Biotechnology Industry Organization

March 4, 2014

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

Re: Docket No. FDA–2013-N-1523: Request for Nominations: Drug Products that Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B 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 "Request for Nominations: Drug Products that Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act."

BIO represents more than 1,000 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.

Introduction

BIO and its member companies work closely with 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 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 compounding, as specified under FFDCA Sections 503A and 503B, 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 cross the line into large-scale manufacturing of prescription drugs and do not comply with the same rigorous standards for FDA pre-marketing approval, including rigorous cGMP standards for quality required of manufacturers by FDA. Such an approach fundamentally 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 regulations.

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Accordingly, BIO urges FDA to use its full range of regulatory and enforcement authorities to ensure compounding activities do not endanger the public health.[1] Without adequate regulation (and vigilant oversight and enforcement), compounding under both 503A and 503B may undermine patient safety, and 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.

The enactment of the Drug Quality and Security Act (DQSA)[2] was the first of several steps needed to adequately protect patients from the potential dangers associated with compounding. It is imperative that FDA work diligently to ensure full enforcement of the FFDCA to achieve the desired public health and safety objectives. This is particularly the case with respect to biological products – complex molecules manufactured in a living system.

Compounding in compliance with 503A only exempts the compounder from three specific sections of the FFDCA: new drug approval under section 505, GMPs under section 501, and labeling regarding adequate directions for use under section 502.[3] Among other requirements, one condition of 503A is that the compounded product is not a "drug product identified by the Secretary 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." The recently enacted drug compounding provisions of the DQSA, separately known as the Compounding Quality Act (CQA), also adds a new section 503B to the FFDCA that exempts self-identified sterile drug compounders ("outsourcing facilities") from three sections of the FFDCA: new drug pre-marketing approval under section 505, labeling regarding adequate directions for use under section 502, and distribution requirements (*i.e.*, track and trace) under newly added FFDCA section 582. Unlike "traditional" compounding under 503A, outsourcing facilities must comply with GMP requirements and can only compound using drug substances that are on a "clinical need" list established by FDA. In addition to other requirements, and similar to 503A compounders, outsourcing facilities also are prohibited from compounding drugs or categories of drugs "that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety and effectiveness of the drug or category of drugs, taking into account the risks and benefits to patients."

In this regard, and specifically with respect to the compounding of biological products, BIO requests as an initial matter that FDA formally state that biological products subject to FDA approval under section 351 of the Public Health Service Act (PHSA) are not

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[1] With the passage of the Drug Quality and Security Act (DQSA), which amended 503A by removing restrictions on the advertising, promotion and solicitation of drugs found unconstitutional by the Supreme Court in 2002, any prior questions about the scope of FDA regulatory and enforcement authority over compounding now appear settled.

[2] P.L. 113-54 (Nov. 27, 2013).

covered by the limited new drug application exemptions found in FFDCA sections 503A and 503B; and thus compounding these products without an approved biologics license application (BLA) is prohibited and would constitute illegal manufacturing. Further, and regardless of the applicability of pre-market BLA approval requirements, we request that FDA include on its "difficult to compound list" the category of biological products under both 503A and 503B, as the compounding of biological products presents demonstrable difficulties for compounding that meet the statutory standards for listing.

In addition, due to special manufacturing challenges and heightened patient safety concerns, BIO requests that FDA include drug products with a narrow therapeutic index on the 503A and 503B "difficult to compound list," and include drug products that are subject to a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use (ETASU) and/or such other requirements as a patient medication guide or a communication plan on the 503A "difficult to compound list."

The Exemptions for Pre-Marketing Approval under FFDCA Sections 503A and 503B Do Not Apply to Biological Products Subject to Approval under Section 351 of the PHSA

As an initial matter, it is important to recognize that the CQA did not alter current law in regard to the compounding or repackaging of biological products. Thus, FDA should affirm that there is still no applicable exemption in the FFDCA compounding provisions for entities that repackage sterile biologicals or engage in any compounding activity that would otherwise require pre-market licensure under section 351a of the Public Health Service Act. In fact, sections 503A and 503B only exempt drug products from the new drug approval requirements under section 505, and not the new product licensure requirements for biological products under PHSA section 351. The language and structure of new section 503B supports this conclusion by defining "approved drug" (in the context of prohibiting any compounding of a drug that is "essentially a copy of one or more approved drugs") as a "drug that is approved under section 505…."[4]

Accordingly, biological products must meet all of the long-standing pre-market licensure requirements in the PHSA 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, they possess an approved BLA in effect for the product.[5] In addition, other FFDCA requirements, such as cGMPs, apply to all biological products[6] – including those that are compounded or repackaged.[7] The compounding or repackaging of biologics absent a BLA therefore constitutes illegal manufacturing under the FFDCA, and as affirmed by the CQA, FDA has full legal authority over such compounders, both traditional and outsourcing facilities, to bring enforcement actions for violating the FFDCA and PHSA.

