdens interstate commerce will raise significant commerce clause issues and perhaps Equal Protection issues as well.

(5) Compounding Processes in Compliance with USP

FDA’s Draft Guidance at page 4 (section A.3, lines 105-108 & n.5) states as follows:

\textit{The drug product is compounded in compliance with the United States Pharmacopeia (USP) chapters on pharmacy compounding\(^{10}\) using bulk substances, as defined in 21 C.F.R. 207(a)(4), that comply with the standards of}

\(^9\) The draft MOU is attached hereto, along with a draft MOU submitted to FDA by the State of Colorado dated September 29, 1998.

\(^{10}\) Footnote 5 of the draft guidance states: “After the Modernization Act was passed in 1997, the USP moved its chapter on compounding to chapter <795> and added chapter <797>, which specifically addresses sterile compounding and is referenced in chapter <795>.”
Comment

FDA’s Draft Guidance recommends using compounding procedures that comply with USP chapters <795> (non-sterile preparations) and <797> (sterile preparations). Section 503A has no parallel provision. Instead, it requires compounding “with bulk substances that comply with standards of an applicable [USP/NF] Formulary monograph if one exists, and the USP chapter on pharmacy compounding.” FDCA § 503A(b)(A)(i)(I) (emphasis added). That is, the ingredients used in compounding, not the processes compounders use, must comply with an applicable USP/NF Formulary monograph and the USP chapters on compounding. When it passed the Compounding Quality Act in November 2013, Congress could have amended Section 503A to require compounding in compliance with USP chapters <795> and <797>. It would appear, absent Congressional action, FDA does not have the legal authority to enforce compliance with USP chapters <795> and <797> for pharmacies exempt under 503A. PCCA fully supports compounding in compliance with USP <795> and <797>, encourages states to adopt these standards (as many have), and provides significant training and education on the same, regulation and enforcement of these provisions should remain a matter of state, not federal law.

Under Section 503A, the regulation of traditional compounding processes and procedures is outside FDA’s purview. PCCA strongly recommends that FDA should
leave the regulation of compounding processes under Section 503A where it has traditionally rested – with State Boards of Pharmacy – and not expand its watchdog role through guidance. PCCA looks forward to working with State Boards of Pharmacy and NABP to further the goal of states’ adoption of USP chapters <795> and <797> to ensure quality and safety of compounded medications. Thus, FDA should delete references to compliance with USP chapters <797> and <795> in any final guidance addressing implementation of Sec. 503A.

(6) Reference to FDCA Section 502(g) (Misbranding)

FDA’s Draft Guidance at page 7, section IV.A.4 (lines 242-244) states as follows:

> If the drug product purports to be a drug that is recognized in an official compendium, it must be packaged and labeled as prescribed in the compendium. (Section 502(g) of the FD&C Act)

**Comment**

Although not referenced in Section 503A, the Draft Guidance refers to FDCA section 502(g), which states that drugs will be deemed misbranded if the drug “purports to be” a drug that is recognized in an official compendium, but it is not packaged and labeled as described in that compendium. PCCA recognizes that drugs compounded pursuant to Section 503A are exempt from certain provisions of the FDCA, but are not exempt from Section 502(g). While the Draft Guidance at 7 (section IV.A.4) addresses compliance with Section 502(g), PCCA recommends that any final FDA guidance remain consistent with the statutory language set forth in Section 502(g). In addition, PCCA
recommends that final guidance states that compounded drugs that are fully compliant with any compounded drug monographs specifically will not fall within FDCA’s misbranding provisions if the drug product is “packaged and labeled” as described in that compendium. As an example, a USP compounded drug monograph exists for Baclofen Oral Suspension (USP 36, pg. 2593-2594) at a 0.5 mg/mL concentration. If a pharmacy compounds a 1 mg/mL concentration or uses a different vehicle than what is described in the monograph and the pharmacy does not label this finished compounded preparation as “Baclofen Oral Suspension USP”, the product should not be deemed misbranded as the pharmacy did not purport the medication to be compounded per the USP monograph.

(7) Drugs that are “demonstrably difficult to compound.”

The Draft Guidance at page 4 (section A.9, lines 139-142) states that in order to qualify for the exemptions under Section 503A,

*The drug product is not a drug product identified by FDA by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product (Section 503A(b)(3)(A)).*

**Comment**

The Draft Guidance states that Section 503A requires FDA to publish, by regulation, a list of drugs that are demonstrably difficult to compound. Furthermore a compounded drug product will not qualify for the exemptions under the statute if that product is identified by FDA through regulation as a drug product that presents
“demonstrable difficulties for compounding” that reasonably demonstrate an adverse effect on the safety or effectiveness of the drug product. Draft Guidance at 6 (Para. B.3).

