Connecting a World of Pharmaceutical Knowledge

29 July 2013

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

Submission of comments on: **Docket No. FDA-2013-D-0558; Guidance for Industry on Contract Manufacturing Arrangements for Drugs: Quality Agreements**.

Dear Sir or Madam,

Thank you for the opportunity to comment on the proposed Guidance for Industry on Contract Manufacturing Arrangements for Drugs: Quality Agreements.

This is clearly a complex and important subject and we are pleased that the FDA has chosen to draft this guidance. There were numerous issues raised by ISPE members in relation to the proposed guidance document. These issues were discussed in detail amongst our ISPE members and the included document summarizes those issues we found significant and having the most impact on quality and compliance within the Quality Agreement itself.

If additional comment detail is required, ISPE would welcome any opportunity for its members to collaborate with the FDA in further developing this guidance document. We support this initiative and aim for such collaboration so that the final version of the document incorporates FDA and industry's compliance perspectives in developing Quality Agreements between Drug Owners and the facilities they engage for contract manufacturing.

The International Society for Pharmaceutical Engineering (ISPE) is an individual membership Society of more than 20,000 professionals involved in the manufacture of pharmaceuticals and related products. All scientific and technical areas of the pharmaceutical manufacturing industry are represented among the ISPE Membership. ISPE is committed to creating a forum for uniting the world's pharmaceutical manufacturing community and regulators.

Thank you again for the opportunity to comment on the proposed draft guidance. Please feel free to contact me if you have any questions.

Yours sincerely,

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Proposed Regulation/Guidance Document: **Guidance for Industry Contract Manufacturing Arrangements for Drugs: Quality Agreements, Docket No. FDA-2013-D-0558**

Comments submitted by: **ISPE (International Society for Pharmaceutical Engineering)**

GENERAL COMMENTS	
1. Clarification of Owner	It is preferable to more clearly define the term 'product owner' as it relates to manufacturing. The term as defined ("the party that introduces (or causes the introduction of) a drug into interstate commerce") could be misinterpreted as applying to the 'owner' as a distributor or promoter of another firm's products. We understand that this guidance is intended for contract manufacturing relationships, and is not intended to describe distribution relationships. Therefore we suggest the term's definition should be clarified in this regard, and defined to clearly indicate that the 'product owner' is usually the holder of the NDA, ANDA or BLA for the product, if there is one, whilst appreciating some product types do not require a license holder (e.g. OTC products).
2. Scope	It is recommended that additional key quality elements be included in the scope of the document. A subsection particular for exception related events and outcomes; involvement of the "Owner" in the decision to rework/reprocess/re-inspect product/product acceptance. This is a critical aspect as part of the "Owner's" management oversight of the Contract Facility. Additional items to be considered for scope inclusion are: a subsection for Complaints and Safety Events that includes direction around timeliness, responsibilities and communication; a subsection for Field Action/Recall roles and responsibilities; and a definition section to clearly define specific terms.
3. Typographical Errors	Typographical errors have been identified. Please refer to lines 113, 169-170 (delete parentheses) 292, 300, 329-331 (use of ":" should be changed to ";"), 354, 372, 409 and 458 (numbering error in section headings)

Specific Comments on the Text

ISPE indicates text proposed for deletion with strikethrough formatting and text proposed for addition with bold and underlining.

Line Number	Current Text	Proposed Change	Rationale and Comment
25-26	...their intermediates), finished drug products, combination products, and biological drug products.[3 4]	Provide explicit definition on what types of combination products to which this guidance should apply	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 this guidance
26, 47 to 50, 133 to 134	Line 26 - …the term "manufacturing" includes processing… Line 47 to 50 - Some of the manufacturing operations …include, but are not limited to: (1) formulation; …packaging and labeling. Line 133 to 134 - When an Owner seeks the services of a Contracted Facility to perform all or part of the manufacturing, …	Define and use the term "manufacturing" consistently throughout the document.	For the purpose of harmonization the term 'manufacturing' should be used in the same way throughout the document. Ideally, the definition should be consistent with the definition in 21CFR210.3(b)(12)
54 - 56	… All Contracted Facilities must assure compliance with applicable Current Good Manufacturing Practices for all manufacturing, testing or other support operations performed to make a drug(s) for the Owner.	Add at the end of line 56 - **Contracted facility should also ensure compliance with the clauses mentioned in the Quality Agreement made between contract manufacturer and drug owner.**	N/A
111	Before outsourcing manufacturing activities, the Owner should conduct a risk review that…	Before outsourcing manufacturing activities, the Owner should conduct a **risk assessment** and review that…	A risk review cannot be performed individually. First the risks need to be identified and assessed. The risk control step can be skipped under these circumstances.
119	Owners should monitor and review the	Owners should monitor and review the	This implies that an owner can force a

