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

Reference: FDA Draft Guidance Contract Manufacturing Arrangements for Drugs: Quality Agreements

Dear Sir/Madam,

PDA commends FDA on writing this guidance which highlights common gaps which have occurred in the past between CMOs and Owners and clearly points out many elements of current best industry practice. PDA suggests that FDA further emphasize in this guidance, the importance of establishing a collaborative relationship between the parties in addition to clearly assigning and defining the appropriate responsibilities.

In some instances the guidance appears to be asking that the Quality Agreement include listings of parts of the CMO's quality system. We recommend clarifying that the intent is for the Quality Agreement to assign responsibilities to parties by general categories rather than a restatement of individual GMP elements. PDA also recommends against requiring specific procedures to be included in the Quality Agreement since such an approach might inhibit the effective functioning of either party's quality system with respect to continual improvement.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in pharmaceutical manufacturing including members representing our Board of Directors and our Regulatory Affairs and Quality Advisory Board.

If there are any questions, please do not hesitate to contact me.

Sincerely,

Richard Levy
Senior Vice President, PDA Scientific and Regulatory Affairs

General Comments

1. Collaboration and Communication	PDA commends FDA on writing this guidance which highlights common gaps which have occurred in the past between ~~CMOs~~ Contract Givers and ~~Owners~~ Contract Acceptors and clearly points out many elements of current best industry practice. PDA suggests that FDA add emphasis in this guidance on the importance of establishing a collaborative relationship between the parties in addition to clearly defining the appropriate responsibilities.
2. Level of Detail Prescribed for Quality Agreements	In some instances the guidance appears to be asking that the Quality Agreement include lists of parts of the ~~CMO's~~ Contract Acceptor's quality system. We recommend this guidance provide for the Quality Agreement to assign responsibilities to parties by general categories rather than through a restatement of each individual GMP element. PDA also recommends against requiring specific procedures be included in the Quality Agreement as that limits the ability of either party to revise those procedures when necessary. Please refer to suggested text modifications in the detailed comments below. (lines 252-255, 261-264, and 273-277, 310, and 327).
3. Terminology	PDA suggests that the document be aligned with ICH terminology, specifically Q10 which uses "C~~c~~ontract G~~g~~iver" and "C~~c~~ontract A~~a~~cceptor." The term "Owner" seems to imply ownership of the NDA or ANDA. In complex business arrangements, the contract giver might not be the owner of the product or the holder of the application. A Quality Agreement is needed between a manufacturer and a subcontracted laboratory even if neither party is the NDA holder. PDA suggests terms may be further clarified in a glossary.
4. Quality Agreements and Audits	A initial quality system audit of the ~~CMO~~ Contract Acceptor should precede the signing of a Quality Agreement. During this audit, the ~~owner~~ Contract Giver is responsible for verifying and accepting (or rejecting) the ~~CMO's~~ Contract Acceptor's quality system and the ability of the ~~CMO~~ Contract Acceptor to meet GMPs. With this approach, the purpose of the Quality Agreement should then be limited to defining the roles and responsibilities for the specific product(s) processes and activities covered by the agreement. The Quality Agreement should also address responsibilities of each party in subsequent audits such as how to schedule, notice, response and corrective actions

5. Communication Related Topics	PDA proposes moving all matters related to the communication plan to a single section. The plan should address how adverse events, complaints, recalls, field alerts, and biological product deviation reports are relayed by the ~~Owner~~ Contract Giver to the ~~CMO~~ Contract Acceptor in a timely manner, and how, by whom, and in what time frame they are handled. (PDA suggests moving lines 331-345 to after 185-188 for continuity to Line 190)
6. Scope	Since it is common for virtual companies to use ~~CMOs~~ contracted parties in all phases of development, it would be valuable if the guidance could be extended to include manufacture of clinical trial materials. The footnote #2 might be revised as follows: For purposes of this guidance, while the term commercial manufacturing does not include research and development activities or the manufacture of material for clinical trials or treatment Investigational New Drugs (INDs), or for veterinary investigational files (INADs or JINADs), the principles and concepts outline herein could be applied and it would be a best practice to have a quality agreement in place for these drugs prior to start of manufacture of any drug intended for human or animal use.