PCCA believes that the Draft Guidance by focusing on the “drug product” alone, ignores rapid innovation in compounding formulations and drug delivery methodologies. It also fails to recognize the skills, training, and facilities of particular pharmacy compounders who employ sophisticated and state-of-the-art techniques to compound products that may otherwise be difficult to compound. PCCA provides training classes to our member pharmacies in both non-sterile and sterile compounding, in accordance to USP chapters <795> and <797>. In addition to varied levels of training that pharmacists receive in pharmacy schools and other educational programs, pharmacists can receive additional training on specific dosage forms to further their knowledge and expertise in accordance to what the current market demands. In other words, compounding pharmacies are heterogeneous; FDA’s Draft Guidance seeking a list of those drugs that are demonstrably difficult to compound does not account for pharmacy differences and thus unduly limits patient access. Limiting innovation and access to new avenues of patient treatment and care could in turn affect that care because what is “demonstrably difficult” now may not be so in the future.

Furthermore, the Draft Guidance does not address the following question: “demonstrably difficult’ for whom?” A drug product that may be difficult for one particular pharmacy to compound may be readily compounded by another pharmacy with
the equipment, skills, and training. It would be equivalent to saying that “neurosurgery” is “demonstrably difficult” as a type of surgery in general, even though neurosurgeons specializing in that discipline routinely perform that procedure with excellence. Lastly, while FDA could theoretically update any list of products that are demonstrably difficult to compound, this list would tend to be static, thus not reflecting the rapid innovation in compounding formulations and drug delivery methodology. As an alternative, FDA could establish conditions that would limit compounding of certain products based on the training, expertise, facilities, and practice of the pharmacy compounder.

PCCA also recommends that FDA, working closely in conjunction with the Pharmacy Compounding Advisory Committee, the State Boards of Pharmacy and NABP, permit compounders to compound certain products that may be “demonstrably difficult” to some pharmacies so long as pharmacies or pharmacists exercise certain controls or demonstrate their ability to safely compound such drug products, rather than rendering the compounded medication unavailable to patients that need it. Ultimately, regulation and enforcement of these compounding processes and controls, in relation to 503A, rests with the State Boards of Pharmacy.
PCCA would again like to express our appreciation for the opportunity to comment on this Draft Guidance. We look forward to continuing to work with the FDA in the future on this and other important issues as they relate to the practice of pharmacy compounding.

Sincerely,

Jim Smith

President, PCCA

Attachments
MEMORANDUM OF UNDERSTANDING ON
INTERSTATE DISTRIBUTION OF COMPOUNDED DRUG PRODUCTS
BETWEEN THE [STATE AGENCY] AND
THE U.S. FOOD AND DRUG ADMINISTRATION

I. PURPOSE

This Memorandum of Understanding (MOU) establishes a cooperative program between the [State agency] and the U.S. Food and Drug Administration (FDA) regarding the regulation of interstate distribution of compounded drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 353a.

II. BACKGROUND

B. Section 503A(a) exempts a drug product from certain provisions of the FFDCA provided that the drug product meets the requirements of, and is compounded in accordance with, section 503A. Section 503A(a) specifies that a drug product may not be deemed adulterated under section 501(a)(2)(B), misbranded under section 502(f)(1), or an unapproved new drug under section 505 if the drug product "is compounded for an identified individual patient based on the unsolicited receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient, if the drug product meets the requirements of this section" and the compounding is performed as follows:

1. By a licensed pharmacist in a State-licensed pharmacy or Federal facility or by a licensed physician on a prescription order for an individual patient made by a licensed physician or other licensed practitioner authorized by State law to prescribe drugs; or

2. By a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid
prescription order for an individual patient and is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for compounding the drug product that have been generated solely within an established relationship between the licensed pharmacist/physician and (a) the individual patient for whom the prescription order is provided or (b) the physician or other licensed practitioner who writes the prescription order.

C. Section 503A(b)(3)(B) establishes that to qualify for the exemptions in section 503A, the drug product must be compounded in accordance with either of the following:

1. It is compounded in a State that has entered into a memorandum of understanding with FDA that addresses the interstate distribution of inordinate amounts of compounded drug products and provides for investigation by a State agency of complaints related to compounded drug products distributed outside such State; or

2. It is compounded in a State that has not entered into such an MOU but the licensed pharmacist, pharmacy, or
physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician.

