Biotechnology Industry Organization

September 2, 2014

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

Re: Docket No. FDA-2014-D-0779: Draft Guidance for Industry on Current Good Manufacturing Practices—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under the Federal Food, Drug and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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Current Good Manufacturing Practices—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under the Federal Food, Drug and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.

GENERAL COMMENTS:

BIO recommends that the Agency clearly state that this Guidance only applies to small molecule products that are approved under the Federal Food, Drug and Cosmetic Act (FFDCA) and not to biological products approved under the Public Health Service Act (PHSA). Specifically, BIO recommends that the Guidance clearly state that the compounding of biotherapeutic products is not covered under this Guidance because the Compounding Quality Act (CQA) provisions of the Drug Quality and Security Act (DQSA) did not alter current law in regard to the compounding or repackaging of biological products, as noted in previous BIO comments.[1] Accordingly, biological products must

[1] "BIO Comments on Request for Nominations: Drug Products that Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act" March 4, 2014 http://www.bio.org/sites/default/files/2014-03-04%20BIO%20Comments%20on%20Pharmacy%20Compounding%20Demonstrable%20Difficulty%20-%20FINAL.pdf

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meet all of the long-standing pre-market licensure requirements in the PHSA and FFDCA designed to protect the public health.

BIO has also previously recommended[2] that biotherapeutic products be placed on the difficult to compound list(s) because of the inherent complexity and interdependence of their manufacturing processes and the fact that the quality and consistency of biotherapeutic products (BTPs) can only be defined and ensured through individual and comprehensive process and product-specific control strategies.

1. *Ensure patient safety by maintaining a rigorous cGMP environment for outsourcing facilities compounding approved products*

As is noted in our detailed comments below, it is imperative that FDA ensures that any current Good Manufacturing Practices (cGMPs) for outsourcing facilities apply well established and standard industry requirements in order to ensure consistent and adequate protection of public health. It is important that a rigorous cGMP environment be maintained for outsourcing facilities given the risk of contamination to a drug product and the ramifications of that risk to patient safety and the number of the patients that could be harmed by such drug product. As demonstrated by the New England Compounding Center tragedy, without a rigorous cGMP environment, compounded drug products have a risk for contamination that may ultimately endanger many patients.

With traditional compounding, where a pharmacist compounds a single dose for a single patient based on a prescription, the risk of contamination remains. However the magnitude of risk is mitigated because the individual pharmacist has a specific patient prescription and volume will be low.

2. *Establish a distinction between non-sterile to sterile compounding and sterile-to-sterile compounding*

A distinction should be made within cGMP requirements between (a) sterile drug products that are compounded by the aseptic combination of licensed, commercially manufactured sterile drug products under aseptic conditions (sterile-to-sterile [S-S]) and (b) sterile drug products that are compounded from non-sterile bulk active pharmaceutical ingredients (API). The risks associated with the compounded drug product differs between these two types of products, necessitating different controls.

3. *FDA's proposed alternative approach for reducing the need for laboratory testing of incoming components*

We believe that the alternative approach to testing should not be permitted exclusively for outsourcing facilities. These sites should be accountable for maintaining the same level of control over their contract sites as would any other pharmaceutical manufacturer. This alternative approach fails to apply well established and standard industry

[2] Ibid

requirements to all manufacturers, both outsourcing facilities and pharmaceutical manufacturers, and does not provide adequate protection of public health.

If however, the FDA decides to implement this approach, then the Agency should require the outsourcing facility to establish a Quality Agreement with the laboratory specifying their respective responsibilities. This should include periodic on-site audits of the laboratory in addition to the review of the data generated by the laboratory. Additionally, if implemented (with additional requirements to ensure protection of public health), pharmaceutical manufacturers should be permitted to take the same approach.

4. *FDA's proposed alternative approach to minimize the need for facilities to have an in-house laboratory*

While outsourcing facilities may contract release testing to an outside laboratory, we believe that they should be required to comply with the same requirements and expectations as would need to be met by a pharmaceutical manufacturer. It is important that FDA apply the same well established and standard industry requirements to ensure adequate and consistent protection of public health.

The suggested alternative should only be permitted if it ensures protection of public health, and is applied to both outsourcing facilities and pharmaceutical manufacturers.

CONCLUSION:

We would like to reiterate that it is important to make clear that biological products subject to FDA approval under section 351 of the PHSA are not covered by the limited drug application exemptions found in FFDCA sections 503A and 503B; and thus compounding or repackaging these products without an approved biologics license application is prohibited and would constitute illegal manufacturing. As such, outsourcing facilities are not exempt from the obligations that manufacturers of biological products must satisfy.

