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August 12, 2013

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

Re: Docket No. FDA-2013-D-0558

Dear Sir or Madam:

Enclosed herein are comments on “Guidance for Industry; Contract Manufacturing Arrangements for Drugs: Quality Agreements”, published as *Draft Guidance*<sup>1</sup>. The Consumer Healthcare Products Association (CHPA) is the national trade association representing the leading manufacturers and distributors of over-the-counter (OTC) medicines and dietary supplements in the United States. CHPA and its member companies have an interest and expertise in contract manufacturing agreements and support FDA’s efforts to develop guidance for industry on this important topic.

Overall, the concepts presented are sound and reasonable. It should be recognized that industry will need time to update current templates/quality agreements and to extend them throughout the supply chain defined in the guidance. A risk based approach in development and deployment of quality agreements is recommended. We were generally surprised by the overall level of detail for these nonbinding recommendations. CHPA’s comments on the *Draft Guidance* are organized into three General Comments and Detailed Comments by Section (Attachment 1).

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<sup>1</sup> **Federal Register**, Vol. 78, No. 102, pp 31943, May 28, 2013.

## 1. General Comments

### a. Separate Quality Agreement

We agree that Quality Agreements should be separate, or at least severable, from commercial contracts and that each party's Quality Unit should participate actively in the negotiation and drafting of the Quality Agreements.

### b. Use and Meaning of the Word "Owner"

We recommend replacing the word "Owner" with "contract giver," consistent with ICH Q7 16.12, ICH Q10 2.7b, common industry understanding, and with the needs of a complex supply chain. We also recommend that the term "Contract Facility" be replaced with "contract acceptor."

The use of the term "Owner" is confusing. FDA seems to presume that every holder of a product application is also a "manufacturer." FDA seems to be stating that the obligations for compliance with good manufacturing practices (CGMP) apply to the holder of an application, even if that application holder does not conduct any manufacturing activities. The term "Owner" is used throughout the draft guidance and defined in line 42 as "*the party that introduces (or causes the introduction of) a drug into interstate commerce.*" While "*the party who introduces a drug into interstate commerce*" is clear, "*the party that causes the introduction of a drug into interstate commerce*" is very vague. In some contexts in the document, the term "Owner" seems to imply ownership of the NDA or ANDA. (See, e.g., reference in line 96 to "*Product Owner.*") However, in line 67, the draft guidance states that "*manufacturers are liable for introducing or causing the introduction of adulterated or misbranded drugs into interstate commerce.*" (Emphasis added.) Reading these statements together, the draft guidance seems to presume that the activities of a holder of an application are included within the definition of "manufacturing."

In fact, the holder of an NDA or ANDA may not be involved in manufacturing. Specifically, in 21 CFR 207.3(a)(8) FDA defines *manufacturing or processing* as follows:

*Manufacturing or processing means the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.*

Similarly, in 21 CFR 210.3(22), FDA defines *manufacture, processing, packing, or holding of a drug product* as follows:

*Manufacture, processing, packing, or holding of a drug product includes packaging and labeling operations, testing, and quality control of drug products.*

The holder of an application might not participate in any of the above activities and, in such a case, would not be subject to the regulations governing CGMP; although the holder of an application is prohibited from introducing adulterated product into commerce. (21 U.S.C. 301(a)). As a result of the above definitions, the application holder would not be subject to a CGMP inspection at its offices. The draft guidance seems to equate the ownership of an application or of a “product” with the activities of a manufacturer.

### c. The Requirements of the Draft Guidance are Inconsistent with Complex Business Arrangements

In complex business arrangements, the contract giver might not be the owner of the product or the holder of the application. For example, in the draft guidance, FDA does not define “Product Owner.” It is not clear whether this refers to the holder of an application, the owner of the intellectual property rights for the product, or a company that books the sales of the product (such as a sole distributor who licensed such distribution rights from the application holder). The term “Owner” and its definition do not address the complex license agreements that can arise in today’s pharmaceutical supply chain. Due to the complexities of licensing agreements, there are situations where the “ownership” of the application or of the intellectual property rights for the product is different from the contract giver. For example, a company may license from the application holder the distribution rights and may also take responsibility for the supply of the product. In such a case, the distributor would contract with the contract manufacturer and would enter into a Quality Agreement. However, such a distributor would own neither the application nor the intellectual property for the product. It is not clear who would be the “Owner” in such an arrangement. If the holder of the application in such an arrangement is a small business that discovered the product, it might not have the expertise or resources to oversee a manufacturer.

