ANIMAL HEALTH INSTITUTE
Representing manufacturers of animal health products

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Division of Dockets Management (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Re: Docket No. FDA–2013–D–0558; Draft Guidance for Industry on Contract Manufacturing Arrangements for Drugs: Quality Agreements; Availability

The ANIMAL HEALTH INSTITUTE ("AHI") submits these comments to Docket No. FDA–2013–D–0558; Draft Guidance for Industry on Contract Manufacturing Arrangements for Drugs: Quality Agreements; Availability**.** AHI is the national trade association representing manufacturers of animal health products -- the pharmaceuticals, biological products and feed additives used in modern food production, and the medicines that keep livestock and pets healthy. AHI member companies represent the majority of animal pharmaceuticals and animal insecticides, as well as serving a significant segment of the world market. As such, we have a tremendous interest in the regulation of Quality Agreements.

AHI offers a general comment about the necessity of the draft guidance. This draft guidance offers too much detail and should be at higher level to ensure cGMP's are followed by Contracted Facilities and the responsibility falls ultimately back to the sponsor (Owner). FDA's Center for Veterinary Medicine (CVM) should point to existing cGMP and existing guidance for specific detail.

Additional, specific recommendations, comments and questions on the draft are provided in the attached table.

Thank you in advance for your consideration of these comments. Should you have any questions, please do not hesitate to contact AHI at (202) 637-2440.

Sincerely,

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				Document: Draft Guidance for Industry on Contract Manufacturing Arrangements for Drugs: Quality Agreements
Commenter	**Page No.**	**Line(s)**	**Current Text**	**Recommendations/Comments/Questions**
AHI	Page 4	Lines 119-120	• Owners should monitor and review the performance of the Contracted Facility and identify and implement any needed improvements.	AHI Comment: We are not sure how the Owner can implement needed improvements at the Contracted Facility. We may request these improvements, but not implement them.
AHI	Page 5	Line 178	• Dispute Resolution	AHI Comment: Dispute resolution is mostly covered in the business/manufacturing agreement.
AHI	Page 6	Lines 194-205	*1. Responsibilities* Owners and Contracted Facilities may opt to document the specific terms of their Quality Agreements with respect to CGMP responsibilities in a wide variety of formats, such as charts, matrices, or narratives, or a combination of these. Regardless of the format, however, each Quality Agreement should clearly document which party is responsible for CGMP activities relevant to the particular services or operations covered by the Quality Agreement. The Quality Agreement should cover any and all CGMP responsibilities relevant to the scope of the agreement. Depending on the scope of the services to be provided under the contract manufacturing arrangement, the Quality Agreement should indicate whether the Owner or Contracted Facility (or both) will handle specific activities related to each of the following topics:	AHI Comment: These responsibilities seem to fall squarely with the Contracted Facility. The Owner needs to ensure the Contracted Facility is handling the activities it is responsible for, but this is why they audit and evaluate Contracted Facilities.

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AHI	Page 6	Lines 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)).[11]	AHI Comment/Recommendation: This is an interesting use of wording. In many markets outside of the US, the Owner maintains 'responsibility' for final release but doesn't actually 'carry it out'. AHI recommends changing the wording from: *"…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)).[11]"* to: *"…final product release of finished goods is performed by the Contracted Facility, and the Owner is fully responsible for the release of the final product into distribution.*" To reiterate the comment above, we do not actually do a 'release' (we do delegate it), but clearly we retain responsibility.
AHI	Page 7	Lines 239-243	Because Contracted Facilities often simultaneously or sequentially provide services to multiple product Owners, 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.	AHI Recommendation: AHI recommends deleting this sentence as it is not clear what the intent of the statement is, therefore it adds no value.
AHI	Page 7	Lines 247-255	b. Facilities and equipment This section of a Quality Agreement should identify the specific site(s) at which manufacturing operations will be performed along with addresses and the particular services to be provided at each. The parties should indicate which party will be responsible for carrying out validation, qualification, and maintenance activities for any relevant equipment or equipment systems, such as information technology and automated control systems, environmental monitoring and room classification, utilities, and any other equipment and facilities that must be maintained to perform the contracted manufacturing operations.	AHI Comment: These are the responsibilities of the Contracted Facility, but these lines are specific to laboratory. Some level of this detail is not necessary. The Owner indicates in the Quality Agreements that the Contracted Facilities must follow the GMPs, and these are all elements of the GMPs, therefore there is no reason to list this specific level of detail.