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Current Good Manufacturing Practices—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under the Federal Food, Drug and Cosmetic Act." Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

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

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
II. BACKGROUND		
Lines 69:	FDA states that it intends to develop specific cGMP regulations applicable to outsourcing facilities. However, we suggest that developing separate GMP regulations for outsourcing facilities is not appropriate or necessary.	Outsourcing facilities are in truth small volume parenteral manufacturing facilities. As such, they should be required to comply with the same laws, regulations and Guidances as any other manufacturer of parenteral products. Adherence to well-established and standard industry requirements ensures consistent protection of the public health. While we do not believe that separate GMPs are necessary, we acknowledge that items such as stability requirements and labeling for outsourcing facilities do require a different approach and any regulation changes should be limited to those topics.
III. CGMPS FOR OUTSOURCING FACILITIES		
A. FACILITY DESIGN		
B. CONTROL SYSTEMS AND PROCEDURES FOR MAINTAINING SUITABLE FACILITIES		
Lines 150-151:	The Draft Guidance states that "Large equipment present in the cleanroom should not obstruct air vents and/or air flow to compromise aseptic operations."	We suggest editing this section to read: "Large equipment present in the cleanroom should not obstruct air vents and/or air flow to compromise aseptic operations. Any equipment not necessary to conduct the specific operations performed in the cleanroom should not be present. The cleanroom should not be used as a storage area."

SECTION	ISSUE	PROPOSED CHANGE
Lines 156-157:	The Draft Guidance states that "If a problem cannot be immediately corrected, production should stop until it is corrected."	We suggest editing this section to read: "If a problem cannot be immediately corrected, production should stop until it is corrected. The impact to product that is already in process should be evaluated and documented in both the case where the problem is corrected immediately, or when production is stopped temporarily."
Lines 190-192:	The Draft Guidance states that "Published literature and supplier certificates can be relied on when initially determining the effectiveness of agents used to clean and disinfect the facility and equipment surfaces provided that the supplier's cleaning procedures are followed."	We believe that the firm should not be permitted to rely exclusively on literature data and should, at some point, be required to address activity against specific facility isolates. As such, we suggest adding the following text: "The firm should evaluate the effectiveness of the cleaning agents against specific facility isolates within 6 months of the initial use of the cleaning agent."
C. ENVIRONMENTAL AND PERSONNEL MONITORING		
Line 217:	The Draft Guidance states that an environment monitoring program should "Establish alert and action limits and appropriate responses to each."	We suggest editing the statement to read: "Establish alert and action limits and appropriate responses ~~to each~~ and actions to be taken when values are not within the specified limits."
Lines 229-230:	The Draft Guidance states that personnel monitoring program should "Establishes limits that are based on the criticality of the operation relative to the contamination risk to the product."	We suggest editing the statement to read: "Establishes limits that are based on the criticality of the operation relative to the contamination risk to the product. The firm should document the justification for personnel monitoring with regard to the criticality of the

SECTION	ISSUE	PROPOSED CHANGE
		operation and potential for contamination of product."
D. EQUIPMENT, CONTAINERS, AND CLOSURES		
E. COMPONENTS		
Lines 353-358:	The Draft Guidance addresses testing of purchased high purity water.	We suggest adding the following text to this section: "Point of use tests for high purity water produced on-site, and used as a component, processing aid, or cleaning solvent should be tested regularly at point of use to verify acceptable microbial quality, endotoxin limits and chemical quality. Testing and acceptance limits should conform to those specified in the USP."
Lines 367-426:	The Draft Guidance lays out a possible alternative approach for reducing the need for laboratory testing for incoming components.	As was mentioned in our general comments above, we do not believe that the suggested alternative approach to testing should be permitted exclusively for outsourcing facilities. If this approach is implemented, entities should be required to establish a Quality Agreement with the laboratory specifying their respective responsibilities which includes periodic on-site audits of the laboratory in addition to the review of the data generated by the laboratory. Additionally, pharmaceutical manufacturers should be permitted to take the same approach.
F. PRODUCTION AND PROCESS CONTROLS		
Lines 517-519:	This section of the Draft Guidance discusses aseptic processing of sterile	We believe that the frequency of media fill simulations should be the same as what is expected of a pharmaceutical

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	drug products and validation with media fills. However, the frequency of media fill simulations is not specified. As such, we do not believe that this provides adequate protection of public health as it is likely that the frequency of media fill simulations may vary widely without guidance.	manufacturer and the Draft Guidance should be amended to reflect this well established and standard industry requirement.
G. RELEASE TESTING		
H. LABORATORY CONTROLS		
Lines 649:	The Draft Guidance lays out a possible alternative approach to minimize the need for facilities to have an in-house laboratory.	As was mentioned in our general comments above, we believe that outsourcing facilities should be required to comply with the same requirements and expectations as a pharmaceutical manufacturer and that the suggested alternative should only be allowed if it applied to both entities equally.
I. STABILITY/EXPIRATION DATING		
Lines 650:	This section of the Draft Guidance discusses stability and expiration dating.	We believe that stability testing should incorporate the use of stability indicating methods. Additionally, storage conditions should be the same as for the FDA approved similar product unless data are provided to support difference in storage conditions.
J. PACKAGING AND LABELS		

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K. QUALITY ASSURANCE ACTIVITIES/COMPLAINT HANDLING		
Lines 738-739:	The Draft Guidance states that "In very limited circumstances, a single individual can perform both production and quality functions." For traditional compounding pharmacies the same individual may perform both production and quality functions. However, outsourcing facilities are necessarily larger organizations and should be required to have a separate quality individual or unit.	We suggest deleting the current statement and revising to read: "An outsourcing facility should have a separate individual performing quality functions."
IV. REFERENCES		
V. GLOSSARY		