The “ownership” structure presumed in the draft guidance, and the use of the term “Owner” in the draft guidance, appear to be based upon the historically typical situation in which one company owns the product intellectual property, holds the application and distributes the product. That one company would then contract with a contract manufacturer. As noted above, there are numerous other, much more complicated structures in the current industry.

It is recommended to replace the word “owner” with “contract giver,” consistent with ICH Q7 16.12 and ICH Q10 2.7b, consistent with common industry understanding and with the needs of a complex supply chain. For clarity, and for further consistency, the term “Contract Facility” should be replaced with “contract acceptor.”

CHPA and its members look forward to working with FDA to further develop this guidance.

Respectfully submitted,

A handwritten signature in blue ink, appearing to read "J.S. Punzi". The signature is fluid and cursive, with a prominent initial "J" and a long, sweeping underline.

John S. Punzi, Ph.D.  
Director, Quality Assurance and Technical Affairs



**Attachment 1**

**CHPA Detailed Comments on Draft Guidance for Industry on  
Contract Manufacturing Agreements for Drugs: Quality Agreements**

<b>Line Numbers</b>	<b>Section Title</b>
<b>I.</b>	<b>Introduction</b>
	No comments
<b>II.</b>	<b>Defining The “Who” and “What” of Contract Manufacturing</b>
General	We disagree with the definition of “Owner”. We recommend that FDA replace the word “owner” with “contract giver” consistent with ICH Q7 16.12, ICH Q10 2.7b, common industry understanding, and with the needs of a complex supply chain.
<b>III.A</b>	<b>Statutory and Regulatory Framework</b>
73	Typographical error: ...possess.” .
<b>III.B</b>	<b>Existing Guidance</b>
General	No Comments
<b>IV.A</b>	<b>What is an Agreement</b>
General	No Comments
<b>IV.B</b>	<b>Elements of a Quality Agreement</b>
186	<p>The term “Communication Plan” is used several times in the document. Quality Agreements should assign responsibilities for each party to notify the other party of various events and to identify contact persons for key quality topics. However, referring to a “communication plan” implies the need for a new formal CGMP document.</p> <p>If owners are subject to the regulations governing CGMP, and if a communication plan is a new CGMP document, then owners can be cited in a Form 483 for not having a communication plan or for having an inadequate communication plan.</p> <p>Recommended revision: <i>The parties to a Quality Agreement should include a description of how manufacturing deviations will be communicated to the Contract Giver by the Contract Acceptor, and how such deviations will be investigated, documented, and resolved. Dispute resolution provisions should also be included if not currently in the supply agreement.</i></p>
<b>IV.B.1.a</b>	<b>Quality Unit Responsibilities</b>
218-221	<p>The statement that “Owners” are responsible for performing the release of products seems to create a new CGMP obligation for Owners. FDA states:</p> <p><i>Although the Quality Unit of each Contracted Facility is responsible for release of the product of the operations it performs, final product release of finished goods for distribution must be carried out by the Owner and cannot be delegated to a Contracted Facility under the CGMP regulation or any terms of the Quality Agreement (21 CFR 211.22(a)). Similarly, in Footnote 11, FDA states:</i></p>

*Agreement (21 CFR 211.22(a)). Similarly, in Footnote 11, FDA states:*

*The responsibility to approve release of a drug product for distribution must rest with the owner of the drug product. (43 FR 45014 at 45034 (29 September 1978))*

While it is agreed completely that an “owner” is prohibited from introducing an adulterated product into market, the task of release could be, and in many cases is, delegated. The circumstances of such delegation should be defined in the quality agreement. Many companies have outsourced the task of releasing product. It is not uncommon for an “Owner” to conduct a thorough due diligence of a contract manufacturer’s ability to test and release product. Once that due diligence is completed, the contract manufacturer’s release of product would then be the final release. The “Owner” would not conduct a separate release of product.

The draft guidance represents a major change to how business is currently conducted and could have a significant economic impact within the industry, particularly upon smaller businesses that may not have the expertise or resources to review batch records and to perform other work necessary to release product.

