Biotechnology Industry Organization

July 29th, 2013

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

Re: Docket No. FDA–2013-D-0558: Draft Guidance for Industry on Contract Manufacturing Agreements for Drugs: Quality Agreements

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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Contract Manufacturing Agreements: Quality Agreements."

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BIO appreciates FDA's release of this Draft Guidance to help manufacturers better utilize Quality Agreements when dealing with a Contracted Facility.

Definition of "Manufacturing" and "Owners"

BIO asks that for the purpose of consistency and clarity the term "manufacturing" should be used in the same way throughout the document. Ideally, the definition should be consistent with 21 CFR 210.3(b)(12) defining manufacturing as "*Manufacture, processing, packing, or holding of a drug product* includes packaging and labeling operations, testing, and quality control of drug products."

BIO asks the Agency to clarify the definition of "Owners" under the Guidance. The Guidance defines Owner as any "party that introduces (or causes the introduction of) a drug into interstate commerce." (See lines 41-42.) As currently drafted, this definition may be read to include distributors and therefore may affect manufacturer product guarantees permissible under the Federal Food Drug and Cosmetic Act (FFDCA) section 303(a). BIO is concerned that there may be a conflict between FFDCA section 303(a) and lines 52-54 of the Guidance. FFDCA section 303(a) permits manufacturers to

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provide product guarantees that exempt distributors from the responsibility for distributing adulterated or misbranded products received in good faith. However, Guidance lines 52-54 state that owners are "responsible for assuring that drugs introduced for interstate commerce are neither adulterated nor misbranded as a result of the action of their selected Contracted Facilities." BIO asks the Agency to please confirm that the Draft Guidance did not intend to sweep distributors into the definition of owners and that product guarantees provide adequate liability protections as intended by FFDCA section 303(a).

Scope of Guidance

The Draft Guidance applies to commercial manufacturing of product (line 24). However, BIO notes that quality agreements are equally important during the development phase. They are a useful tool to provide both thoughtful consideration of reasonable quality expectations based on the item being procured and to provide standards during development and manufacturing. Limiting the guidance to commercial manufacturing may lead contract manufacturers to conclude that such agreements are unnecessary during drug development. An important part of commercial approval is the quality of the product and the ability to withstand regulatory scrutiny of the development endeavor. BIO notes that quality agreements have become an integral part of success in drug development. We ask FDA to consider expanding the scope of the guidance to include quality agreements for investigational product during the development phase.

Contract manufacturing of drugs may also be subject to good laboratory practices (GLPs) as applicable. While the Draft Guidance is appropriately focused on good manufacturing practices (GMPs), it does not appear to allow for a contract laboratory to perform certain tests in accordance with GLPs. BIO asks that the Guidance recognize that manufacturing of drugs may also be subject to GLPs and therefore, are also included in the scope of the Guidance.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Contract Manufacturing Agreements: Quality Agreements." 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 (BIO)

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Footnote 3:	Footnote 3 is vague regarding the reference to "certain combination products." The Guidance should be definitive on the types of combination products that fall under the scope of the guidance.	Please provide an explicit definition and/or examples on what types of combination products apply to this Guidance.
Lines 26-27:	The term manufacturing should be used consistently throughout the Guidance and conform with the term as defined in related regulations.	Please see comments above regarding the definition of manufacturing and consistency with 21 CFR 210.3(b)(12).
II. DEFINING THE "WHO" AND "WHAT" OF CONTRACT MANUFACTURING		
Lines 41-42:	As currently drafted, the definition of "Owner" may be read to include distributors.	Please see general comments above asking FDA to clarify that the definition of "Owner" is not meant to include distributors or interfere with product guarantees under FFDCA section 303(a).
Lines 47-50:	The list of manufacturing operations Contracted Faculties perform should include storage and distribution.	Please add storage and distribution to the list of manufacturing operations Contracted Facility perform as provided below. "Some of the manufacturing operations Contracted Facilities perform for Owners include, but are not limited to: (1) formulation; (2) fill and finish; (3) chemical synthesis; (4) cell culture and fermentation, including biological products; (5) analytical testing and other laboratory services; (6) storage and distribution; and (7) packaging and labeling.

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Lines 58-60:	Some regional regulations require intra-company agreements. Such documents are also usually reviewed by FDA in inspections. In order to avoid confusion we suggest the Guidance reference intra-company agreements.	Please add language referencing intra-company agreements as provided below. "This guidance describes how contract manufacturing operations fit within the larger scheme of pharmaceutical quality systems and presents the Agency's current thinking on the roles and responsibilities of entities involved in contract manufacturing arrangements. In the same context intra-company agreements might be managed."
III. ESTABLISHING RESPONSIBILITIES OF CONTRACT MANUFACTURING		
A. CONTRACT MANUFACTURING AND QUALITY MANAGEMENT: EXISTING GUIDANCE		
Lines 111-115:	In conducting activities to control and review contracted manufacturing activities we note that a risk review cannot be performed individually. First the risks need to be identified and assessed and therefore, under these circumstances the risk control step may be skipped.	Please edit the text as provided below in order to accurately reflect risk review activities. "Before outsourcing manufacturing activities, the Owner should conduct a risk assessment and review that evaluates the extent of controls required for the particular supplier and the particular product or service covered by the agreement, and based on this risk, assess the oversight appropriate and assess the suitability and competence of the potential Contracted Facility(ies) to carry out the activity (e.g., audits, material evaluations, qualification)."
IV. DOCUMENTING CONTRACT MANUFACTURING ARRANGEMENTS IN QUALITY AGREEMENTS		
A. WHAT IS A QUALITY AGREEMENT?		