D. Section 503A(b)(3) directs FDA, in consultation with the National Association of Boards of Pharmacy (NABP), to develop a standard MOU for use by States in complying with these provisions concerning the interstate distribution of compounded drug products. In developing this standard MOU, FDA and the NABP recognized that it is important that Federal and State officials cooperate, communicate, and share information regarding pharmacies and compounding. The standard MOU also reflects FDA's policy to defer to State and local officials for the regulation of the day-to-day practice of pharmacy, to the extent permitted under the FFDCA.

III. SUBSTANCE OF AGREEMENT

A. This MOU sets forth the responsibilities of the [State agency] and FDA regarding the following matters involving
the interstate distribution of compounded drug products:
(1) investigation of and response to complaints relating to
compounded drug products distributed outside of [State] and
(2) response to the distribution of inordinate amounts of
compounded drug products in interstate commerce. By signing
this MOU, the [State agency] affirms that it now possesses
and shall maintain, at the discretion of the State
legislature, the legal authority (under State statutes
and/or regulations) and the resources necessary to
effectively carry out all aspects of this MOU.

B. Complaints About Compounded Drugs

1. The [State agency] has primary responsibility for
collecting complaint information and investigating
complaints associated with the use of drug products
compounded by a pharmacist, pharmacy, or physician
located in [State]. Primary responsibility for
investigating complaints involving pharmacy-compounded
drug products will generally lie with the [State Board
of Pharmacy] and similar responsibility for physician-
compounded drug products will generally lie with the
[State Medical Licensing Board], except where State
laws otherwise require. The [State Board of Pharmacy] and [State Medical Licensing Board] should cooperate in investigating any complaints involving overlapping jurisdiction.

2. Complaints to be investigated include, but are not limited to, reports of serious adverse drug experiences and alleged violations of the FFDCA, including, but not limited to, (1) compounding that may not qualify for the exemptions in section 503A and (2) compounding of a drug product that is in violation of Section 501(b) or (c) of the FFDCA, i.e., the drug product's strength differs from, or its purity or quality falls below, the standards in an official compendium (or, for a noncompendial drug, the strength, purity, or quality that the product purports or is represented to possess). A serious adverse drug experience is defined, for purposes of this MOU, as an experience that results in death, immediate risk of death, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect, or an experience that may jeopardize the patient and
require medical intervention to prevent one of the outcomes listed above.

3. The compounding of a drug product (or products) that meets any of the following criteria fails to qualify for the exemptions in section 503A of the FFDCA and, therefore, may be in violation of one or more provisions of the FFDCA:

   a. It is not compounded for an identified individual patient based on the unsolicited receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient.

   b. It appears on a list of drug products published in an FDA regulation that have been withdrawn or removed from the market because they have been found to be unsafe or not effective.

   c. It has been identified in an FDA regulation as presenting demonstrable difficulties for
compounding that reasonably demonstrate an adverse effect on its safety or effectiveness.

d. It has been prepared using a bulk drug substance that was not manufactured by an establishment registered with FDA or is not accompanied by a valid certificate of analysis.

e. It has been prepared using a bulk drug substance that does not comply with a United States Pharmacopeia (USP) or National Formulary monograph and the USP Chapter on Pharmacy Compounding; or, if such a monograph does not exist, it is prepared using a bulk drug substance that is not a component of a drug approved by FDA; or if such a monograph does not exist and the bulk drug substance is not a component of a drug approved by FDA, the bulk drug substance does not appear on a list of such substances published in an FDA regulation.

f. It has been improperly advertised or promoted contrary to section 503A(c) of the FFDCA. [Stayed
pending ongoing judicial proceedings]

g. It is essentially a copy of a commercially available drug product and has been compounded on a regular basis or in inordinate amounts contrary to section 503A(b)(1)(D) of the FFDCA.

h. It has been distributed interstate in inordinate amounts (either individually or along with other drug products), as described below in Section III.C, contrary to section 503A(b)(3)(B)(i) of the FFDCA.

4. By statute and/or regulation, the [State agency] agrees to investigate complaints in accordance with the following:

a. The [State agency] agrees to investigate complaints regarding drug products compounded by a pharmacist, pharmacy, or physician located in [State] that are shipped interstate. Such investigation should include communication in accordance with any applicable State statutes,
regulations, and administrative procedures with officials in the State(s) into which the compounded product was distributed and with the individuals reporting the complaint or the patients themselves.

b. Although the State in which the compounding pharmacy or physician is located will have primary responsibility for collecting complaint information and investigating a complaint, either that State or the State into which the subject product was distributed may propose to refer a regulatory or disciplinary matter to the other when it appears resolution can best be achieved under the authority of that other State.