*Recommended revision: Owners are (The contract giver is) prohibited from introducing into interstate commerce drugs that are adulterated including drugs that have not have been manufactured, and processed or packed in accordance with CGMPs, or held under contract by another company.*

*The Quality Unit of the Contracted Facility is responsible for release of the product of the operations it performs. Final product release responsibility of finished goods for distribution must be clearly delineated in the Quality Agreement. The task of conducting the release can be delegated to a Contracted Facility and the Owner can rely on the output of those tasks under the CGMP regulation or any terms of the Quality Agreement (21 CFR 211.22(a)).*

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It is not entirely clear what FDA means by the text “*special consideration should be given to reporting information about objectionable conditions observed during inspections and audits of the Contracted Facility, regardless of which products were covered on inspection.*”

The concepts underlying the above text by FDA are appropriate but it is recommended that the agency utilize consistent terminology including clarification of “special consideration.” Specifically, it is recommended that the sentence be separated into two, distinct concepts i.e., regulatory inspections and audits.

*Recommended revision: Because Contracted Facilities often simultaneously or sequentially provide services to multiple product Owners, special consideration should be given to reporting information about observations and findings made during regulatory inspections and audits of the Contracted Facility, regardless of which products were covered on the subject of the inspection. In addition, in the event that the Contracted Facility becomes aware, either through internal*

	<u>processes or through an audit by another customer, of a condition at its site that may not comply with CGMPs or that may impact the quality of the Owner's product, the Quality Agreement should also require the Contracted Facility to report that condition to the Owner.</u>
244	<p>It is recommended that the following phrase be revised for clarity: “<i>communicate information about preventing cross-contamination and maintaining traceability when a Contracted Facility processes or tests drugs for multiple product Owners</i>”.</p> <p>Specifically, Quality Agreements typically prohibit, restrict, or otherwise address the handling of hormones, cytotoxins, and other potent ingredients; however, they often do not include provisions on how parties will communicate the information referenced above. While it is agreed that the concepts should be addressed, it is recommended that the language be rephrased.</p> <p>Recommended revision: “<u>The Quality Agreement should also indicate how the parties will prevent cross-contamination and maintain traceability when a Contracted Facility processes or tests drugs for multiple product Owners. In addition, in the event that the prevention measures outlined in the Quality Agreement are found to be ineffective, the Quality Agreement should also impose on the Contracted Facility the obligation to notify the Owner of any potential cross-contamination.</u>”</p>
<b>IV.B.1.d</b>	<b>Product-specific Items</b>
272	<p>The section “Product – Specific terms” implies that <u>all</u> of the information related to the manufacture of the product should be contained <u>within</u> the Quality Agreement: “<i>...might opt to include this information in an appendix, or directly in the body of the Quality Agreement.</i>”</p> <p>It is agreed that this information must be provided, however it is suggested that this sentence be expanded to include the option whereby the “<i>Quality Agreement defines how this information is shared.</i>” Provided the documents are adequately referenced in the Quality Agreement, there is no added value to including the entirety of the detailed information in each Quality Agreement. In addition, there may be additional information shared after the execution of the Quality Agreement. These details may be defined in other CGMP documents that are shared between the Owner and Contracted Facility.</p> <p>Recommended revision: “<u>A comprehensive Quality Agreement will provide specific terms related to the particular product or products involved. The contract giver and contract acceptor might opt to provide details of how this information will be shared, include this information in an appendix, or directly in the body of the Quality Agreement. Regardless, this section of the Quality Agreement should include or provide clear reference to product/component specifications; ...</u>” <i>The Quality Agreement may also reference information in this section that may be alternatively detailed as part of the direct supply agreement.</i></p>
281	“ <u>The Quality Agreement should also indicate how Owners of application and non-</u>

	<p><i>application drug products will transfer knowledge – e.g., product/process development information to their Contracted Facilities to assure...”</i></p> <p>The example cited implies transfer of the entire development report. While this may be appropriate in some situations, it is not appropriate in all situations.</p> <p>Recommended revision: <i>The Quality Agreement should also indicate how Owners <u>contract givers</u> of both application and non-application drug products will transfer knowledge e.g., product/process development information <u>appropriate information to support the activity to be performed</u> -- to their Contracted Facilities to the <u>contract acceptor</u> to assure a quality product can be produced in compliance with CGMP. Alternatively this level of documentation may be contained in separate supplier quality management process documentation.</i></p>
<b>IV.B.1.e</b>	<b>Laboratory Controls</b>
	<p><i>The Quality Unit of each participating party to a Quality Agreement should have adequate laboratory facilities available to them for testing and approval (or rejection) of drug products.</i></p> <p>The phrase “<i>each participating party</i>” indicates that <u>both</u> the Owner and the Contracted Facility will have equally capable, redundant laboratory facilities and will conduct redundant testing and approval. Compliance with this language would require a major change in the industry. In many cases, the reason for contracting with the external laboratory is to access capabilities that may not exist internally. The CGMP regulations do not require redundant laboratory facilities.</p> <p>This language proposed by FDA seems to be a further example of the apparent presumption that the Owner must be responsible for the task of releasing product. Both the laboratory testing and the release of product can, in fact, be delegated to a contracted entity.</p> <p>We recommend that this sentence be revised to read: <i>The Quality Unit of the party <u>conducting the testing</u> of each participating party to a Quality Agreement should have adequate laboratory facilities available to them for testing and approval (or rejection) of drug products.</i></p>
292 and 300	Typo: “In accordance <u>to with</u> CGMP”
293	<p>“<i>Procedures delineating controls over sampling and testing samples should be established in the Quality Agreement</i>”</p> <p>Approved SOPs and/or test methods at the CMO should govern this process. References to those processes could be included in the Quality Agreement, but the explicit details of the procedures should not be included.</p>
301-302	<p>“... <i>for stability and reserve samples, the Quality Agreement should delineate the frequency of testing and timely communication of the results.</i>”</p> <p>Details of stability testing should be covered in a mutually agreed upon protocol,</p>