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	performance of the Contracted Facility and identify and implement any needed improvements.	performance of the Contracted facility**. Both Owner and Contracted facility should** identify and implement any needed improvements.	Contracted facility to make any change/improvement that they feel is necessary. An owner can work with a Contracted facility to suggest potential improvements. Ultimately, an Owner can decide to not accept and release any product made by the Contracted Facility until a change is made.
121-122 / footnote 8	All parties performing manufacturing operations should monitor incoming ingredients and materials to ensure they are from approved sources using the agreed supply chain.8	All parties performing manufacturing operations should monitor incoming ingredients and materials to ensure they are from approved sources using the agreed supply chain.~~8~~	Remove reference to foot note 8 and the actual foot note 8 because ICH Q10 at 7-8 doesn't discuss an agreed supply chain
152	…obligations and responsibilities of the Quality Units of each of the parties involved in the…	…obligations and responsibilities of the Quality Units **and related operations** of each…	The quality agreement should specify the responsibilities of both parties in the contracted arrangement and should include responsibilities of all functional areas and not be limited to the Quality Unit functions
162-164	While the FDA does not routinely request or review business documents or business agreements on inspection FDA routinely requests and reviews evidence of Quality Agreements (or the lack of Quality Agreements).[10]	While the FDA does not routinely request or review business documents or business agreements on inspection, FDA routinely requests and reviews evidence of the **presence or absence of Quality Agreements**[10]	Clarity needed regarding "…evidence of Quality Agreements.."
182-183	Sought or provided under the agreement.	Sought or provided under the agreement. **A**	It is recommended to add a definitions section

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	Agreement on precise meaning of terms used in the Quality Agreement is an important step in drafting	**definition section may need to be included, where necessary, to ensure agreement on the precise meaning of terms used in the Quality Agreement**	in the agreement itself so that misinterpretations can be avoided.
209-213	The section that addresses Quality Unit responsibilities may be termed "Compliance," "Quality," "Quality Responsibilities," or any similar title. Whatever heading or category is selected by the parties, the section of the Quality Agreement covering Quality Unit responsibilities, perhaps the most critical element of a Quality Agreement, should define in detail the CGMP responsibilities of each party, including the quality activities and measures.	**Quality Unit responsibilities may be termed "Compliance," "Quality," "Quality Responsibilities," or any similar title. Quality Unit responsibilities are perhaps the most critical element of a Quality Agreement and should define in detail the CGMP responsibilities of each party, including the quality activities and measures**.	Quality Unit responsibilities recur throughout every section of the agreement. The current verbiage indicates these responsibilities should be contained within a single section and may have the effect of constraining the flow of the agreement by forcing it to fit within dedicated sections.
219-223	"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 regulations or any terms of the Quality Agreement (21 CFR 211.22(a))"	Delete	We agree that the ultimate/final responsibility remains with the sponsor. This sentence, however, adds a new requirement to the cited GMP regulation. In addition, depending on the circumstances (e.g., "virtual" company), the sponsor may not have the requisite technical knowledge for final release (relying instead on expertise of contracted facility for this knowledge). In these cases, this new requirement would not be feasible or valuable.
240	"special consideration should be given to reporting information about objectionable	"special consideration should be given to reporting information about **observations and**	The concepts underlying the above comment by FDA are appropriate but it is recommended that

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	conditions observed during inspections and audits of the Contracted Facility, regardless of which products were covered on inspection"	**findings made during regulatory inspections of a Contracted Facility, regardless of which products were the subject of the inspection. In addition, in the event that the Contracted Facility becomes aware, either through internal processes or through an audit by another customer, of a condition at its site that may not comply with GMPs 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**.	the agency utilize consistent terminology. Specifically, it is recommended that the sentence be separate into two, distinct concepts, as proposed.
244	"… preventing cross-contamination and maintaining traceability when a Contracted Facility processes or tests drugs for multiple product Owners".	". . . prevent cross-contamination and maintaining 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 Contracted Facility must notify the Owner of any potential cross-contamination due to the production of certain products e.g. hormones, cytotoxics.**"	It is recommended that the phrase be revised for clarity. Specifically, Quality Agreements typically prohibit, restrict, or otherwise address the handling of hormones, cytotoxics, and other potent ingredients; however, they often do not include provisions on how parties will communicate the information.
264-267	Additionally, the Quality Agreement should allocate responsibilities between the parties for storing materials under labelled conditions, including maintenance of required storage conditions until material transfer from one party to the next (whether	Additionally, the Quality Agreement should allocate responsibilities between the parties for storing **and transport** of materials under labelled conditions, including maintenance of required storage **and transport/shipping** conditions until material transfer from one party to the next	The agreement must define shipping conditions as these can vary from storage conditions. Also, if shipping conditions are not explicitly stated, there is room for interpretation.