c. Investigation of complaints by the [State agency] will include use of available laboratory services, where necessary, or, if it would facilitate the investigation, agreement to use another State's laboratory services. FDA's laboratories will also be available to assist the States when necessary and feasible.
d. Based on the findings from the investigation, the State(s) having jurisdiction over the compounding pharmacist, pharmacy, or physician will take regulatory action in accordance with State statutes, regulations, and administrative procedures and/or ensure that corrective action is taken by the compounding pharmacist, pharmacy, or physician.

e. The [State agency] agrees to maintain records for at least three years on complaints, on investigations of complaints, and on any replies to complainants.

f. In the event of a significant dispute between two or more States about the handling of a complaint investigation, any State may request the assistance of the District Director of the appropriate FDA district office (District Director). The District Director will attempt to resolve the dispute so that the investigation of the complaint can proceed. The appropriate FDA district office is the closest district office to
the relevant compounding pharmacist, pharmacy, or physician.

C. Distribution of Inordinate Amounts of Compounded Drugs

1. The [State agency] agrees to take action regarding any pharmacist, pharmacy, or physician within its jurisdiction who distributes inordinate amounts of compounded drugs interstate. Such action may include State regulatory action, referral to FDA for action, or joint State-FDA action. For the purposes of this MOU, interstate distribution of an inordinate amount of compounded drugs occurs under either of the following circumstances:

a. The number of compounded prescriptions dispensed or distributed interstate annually by a pharmacy or physician is equal to or greater than 20% of the total number of prescriptions dispensed or distributed (including both intrastate and interstate) by such pharmacy or physician; or

b. The number of compounded prescriptions dispensed
or distributed interstate annually by a pharmacy or physician is less than 20% of the total number of prescriptions dispensed or distributed (including both intrastate and interstate) by such pharmacy or physician, but prescriptions for one or more individual compounded drug products (including various strengths of the same active ingredient) dispensed or distributed interstate constitute more than 5% of the total number of prescriptions dispensed or distributed.

2. The following are excluded from calculations to determine the number of compounded prescriptions dispensed or distributed interstate annually by a pharmacy or physician under Section III.C.1.a and b:

a. Compounded drug products distributed interstate but "locally." Such "local" interstate distribution is limited to distribution by a pharmacy or compounding physician to patients located within 50 miles of the pharmacy or compounding physician's office, notwithstanding that such patients may reside in another State.
b. Compounded drug products distributed interstate that are compounded in response to a public health emergency or catastrophic situation (such as a flood, hurricane, or earthquake) that creates a need for additional supplies of compounded drug products to provide emergency care.

D. Meetings and Exchange of Information

1. At the end of the first year after signing the MOU, and at least every two years thereafter, FDA and the [State agency] will jointly review [State’s] complaint investigation activities and responses to interstate distribution of inordinate amounts of compounded drugs to ensure that the terms of the MOU have been met.

2. The [State agency] and the District Director agree to meet periodically to discuss the established complaint handling procedures and actions to curtail interstate distribution of inordinate amounts of compounded drugs to ensure that they are adequate to protect the public and meet statutory requirements. The [State agency] and FDA will modify such procedures when determined to
be necessary by both parties.

3. The [State agency] agrees to forward to the District Director information on any significant violation of section 503A of the FFDCA (including significant violations that do not qualify for the exemptions in section 503A of the FFDCA, as described in Section III.B.3 above), violations of section 501(b) or (c) of the FFDCA, reported deaths, serious illnesses, and potential serious health hazards related to the interstate distribution of a drug product compounded in [State]. After appropriate investigation of such incidents by the [State agency] (independently or in conjunction with another State), the State or State(s) may either obtain corrective action through voluntary efforts on the part of the pharmacy or physician compounder or through regulatory sanctions imposed by the State(s), or refer the matter to the attention of the District Director for appropriate action.

4. The [State agency] and FDA may conduct a joint inspection of a pharmacy or physician’s office if requested by either party to investigate a complaint.
The parties agree to share any evidence obtained from such an inspection in accordance with applicable Federal and State laws.

5. FDA and the [State agency] agree to provide each other, upon request and in accordance with Federal and State law, information that each obtains on complaints about drug compounding in [State] and on the distribution of inordinate amounts of compounded drugs into or out of [State], as well as records that each maintains on inspections of compounders, complaint investigations, and actions to curtail interstate distribution of inordinate amounts of compounded drugs.