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[4] *See* 503(B)(a)(5) and 503B(d)(3).
[5] 42 U.S.C. § 262(a).
[6] *See* 42 U.S.C. § 262(j).
[7] *See also* FDA Compliance Guide (CPG) Section 446.100, which governs repackaging of sterile drugs or biologics and is unaltered by the CQA.

To safeguard public health BIO requests that FDA formally affirm that the pre-market approval exemptions under 503A and 503B do not apply to the compounding or repackaging of biologics and that these products continue to be regulated under the PHSA and FFDCA, including the requirement of an approved BLA.

The Science of Biologics and Biologics Manufacturing Supports the Inclusion of Biologic Products on the "Difficult to Compound List"

As discussed in our February 2014 comments on compounding under Section 503A[8], complex biologics and therapeutic protein products present unique scientific considerations with respect to their manufacture, distribution, and handling. It is critical to maintain the integrity and sterility of such products in order to protect patient safety, particularly when they are injected or infused directly into the bloodstream or sensitive organs. Biologics are particularly susceptible to contamination because final sterilization procedures may not be compatible with large proteins. Indeed, recent history has demonstrated that contamination of compounded sterile injectables has resulted in outbreaks of infection leading to death and serious injuries. Many biologics also are sensitive to environmental conditions and can be denatured if special handling is not followed, such as maintaining cold chain temperature controls, reducing physical shearing effects, or mitigating photosensitivity.

Therefore, regardless of the applicability of the pre-market BLA requirements discussed above, we nominate and request that FDA include on its "difficult to compound list" the category of biological products under both 503A and 503B. We also request that FDA issue an enforcement plan to address the unlawful compounding and repackaging of biologics.

This approach is medically and scientifically appropriate as FDA has expressed particular concern with the compounding and repackaging of approved sterile drug products.[9] BIO supports the November 2012 written testimony of FDA Commissioner Dr. Margaret Hamburg before the Senate Health, Education, Labor, and Pension's (HELP) Committee, in which she specifically states that certain products are not appropriate for compounding under any circumstances, including "most biologics."[10] In March 2013, Dr. Hamburg again stated that basic protections should be in place for all pharmacy compounding, including "prohibiting compounding of the most complex and highest risk

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[8] "BIO Comments on Draft Guidance: Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act," February 3, 2014, available at http://www.bio.org/sites/default/files/2014-02-03%20BIO%20Comments%20on%20Pharmacy%20Compounding%20Under%20503A%20-%20FINAL.pdf

[9] CPG 446.100, *supra* note 4.

[10] *See* Statement of Margaret A. Hamburg, M.D., Commissioner of Food and Drugs, Food and Drug Administration, Department of Health and Human Services, Before the Committee on Health, Education, Labor and Pension, United States Senate, on "Pharmacy Compounding: Implications of the 2012 Meningitis Outbreak," November 15, 2012, at page 13, available at http://www.help.senate.gov/imo/media/doc/Hamburg3.pdf.

products – drugs and biologics that should only be made for patients by an FDA-registered drug manufacturer under an approved new drug application."[11]

BIO fully supports FDA's quality systems approach to drug and biologics manufacturing, which is based upon a solid foundation of pre-market Chemistry, Manufacturing, and Controls (CMC) guidelines, pre-approval inspections, and science-based cGMP compliance. To allow compounding of biologics in the absence of these pre-market inspections and quality systems would undermine important process controls for the manufacturing of high-quality products that support patient safety.

In addition to compounding of a product, repackaging of biologics also introduces considerable risks. Both invasive manipulations, where a product is opened and repackaged into a different container, and non-invasive manipulations, where intact containers are repacked with other drugs, needles, gauze, etc., introduce the risk that the product used to treat the patient may not be sterile. Because of this important safety concern, the sponsor of a sterile, injectable biologic must obtain FDA approval prior to distributing its product in a different formulation than what was approved by FDA (*e.g.*, changing the formulation from a vial to a pre-filled syringe).[12] According to FDA Guidance,[13] repackaging is considered a step in the manufacturing process of biologics and, as such, licensing is required under 21 CFR 600.3(u) and 601.

There are many reasons for these requirements, including the need for sterile injectable products to be sterile at the end of the packaging process and the effect such a packaging change might have on the purity of the product. The packaging material can affect the shelf-life, sterility, and stability of the product, and may affect the safety and effectiveness of the product by interacting with the biologic compound (*e.g.*, the silicone used in the syringe barrels or the tungsten used in the syringe). If the sponsor of a sterile injectable biological product repackaged its own product and distributed those products without FDA approval, the sponsor would be selling an unapproved new drug or biological product in violation of federal law.