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	from Contracted Facility back to the Owner or to another Contracted Facility for further operations).	(whether from Contracted Facility back to the Owner or to another Contracted Facility for further operations). **Responsibilities for monitoring or validating shipping conditions should be defined.**	
283-285	Owners of application products should evaluate any application commitments that bear upon CGMP activities and consider sharing relevant information necessary for the Contracted Facility to comply with CGMP and the Act.	Owners of application products should evaluate **what information will be provided to the Contracted Facility to ensure the Contracted Facility is in compliance with applicable application commitments, with any relevant sections of the market authorization, and is aware of any subsequent changes.**	The issue is not the Contracted Facility being in compliance with CGMP or the Act (this is understood throughout). The issue is being in compliance with the Market Authorization (MA), which means the Contracted Facility needs to know exactly what is in the MA and be aware of all changes thereto.
289-291	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 (see 21 CFR 211.22(b)).	**The Owner should ensure the Contracted Facility or any party contracted to perform testing has** adequate laboratory facilities available to them for testing and approval (or rejection) of drug products (see 21 CFR 211.22(b)).	The phrase "each participating party" may indicate that both the Owner and the Contracted Facility will have equally capable, redundant laboratory facilities. This language may create a challenge within the industry to comply if this is interpreted as redundant facilities. In many cases, the reason for contracting with the external laboratory is to access capabilities that may not exist internally.
302	"… for stability and reserve samples, the Quality Agreement should delineate the frequency of testing and timely communication of the results."	"… 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. The Quality Agreement should specify timely communication of the results**."	Details of stability testing should be covered in a mutually agreed upon protocol, rather than be specified in a quality agreement. Language in the Quality Agreement can refer to a mutually agreed protocol for stability testing.

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303-304	The parties should also indicate who will be responsible for investigating deviations, discrepancies, failures, and out-of-specification results in the laboratory.	The parties should also indicate who will be responsible for investigating and approving deviations, discrepancies, failures, and out-of-specification results in the laboratory, **and any associated timeframe requirements**.	Added timeframe requirement because this can be a large point of contention between parties and timely resolution is an agency expectation.
310	The Quality Agreement should indicate procedures for the Owner to review and approve documents and any changes thereto, such as standard operating procedures, manufacturing records, specifications, laboratory records, validation documentation, investigations records, annual reports and any other documents/records related to the product manufactured or services provided by the Contracted Facility.	The Quality Agreement should indicate **what the Owner should review and approve. The rationale and risk assessment for those changes thereto**, such as standard operating procedures, manufacturing records, specifications, laboratory records, validation documentation, investigations records, annual reports and any other documents/records related to the product manufactured or services should be provided by the Contracted Facility.	This is a very broad statement and implies that the Owner would need to sign and approve any document that could (in any way) be related to their product or the services the Contracted Facility provides.
319-320	…stored in such a manner as to maintain their traceability, reliability, and integrity throughout the required record keeping timeframes established in applicable regulations.	…stored in such a manner as to maintain their traceability, reliability, and integrity. **Record keeping timeframes should be defined to ensure applicable regulations and the requirements of all parties are met.**	Add record keeping timeframes because as written, it appeared to pertain only to electronic records. Also, timeframes for each party may exceed applicable regulations and this will need to be defined.
322	This section is titled "Change Control, Including Subcontractors"	Contracted Facility must obtain approval from the Owner to subcontract any responsibilities they were originally contracted to perform. The quality requirements the subcontractor must meet should be agreed and defined within a quality agreement between parties.	There is no mention of subcontractors in the list of items to be addressed. Suggest adding strong wording for Owner approval of subcontracting. Further, we suggest that verbiage is included to cover the requirements and expectations pertaining to the subcontractor of the

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			Contracted Facility, including a Quality Agreement.
327	The Contracted Facility should notify the Owner of changes, including but not limited to, raw…	**The parties should notify each other of changes**, including but not limited to, raw…	As written it assumes that only the Contracted Facility is making changes, however in many cases the Owner may make changes too. Communication about changes must be mutual across all involved parties.
329	The Contracted Facility should notify the Owner of changes, including but not limited to,...additional products brought into the line, train, or facility…"	The Contracted Facility should notify the Owner of changes, including but not limited to, ….additional **types of** products brought into the line, train, or facility…"	It is suggested that the quality agreement should include specific product classes that would indicate a change in the designation of the line, train or facility that would need notification. This potentially poses issues for confidentiality in which a site would have to identify all products manufactured at the facility. While this seems simple and important, it is not always achievable due to 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. The product types should be sufficient to provide the contract giver with appropriate details.
467	…quality, safety, and effectiveness of drug products.	… safety, ~~and~~ **effectiveness and availability** of drug products.	If procedures are clear the availability of the drug product is facilitated