E. FDA Enforcement Authority and Legal Status of Agreement

The parties to this MOU recognize that FDA and the [State agency] retain all appropriate statutory and regulatory authority set forth in the FFDCA and attendant regulations and in State statutes and regulations, respectively. The parties also recognize that this agreement does not restrict either FDA or the [State agency] from taking appropriate enforcement action where necessary to ensure compliance with the FFDCA and attendant FDA
regulations or State statutes and regulations. This MOU does not create or confer any rights for or on any person.

IV. PERIOD OF AGREEMENT

When accepted by both parties, this MOU will be effective from the date of the last signature. This MOU will remain in effect unless it is terminated in writing by either party.

VI. APPROVAL

Approved and Accepted For The

U.S. Food and Drug Administration

By: ______________________________

Title: Associate Commissioner for Regulatory Affairs

Date: ____________________________

Approved and Accepted For

The State of ____________

By: ______________________________

Title: ____________________________

Date: ____________________________
September 29, 1998

Thomas J. McGinnis, RPh
Deputy Associate Commissioner for Health Affairs
Office of Health Affairs
Food and Drug Administration
5600 Fisher Lane, Room 15A-08
Rockville, MD 20857

Dear Mr. McGinnis:

At its meeting on September 3, 1998, the Colorado Board of Pharmacy reviewed and considered various documents relating to compounding pharmacies and the Food and Drug Administration (FDA) Modernization Act of 1997. The documentation included requests from compounding pharmacists asking the Board to adopt a Memorandum of Understanding ("MOU") with the Food and Drug Administration (FDA), proposed by the Board's ad hoc task force. The Board also reviewed a proposed Memorandum of Understanding (MOU) between the Board and the FDA, a memorandum from the Board's Inspectors, correspondence from State Representative Marcy Morrison and a copy of a letter to the FDA from U.S. Senator Wayne Allard.

On behalf of the Colorado State Board of Pharmacy, enclosed is a proposed Memorandum of Understanding (MOU) for acceptance by the Food and Drug Administration (FDA). The Board believes the MOU is responsive to the requirements of Section 127, "Pharmacy Compounding" of the Food and Drug Modernization Act of 1997, by addressing specific compounded drug issues in Colorado.

The Board understands there is a national task force meeting in October, for the purpose of attempting to consider drafting a single MOU that can be endorsed by
the National Association of Boards of Pharmacy and accepted by the FDA. The Colorado Board would consider withdrawing its proposed MOU when and if a suitable "national" MOU has been put in place via NABP.

The Board looks forward to your reply.

Please let me know if there is a question.

Sincerely,

FOR THE BOARD OF PHARMACY

W. Kent Mount
Program Administrator

Enclosure

Xc: Carmen A. Catizone, NABP
Elizabeth E. Hiner, RPh, FDA
State Representative Marcy Morrison
Tom Bader, RPh
MEMORANDUM OF UNDERSTANDING

BETWEEN

THE COLORADO STATE BOARD OF PHARMACY
AND
THE FOOD AND DRUG ADMINISTRATION

I. INTRODUCTION

Pursuant to Section 127 of the Food and Drug Administration Modernization Act of 1997, "Pharmacy Compounding", the Colorado State Board of Pharmacy has developed this memorandum of understanding (MOU) with the United States Food and Drug Administration to address specific issues related to compounded drugs.

II. INVESTIGATION OF COMPLAINTS WITH RESPECT TO COMPOUNDED DRUGS SHIPPED OUT-OF-STATE

In general, the Board of Pharmacy in the state in which the compounding prescription drug outlet is located will investigate complaints about compounded drugs that are shipped out of the state. The Board may obtain the assistance of the Board that is located in the state where the compounded drug was shipped. If a complaint is received, either Board (in the state where the drug was shipped or the state where the compounding prescription drug outlet is located), may initiate the investigation. The Boards will, to the extent practicable, coordinate to determine which Board will investigate the complaint. The results of any investigation of a complaint may be shared with the other Board.

III. INORDINATE DISTRIBUTION OF COMPOUNDED DRUGS OUT-OF-STATE

A prescription drug outlet ("PDO") may dispense prescription orders for compounded drugs to be shipped interstate in an amount greater than 5% of its total prescription orders dispensed during the same calendar year. The PDO shall comply with all applicable state and federal laws, rules and regulations, including out-of-state registration/licensure and other applicable requirements which may be imposed by other states.

For the Colorado State Board of Pharmacy

W. Kent Mount
Program Administrator

For the Food and Drug Administration

Thomas J. McGinnis, RPh
Deputy Associate Commissioner for Health Affairs
Office of Health Affairs
Food and Drug Administration

DATED THIS 29TH DAY OF SEPTEMBER, 1998

DATED THIS ___ DAY OF________, 1998