	<p>rather than be specified in a quality agreement. Language in the Quality Agreement should require or refer to the mutually agreed protocol for stability testing. In addition, handling of reserve samples is not typically addressed in a stability protocol. However, handling and examination of reserve samples can be described in the Quality Agreement. Timely communication of any significant trends for both stability and reserve samples can also be described in the Quality Agreement.</p> <p>Recommended revision: <i>“for stability and reserve samples, the Quality Agreement should reference the specific stability protocol for each product to be tested or define how stability protocols will be written and agreed. <u>The Quality Agreement should delineate the frequency of examination of the reserve samples. The Quality Agreement should specify timely communication of the results of both stability testing and reserve sample examination.</u>”</i></p>
<b>IV. B.2.</b>	<b>Change Control, Including Subcontractors</b>
327-329	<p><i>The Contracted Facility should notify the Owner of changes, including but not limited to, ....additional products brought into the line, train, or facility... ”</i></p> <p>While this seems simple and important, it is not always achievable due to the contractual obligation of the Contracted Facility to maintain the confidentiality of the business information of its other customers. It is expected that the Contracted Facility will share and notify changes by “class of compound”, but disclosure of specifics related to other customers’ products is typically forbidden contractually in order to protect the confidentiality of work being done.</p> <p>Recommended revision: <i>“The Contracted Facility <u>Contract Acceptor</u> should notify the Owner <u>Contract Giver</u> of changes, including but not limited to, ....additional types of products brought into the line, train, or facility... ”</i></p>
331	<p><i>The heading refers to “Subcontractors” but there is no mention of subcontractors in the list of items to be addressed.</i></p> <p><i>Recommend addition of the following language from Q7 16.14 at the end of the sentence in Line 331: “... discontinuation. <u>Where subcontracting is allowed, the contract acceptor should not pass to a third party any of the work entrusted to him under the contract without the contract giver’s prior evaluation and approval of the arrangements.</u>”</i></p>
332	<p><i>“...should be communicated to other parties in the contract manufacturing arrangement: ... Stability studies, process capability analysis and trends, process improvement projects, ...”</i></p> <p><i>These are the elements of an APR mostly. Some suppliers will not provide copies of APRs (or data within), especially authorized generic relationships. Failures and/or significant trends should be communicated but given the broad range of</i></p>

	<i>relationships in the pharma industry, there are elements of these that may be limited to on site reviews.</i>
334	<p><i>“Owners and Contracted Facilities should both be aware that the following may initiate changes and should therefore be communicated to other parties in the contract manufacturing arrangement: investigations into manufacturing deviations and out-of-specification results, new or revised product claims, stability studies, process capability analysis and trending, process improvement projects, field alert reports/biological product deviation reports, customer complaints, recalls, or adverse event report”</i></p> <p><i>This is very prescriptive and indicates that all of this information should be communicated between parties regardless of what type of contract work is being done. It is recommended to delete “new or revised product claims” and “process capability analysis and trending,” which are excessive.</i></p> <p><i>Recommended revision: “Owners and Contracted Facilities <u>Contract Givers and Contract Acceptors</u> should <u>consider the impact of the following and define in the Quality Agreement expected communication regarding:</u> investigations into manufacturing deviations and out-of-specification results, new or revised product claims, stability studies, process capability analysis and trending, process improvement projects, field alert reports/biological product deviation reports, customer complaints, recalls, or adverse event reports.”</i></p>
<b>V.A.1. Case 1</b>	
372	Typo: “...but and the...”