Biotechnology Industry Organization

February 3, 2014

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

Re: Docket No. FDA–2013-D-1444 Draft Guidance: Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act."

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS:

BIO and its member companies work closely with the FDA to ensure that the United States' drug supply is safe, secure, and reliable, and that Americans can be confident that when they use an FDA-approved prescription drug or biologic, the medicine will be safe and effective and work as intended. FDA's regulatory standards for drugs and biologics are among the most rigorous in the world and BIO's members will continue to strictly comply with the requirements of the Federal Food, Drug, and Cosmetic Act (FFDCA or the Act) that ensure the safety of prescription drugs, including Good Manufacturing Practices (cGMPs).

BIO recognizes that traditional pharmacy compounding, as specified under FFDCA Section 503A, can play a useful role in personalizing a treatment for an individual patient with a unique medical need, such as by changing the dosage or formulation, on a case-by-case basis. We are troubled, however, when compounding pharmacies expand beyond small, non-standardized batch compounding of prescription drugs and do not comply with the same rigorous standards for FDA pre-marketing approval, including rigorous cGMP standards for quality and sterility required of manufacturers by FDA, as patients may be placed at unnecessary risk. Such an approach fundamentally

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undermines patient safety and product quality safeguards. It also creates an uneven competitive playing field for responsible drug manufacturers that have made enormous investments in compliance with FDA regulation.

A. Compounding Unapproved Versions of Marketed Products:

For a drug manufacturer that has invested hundreds of millions of dollars and a decade of research into pre-clinical testing, clinical trials, and cGMP compliant manufacturing facilities to meet FDA's standards for pre-marketing approval, it is important that compounding pharmacies not be allowed to undercut this investment by producing unapproved versions of these drugs. When unauthorized versions of drugs - including drugs subject to patent protection – are compounded, it weakens incentives for companies to conduct clinical testing and bring a new drug to market via the traditional FDA-approval pathways for innovative and even generic drugs. Over the long term, this can lead to fewer new drugs, less clinical information available to prescribers about the safety and effectiveness of these products, and fewer approved medical options for patients.

Additionally, when a cGMP compliant version of a FDA-approved drug is available, patient safety should not be placed in jeopardy by allowing compounding pharmacies to produce an unauthorized version of the drug using unapproved processes that – based on well-documented histories – often may present safety, efficacy and manufacturing risks. FDA regulations and guidance should clarify that compounding of commercially available, FDA-approved products is not allowed, except when medically necessary to address an unique individual patient need not met by the approved drug, and when supported by a valid prescription.

B. Compounding and Repackaging of Biologics:

It is also important to note that, in regard to the compounding or repackaging of biological products, the drug compounding provisions of the *Drug Quality and Security Act*[1] (DQSA) did not alter current law. Thus, there is still no applicable exemption in the FFDCA compounding provisions for entities that compound or repackage biologicals. Accordingly, these products must meet all of the long-standing requirements in the Public Health Service Act (PHSA) and the FFDCA designed to protect the public health. Specifically, no person shall introduce or deliver for introduction into interstate commerce any biological product unless, among other things, there is an approved Biologics License Application (BLA) in effect for the product.[2] In addition, other FFDCA requirements, such as cGMPs, apply to all biological products[3] -- including those that are compounded or repackaged.[4] Given the unique and complex nature of biologics and therapeutic protein products, it is critical to maintain the integrity and sterility of the

[1] P.L. 113-54 (Nov. 27, 2013).
[2] 42 U.S.C. § 262(a).
[3] *See* 42 U.S.C. § 262(j).
[4] *See also* FDA Compliance Guide (CPG) Section 446.100, which governs repackaging of sterile drugs or biologics.

product in order to protect patient safety, particularly when it is injected or infused directly into the bloodstream or sensitive organs. Therefore, we request that the FDA issue an enforcement plan to address unlawful compounding and repackaging of biologic products.

C. FDA Enforcement Strategy to Ensure Compounding Does Not Endanger the Public Health

With the passage of DQSA, which amended Section 503A by removing restrictions on the advertising, promotion and solicitation found unconstitutional by the Supreme Court[5], any prior questions about the scope of FDA authority in this area now appear settled. BIO thus urges FDA to use its full range of regulatory and enforcement authorities to ensure that compounding does not endanger the public health. Without adequate regulation (and vigilant oversight and enforcement), compounding under Section 503A may continue to create a potentially enormous legal loophole for the manufacture and sale of unapproved drugs, undermining not only public safety, but also the integrity of the traditional New Drug Application (NDA), Supplemental New Drug Application (sNDA), and Abbreviated New Drug Application (ANDA) approval processes by providing a far less regulated alternative pathway for less responsible companies.

D. Additional Specific Concerns and Recommendations:

In addition to the above general thoughts, BIO has the following specific concerns with the Draft Guidance.