As the compounding or repackaging of biological products is only appropriate under an FDA-approved BLA, and given the science of biologics and biologics manufacturing, it is both necessary and appropriate for FDA to include biologics as a class on the "difficult to compound lists" under 503A and 503B. Furthermore, as too many recent tragedies have proven, it is critical that FDA take vigorous enforcement action against the illegal compounding and repackaging of biological products, particularly sterile biologic injectables.

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[11] "FDA Must Have New Authorities to Regulate Pharmacy Compounding," *FDA Voice,* March 22, 2013, available at http://blogs.fda.gov/fdavoice/index.php/2013/03/fda-must-have-new-authorities-to-regulate-pharmacy-compounding/.
[12] 21 C.F.R. § 601.12.
[13] "Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics" May 1999 http://www.fda.gov/downloads/Drugs/Guidances/ucm070551.pdf.

Other Drug Categories that Present Demonstrable Difficulties to Compound and Patient Safety Concerns

Compounding of Narrow Therapeutic Index Drugs Presents Special Manufacturing Challenges and Raises Heightened Patient Safety Concerns

The therapeutic index is a comparison of the relative amount of a therapeutic agent that causes the therapeutic effect to the amount that causes death (in animal studies) or toxicity (in human studies). Quantitatively, it is the ratio given by the lethal or toxic dose divided by the therapeutic dose. A drug or other therapeutic agent with a narrow therapeutic range has little difference between toxic and therapeutic doses.[14]

Precise manufacturing, controls of excipients used and qualification of personnel are even more critical for narrow therapeutic index drugs than for other products. The margin of error for differences before patient safety is impacted is much smaller, so that the acceptable range of variability between the approved brand product and a compounded version will be slight. This is especially magnified for highly potent drugs that are administered at a low dose.

In addition, differences in release profiles for drugs with a narrow therapeutic index (e.g., between immediate and extended release formulations, or between different extended release preparations) can result in higher or more or less sustained concentrations of drug plasma levels in patients, affecting safety and/or efficacy. Differences in excipients could also affect product absorption by the patient, likewise affecting safety and/or efficacy.

For these reasons, FDA should not permit compounding of drugs with narrow therapeutic indexes, as defined by FDA.

Compounding REMS Products under 503A Jeopardizes Patient Safety

A drug product subject to a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use (ETASU)[15] should be included on the 503A specific "do not compound" list. Risk management programs such as REMS ETASU help facilitate patient access to efficacious therapies with known safety issues that may otherwise not receive FDA approval. The compounding of these products without the assurance of the corresponding FDA-required safety and risk management protocols and controls more than "reasonably demonstrates an adverse effect on the safety or effectiveness of that drug product."

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[14] 21 CFR 320.33 defines a drug product as having a narrow therapeutic ratio if there is less than a two-fold difference in minimum toxic concentration and minimum therapeutic concentration in the blood. Also, any drug where safe and effective use requires careful titration and monitoring or where there is a less than two-fold difference in median lethal dose and median effective dose is considered to have a narrow therapeutic ratio.

[15] *See* FFDCA section 505-1.

Congress specifically recognized the patient safety risks and difficulty of compounding REMS ETASU products by prohibiting the compounding of such products under 503B unless the outsourcing facility demonstrates to the Secretary, prior to compounding, that the facility "utilize[s] controls comparable to the controls applicable under the relevant risk evaluation and mitigation strategy."[16] The 503B requirement of prior demonstration of comparable controls coupled with the requirement of cGMPs compliance together serve to safeguard against the increased patient safety risks that the REMS ETASU is meant to mitigate. As traditional compounding subject to 503A does not provide the dual patient protections of prior demonstration of adequate controls and cGMP compliance, REMS ETASU products should be included on the 503A specific "do not compound" list.

CONCLUSION:

BIO respectfully requests that FDA formally state that biological products subject to FDA approval under section 351 of the PHSA are not covered by the limited new drug application exemptions found in FFDCA sections 503A and 503B; and thus compounding these products without an approved BLA is prohibited and would constitute illegal manufacturing. In addition, regardless of the applicability of pre-market BLA approval requirements, we request that FDA include on its "difficult to compound list" the category biological products under both 503A and 503B, as the compounding of biological products present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of those products and is also likely to lead to an adverse effect on their safety or effectiveness when taking into account the risks and benefits to patients. Finally, due to the special manufacturing challenges and heightened patient safety concerns, BIO requests that FDA include drug products with a narrow therapeutic index on the 503A and 503B "difficult to compound" list, and include drug products that are subject to a REMS ETASU on the 503A "difficult to compound" list.

BIO appreciates this opportunity to comment on the "Request for Nominations: Drug Products that Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act." We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

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/S/

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[16] FFDCA section 503B(a)(7).