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Lines 151-153:	As currently drafted, the Guidance limits quality agreements to only Quality Unit functions. However, related operations are equally as important and should be included in the obligations and responsibilities of each party.	Please edit the text as provided below to incorporate Quality Units and other related operations. "A Quality Agreement is a comprehensive written agreement that defines and establishes the obligations and responsibilities of the Quality Units and related operations of each of the parties involved in the contract manufacturing of drugs subject to CGMP."
B. ELEMENTS OF A QUALITY AGREEEMENT		
Lines 190-192:	The section of a Quality Agreement that delineates the parties' respective responsibilities and the discussion of change control should incorporate quality risk management findings identified as part of a risk assessment and risk reviews of the contracted operation as discussed in lines 111-115.	Please edit the text as provided below to reflect results of risk assessments and risk reviews of the contracted operation. "From a CGMP perspective, the most critical elements of a Quality Agreement are the sections delineating the parties' respective responsibilities and the discussion of change control. The Quality Agreement needs to consider elements identified as part of risk assessment and risk review of the contracted operation. We take those topics up in turn here:"
Lines 241-243:	It is unclear what "special consideration" means with respect to "reporting information about objectionable conditions observed during inspections and audits of the Contracted Facility, regardless of which products were covered on inspection." It is also unclear if manufacturers should be inspecting other production lines in the Contracted Facility.	Please clarify what is meant by "special consideration" regarding "reporting information about objectionable conditions observed during inspections and audits of the Contracted Facility, regardless of which products were covered on inspection" and that manufacturers are not responsible for inspecting other product lines in the same facility.

SECTION	ISSUE	PROPOSED CHANGE
Lines 273-278:	Since product and component specifications change, they are best addressed in the section dealing with change control (see lines 327-337) in order to better manage and facilitate the quality agreement review and approval process.	Please delete the reference to product specification: "Regardless, this section of the Quality Agreement should include ~~product/component specifications;~~ defined manufacturing operations, including batch numbering processes; responsibilities for expiration/retest dating, storage and shipment, and lot disposition; responsibilities for process validation, including design, qualification, and ongoing verification and monitoring; and provisions for the presence of Owner personnel ("person in the plant") in the Contracted Facility as agreed upon by the parties."
Lines 280-283:	Under the life cycle approach to drug development information is only one part of knowledge management, commercial manufacturing information is also important and should also be reflected in the Guidance.	Please edit the text as provided below to include commercial manufacturing. "The Quality Agreement should also indicate how Owners of both application and nonapplication drug products will transfer knowledge—e.g., product/process development and commercial manufacturing information -- to their Contracted Facilities to assure a quality product can be produced in compliance with CGMP."
Lines 327-331:	It is important to keep the confidentiality of the operations of contract manufactures. The product types should be sufficient to provide the contract giver with appropriate details.	Please edit the text as provided below to acknowledge product type is sufficient detail for the Contracted Facility to provide to an Owner. "The Contracted Facility should notify the Owner of changes, including but not limited to, raw materials and starting materials and their suppliers; establishment locations; manufacturing processes; additional products specified by type brought into the line, train, or facility: testing procedures: major manufacturing equipment:

SECTION	ISSUE	PROPOSED CHANGE
		shipping methods; lot numbering scheme: container closure systems; tamper evidence features: key personnel; and product discontinuation."
V. ILLUSTRATIVE SCENARIOS		
A. A QUALITY AGREEMENT DOES NOT EXEMPT CONTRACTED FACILITIES FROM CGMP REQUIREMENTS RELATED TO THE OPERATIONS THEY PREFORM REGARDLESS OF WHETHER SUCH CGMP REQUIREMENTS ARE SPECIFICALLY DISCUSSED IN THE QUALITY AGREEMENT		
Lines 369-372:	In the example, the Owner is responsible for upgrades and maintenance of the facilities and equipment. However, under the Guidance it not entirely clear whether responsibility for upgrades and maintenance of facilities and equipment should be addressed in the Quality Agreement.	Please clarify whether Quality Agreements should specifically delineate Owner and Contracted Facility related responsibilities as to upgrades and maintenance of facilities and equipment.
Lines 371-374:	There is a typo in the following: "The Owner fails to provide the requisite resources or carry out the necessary upgrades and maintenance, but and the Contracted Facility continues to manufacture the product under non-CGMP conditions that could result in product contamination."	Please edit to read: "The Owner fails to provide the requisite resources or carry out the necessary upgrades and maintenance, ~~but~~ and the Contracted Facility continues to manufacture the product under non-CGMP conditions that could result in product contamination.
Lines 409-411:	There is a typo in the following: "Depending on the evidence gathered, FDA	Please fix typo to read: "Depending on the evidence gathered, FDA could also hold

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	could also hold the Owner liable responsible for CGMP failures, or for oversight failures in monitoring the activities of the Contracted Facility in order to ensure that its products are manufactured under CGMP conditions."	the Owner ~~liable~~ responsible for CGMP failures, or for oversight failures in monitoring the activities of the Contracted Facility in order to ensure that its products are manufactured under CGMP conditions."
VI. CONCLUSION		
Lines 465-467:	The Guidance should acknowledge that when procedures between an Owner and Contracted Facility are clear the availability of the drug product may also be facilitated.	Please edit the text as provided below to reflect availability of the drug product. "Accordingly, FDA recommends that Owners and Contracted Facilities implement written Quality Agreements as a tool to delineate responsibilities and assure the quality, safety, ~~and~~ effectiveness and availability of drug products."