- Application of the FFDCA beyond the 503A Exemptions: BIO asks the FDA to clarify its position that Section 503A only describes the conditions that exempt "traditional compound products" from three specific FFDCA sections: 501(a)(2)(B) - GMPs; 502(f)(1) - labeling of drugs with adequate directions for use; and 505 (new drug and abbreviated approvals); and that at all times the rest of the full FFDCA applies. Further, we ask that FDA clarify that Section IV of the Draft Guidance is correctly interpreted to mean that any violation of the FFDCA, including Section 503A's conditions, may subject the compounder to FDA action for failure to comply with any or all sections of the FFDCA, including the Section 503A exemptions.

- Labeling of Compounded Products: BIO also asks that FDA clarify that the labeling exemption solely relates to adequate directions for use, and that FDA agrees it has the authority to otherwise regulate labeling, including by requiring a compounded product label to carry a statement such as "this is a compounded drug; this product is not FDA approved." BIO believes it is important that compounded products be clearly identified in the label as such so that providers are fully informed that the product has been compounded, is not the FDA-approved product, and has not been manufactured or modified in an FDA-

[5] *See Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002).

approved facility. Similarly, as many of these drugs are administered in clinics and physician office settings where patients may not readily see or access the FDA-mandated label information, patients should be informed that the product is a compounded product and is not the FDA-approved product.

- Labeling of Known Safety Issues: We also believe that it would be useful for the Draft Guidance to include examples of required labeling for compounded drugs in certain circumstances (*e.g.,* drugs recognized in an official compendium), but also under other circumstances where patient safety may be compromised by lack of certain labeling, such as drugs with Risk Evaluation and Mitigation Strategies (REMS), "black box" warning, serious adverse events (AEs), or any other situation where compounding could raise additional issues regarding patient safety that could be mitigated by appropriate labeling. This could well also be the case for drugs with a narrow therapeutic index, where compounding of deliberate (or inadvertent) higher or lower dose forms could result in significant safety issues or lack of efficacy.

- Promotional Statements or Claims: The marketing and promotional statements or claims regarding a compounded drug should also be regulated under the same standards that govern approved drugs. This should include that compounders are not allowed to claim that their products are as safe and effective as, or otherwise make comparisons to, an approved drug, or make any claims regarding product safety and efficacy without adequate and well-controlled clinical studies. Also, the guidance should provide that directions for use need to be supplied by the prescribing physician, and not taken from labeling for an approved product.

- Adequate Directions for Use: As compounders under Section 503A are not required to have approved NDAs and are exempt from the labeling requirements regarding adequate directions for use, we see a potential for a significant increase in promotion and use of compounded versions of approved drugs for unapproved indications, as well as the potential for the administration of compounded drugs by unapproved routes or methods. Both of these circumstances pose significant potential safety issues for patients, and should be regulated.

- Clarification of Key Definitions: BIO is concerned that FDA's Draft Guidance uses critically important phrases, such as "essentially copies of commercially available drug products," "limited quantity," and "regularly or inordinate amounts" without providing any clear definitions or parameters for them. We believe that definitions for these terms are imperative for proper adherence to the Draft Guidance and Section 503A. Accordingly, BIO suggests the following definitions, and comments further on this issue in the chart below.

    - *"Essentially Copies of Commercially Available Drug Products":* With respect to the use of the term "essentially copies of commercially available drug products," we would propose that FDA clarify this provision such that a compounded drug is not essentially a copy of a commercially approved drug only where the compounded variation is necessary to address an individual patient's clinical need that would otherwise not be satisfied by

an approved drug or drugs available to treat that condition, and where a prescribing physician unaffiliated with the compounder makes such a determination. It also is important that this phrase be interpreted broadly enough to capture all of the types of non-clinically meaningful changes that compounders have made in the past to approved drugs, just to avoid the FDA regulatory process and build their own market. For example, we think there needs to be some parameters around what constitutes a "copy" of a commercially available drug product. BIO suggests the use of Congress' definition in the context of the new FFDCA 503B compounding provisions:

  - "a drug that is identical or nearly identical to an approved drug under section 505, or a marketed drug not subject to approval in an application under section 505; or
  - "a drug, a component of which is a bulk drug substance that is a component of an approved drug under section 505 or a marketed drug not subject to approval under 505, unless there is a change that produces for an individual patient a clinical difference, as determined and documented by the prescribing practitioner, between the compounded drug and comparable approved drug."

- *"Limited Quantity":* With respect to the term "limited quantity" BIO suggests any definition be consistent with the overall framework of traditional patient compounding where a history of prescriptions is tied to individual specific patients. Accordingly, BIO suggests the following definition of limited quantities: "No more than the quantity necessary to fill the number of prescriptions expected to be received for a one-week period based on a documented history of the receipt of such prescription orders for individual identified patients by the licensed pharmacist."