Specific Comments on the Text
PDA 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
75-76	Additionally, drug products may be deemed misbranded under a variety of provisions (section 502 of the FD&C Act (21 U.S.C. 352)	Additionally, drug products may be deemed misbranded under a variety of provisions [section 502 of the FD&C Act (21 U.S.C. 352) **and section 351 of the PHS Act and the regulations under 21 CFR 600.3 (t)]**	For completeness, PDA suggests referencing the statutory requirements for biologicals, where "manufacturer" includes any person or legal entity who is an applicant for a license, and assumes responsibility for compliance with the applicable product and establishment standards.
121-122	All parties performing manufacturing operations should monitor incoming ingredients and materials to ensure they are from approved	Add the following at the end of the sentence: **The Quality Agreement should assign responsibility for specific activities to one or the other party.**	"all parties should" – indicates shared responsibilities. The agreement should assign responsibility to one or the other party.

	sources using the agreed supply chain.		
186	Explains how manufacturing deviations will be relayed	Explains how ~~**manufacturing**~~ deviations will be communicated.	PDA suggests for clarity that all types of deviations need to be communicated not just manufacturing deviations.
209-213	The section that addresses Quality Unit responsibilities may be termed…. 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 section that addresses**~~ Quality Unit responsibilities may be termed … 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 ….	Quality Unit responsibilities recur throughout every section of a Quality 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 QA.
252-255	The parties should indicate which party will be responsible… to perform the contracted manufacturing operations.	Add at the end of the sentence: **It is acceptable to assign one party general responsibility for a category of activities rather than including an exhaustive list. For example, the CMO, offering the facilities, equipment and utilities is responsible for these being validated/qualified, maintained and calibrated.**	The Quality Agreement is not required to include a complete detailed list of all responsibilities; however the roles of each party should be clear. Refer to general comment #2 above

261-264	The Quality Agreement should … including procedures for labeling, label printing, and reconciliation, as well as procedures for quarantine …	The Quality Agreement should also address how the parties are to ensure appropriate inventory management, **for example ~~procedures for~~** labeling, label printing, and reconciliation, as well as ~~procedure~~s **the approach** for quarantine and prevention of mix-ups and cross-contamination.	PDA does not recommend including procedures in the Quality Agreement. Refer to general comment #2 above.
273 - 277	Regardless, this section of the quality agreement should include product/component specifications…	**..should address and assign responsibilities between the parties for** product/component specifications…	See general comment #2.
290	The Quality Unit of each participating party…should have adequate laboratory facilities available to them…	The Quality Unit of each participating party…should ~~have~~ **ensure the availability of** adequate laboratory facilities **and have** available to them **upon request any necessary data generated by contract acceptor** …	The phrase "each participating party" seems to imply that both the ~~Owner~~ Contract Giver and the ~~Contracted Facility~~Contrac Acceptor will have equally capable, redundant laboratory facilities and will conduct redundant testing and approval.
310	The Quality Agreement should indicate procedures for the Owner to review and approve documents and any changes ….	The Quality Agreement should **assign responsibilities between the CMO and** the Owner for review and approval of relevant documents and any changes thereto…	See general comment #2.
327	The Contracted Facility should notify the Owner of changes, including but not limited to, raw materials…	The **parties should notify each other** of changes **which have the potential to impact the outsourced activity e.g**. raw materials…	As written it seems only the ~~CMO~~ Contract Acceptor is making changes, but in many cases the ~~Owner~~ Contract Giver makes changes too. Since some of the elements of this list may not be relevant for all operations, PDA suggests changing "including" to "e.g."
341-45	Some changes may be deemed to present lower risk to product quality and may not necessitate	Some changes may be deemed to present lower risk to product quality and may not necessitate notification at all, but **the types**	PDA agrees that change control is critical and that the ~~owner~~ Contract Giver may have a different risk tolerance than the ~~CMO~~Contract Acceptor. It is

	notification at all, but those should be carefully considered by the Owner and clearly set forth in the Quality Agreement.	**of changes** should be carefully considered by the Owner and clearly set forth in the Quality Agreement.	important to agree upon the **types** of changes that will be reported by either side because a list cannot be inclusive. The key is agreement and communication between the parties.