- *"Regularly"*: The term "regularly" may be misinterpreted as referring to recurrent compounding on a commercial scale. Since compounding is intended to address unique medical needs for an individualized patient, BIO requests that the Draft Guidance clarify the Agency considers compounding under Section 503A as a limited case-by-case exception to general pharmacy activities.

- FDA-State MOUs: While the Draft Guidance contains a section on memorandums of understanding (MOU) between FDA and the states, BIO asks that these ideas be explained in more detail. We ask FDA to act as expeditiously as possible to establish the state coordination and MOU process, and ask that all MOUs be made publically available. Additionally, we would like more granularity on how FDA intends to enforce the limitations of Section 503A if a state does not enter into a MOU. Finally, we would like clarity on how long "made available to the States for their consideration and signature" will be.

- Importing and Exporting of Compounded Products: The Draft Guidance should specifically state a ban on the importing and exporting of compounded products.

- Frequently Asked Questions Document: Given the need of the regulated community for clear direction from FDA on how the Agency views the scope of its authority and its priorities for risk-based enforcement, FDA should develop, in addition to the Draft Guidance, a Frequently Asked Questions document subject to public comment.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Pharmacy Compounding of Human Drug Products under Section 503A of the Federal Food, Drug, and Cosmetic Act." Specific, detailed comments are also included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Tom DiLenge
General Counsel & Head of Public Policy
Biotechnology Industry Organization

/S/

Andrew J. Emmett
Managing Director, Science & Regulatory Affairs
Biotechnology Industry Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
III. POLICY		
A. Conditions of Section 503A		
Lines 95-96:	The Draft Guidance states that a compounded drug product qualifies for the exemption if the compounding is performed "by a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order…" However, the Draft Guidance does not define the term "limited quantities." BIO believes having a specific definition is imperative, especially since compounded products are not required to undergo stability testing to support shelf life, and without proper restriction could be made far in advance of the actual need.	BIO suggests defining the term "limited quantities" as: "No more than the quantity necessary to fill the number of prescriptions expected to be received for a one-week period based on a documented history of the receipt of such prescription orders for individual identified patients by the licensed pharmacist."
Lines 105-108:	The Draft Guidance states that one of the requirements for exemption is that the drug product is compounded in compliance with the United States Pharmacopoeia (USP).	BIO requests FDA to clarify that the Agency is requiring that all traditional compounding comply with USP chapters on compounding, as opposed to just requiring that bulk substances comply with standards of an applicable USP or National Formulary (NF) monograph. We note that not all states require compliance with USP chapters on compounding and therefore request FDA explain necessary enforcement activities.

SECTION	ISSUE	PROPOSED CHANGE
		We also note that the USP and NF monographs do not include stability or shelf life standards, which are very important for drug efficacy and safety. Such standards should be required for compounded drugs for the same reason they are required for approved drugs.
Lines 122-124:	The Draft Guidance requires a valid certificate of analysis for each bulk drug substance, but not for other ingredients.	BIO believes it is important to have a valid certificate of analysis for each ingredient in the final drug product. As such, we request that FDA edit the text as follows: "The drug product is compounded using ~~bulk drug substances~~ ingredients that are accompanied by valid certificates of analysis for each ~~bulk drug substance~~ ingredient in the final drug product."
Lines 135-137:	The Draft Guidance uses the terms "regularly or in inordinate amounts" and "essentially copies of commercially available drug products," but does not define either.	BIO suggests defining "regularly" as "any compounding of a drug product that is essentially a copy of a commercially available drug product under routine business circumstances." BIO suggests defining "inordinate amounts" as "an amount that is more than is necessary to fill an individual prescription order for a specific identified patient". BIO suggests defining "essentially copies of commercially available drug products" as: • "a drug that is identical or nearly identical to an approved drug under section 505, or a marketed drug not subject to approval in an application under section 505; or • "a drug, a component of which is a bulk drug substance that is a component of an approved drug under section

SECTION	ISSUE	PROPOSED CHANGE
		505 or a marketed drug not subject to approval under 505, unless there is a change that produces for an individual patient a clinical difference, as determined and documented by the prescribing practitioner, between the compounded drug and comparable approved drug."
B. Provisions of Section 503A That Require Regulations or Other FDA Actions		
Lines 165:	FDA mentions the current "withdrawn or removed" list, but does not provide a citation.	BIO asks that FDA either append or provide a link to the current "withdrawn or removed" list in this section.
Lines 196-213:	FDA mentions it plans on publishing a new draft memorandum of understanding (MOU) with states and the consequences of not entering in a MOU with FDA.	BIO asks that FDA act as expeditiously as possible to establish the state coordination/MOU process. We also ask that all MOUs be made publically available. Further, we would like FDA to clarify how FDA intends to enforce the limitations if the state does not enter into an MOU with FDA, as well as defining how long the FDA is planning on giving states "for their consideration and signature."