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AHI	Page 7	Lines 271- 278	A comprehensive Quality Agreement will provide specific terms related to the particular product or products involved. The Owner and Contracted Facility might opt to include this information in an appendix, or directly in the body of the Quality Agreement. 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.	AHI Comment: This section requires too much detail to be documented. The Quality Agreement requires compliance with the regulatory dossiers but does not need to append the manufacturing instructions. Those are in the NADA, and the Quality Agreement only needs to reference compliance to those regulatory files and a commitment to provide the required regulatory information to the Contracted Facility. Further, there is too much detail around validation. Validation includes all the qualifications and the GMPs require the contract manufacturer to be guided by the FDA validation guidance document…so design qualification, ongoing monitoring, those need not be singled out here.
AHI	Page 8	Lines 280-285	The Quality Agreement should also indicate how Owners of both application and non-application drug products will transfer knowledge—e.g., product/process development information -- to their Contracted Facilities to assure a quality product can be produced in compliance with CGMP. 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.	AHI Recommendation: AHI recommends removing the following text: *"…to their Contracted Facilities to assure a quality product can be produced in compliance with CGMP. 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."* These recommendations could compromise confidentiality for either the sponsor or the Contracted Facility.

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AHI	Page 8	Lines 287-304	e. Laboratory controls 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)). Quality laboratory operations performed by any party in relation to a finished pharmaceutical should be performed in accordance to with CGMP at each site with which the applicable laboratory operations occur. Procedures delineating controls over sampling and testing samples should be established in the Quality Agreement. Both the Owner and Contract Laboratory should be responsible for ensuring that the methods used are validated and have been transferred appropriately (if the development, qualification, and validation have not been done on site). Laboratory equipment used to perform CGMP operations should be qualified, calibrated, and maintained in a controlled state with the primary responsibility resting on the Contract Laboratory; however, the Owner should ensure that the Contract Laboratory is functioning in accordance to with CGMP through routine auditing. If the Owner uses Contracted Facilities for the storage and routine testing for stability and reserve samples, the Quality Agreement should delineate the frequency of testing and timely communication of the results. The parties should also indicate who will be responsible for investigating deviations, discrepancies, failures, and out-of-specification results in the laboratory.	AHI Recommendation: AHI recommends removing the following strikethrough text: *e. Laboratory controls* ~~*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)). Quality laboratory operations performed by any party in relation to a finished pharmaceutical should be performed in accordance to with CGMP at each site with which the applicable laboratory operations occur. Procedures delineating controls over sampling and testing samples should be established in the Quality Agreement.*~~ *Both the Owner and Contract Laboratory should be responsible for ensuring that the methods used are validated and have been transferred appropriately (if the development, qualification, and validation have not been done on site).* ~~*Laboratory equipment used to perform CGMP operations should be qualified, calibrated, and maintained in a controlled state with the primary responsibility resting on the Contract Laboratory; however, the Owner should ensure that the Contract Laboratory is functioning in accordance to with CGMP through routine auditing.*~~ *If the Owner uses Contracted Facilities for the storage and routine testing for stability and reserve samples, the Quality Agreement should delineate the frequency of testing and timely communication of the results. The parties should also indicate who will be responsible for investigating deviations, discrepancies, failures, and out-of-specification results in the laboratory.* AHI Recommendation: At the very least, if the text cannot be removed, we recommend changing Line 292 to "*finished pharmaceutical* ***must*** *be performed in accordance to with CGMP…*"

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AHI	Page 8	Lines 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)).	AHI Comment: This implies that the Owner needs to have laboratory facilities, which is often not the case and not necessary. Each participating party does not need adequate laboratory facilities, as there is only the one party doing laboratory testing.
AHI	Page 8	Lines 297-300	Laboratory equipment used to perform CGMP operations should be qualified, calibrated, and maintained in a controlled state with the primary responsibility resting on the Contract Laboratory; however, the Owner should ensure that the Contract Laboratory is functioning in accordance to with CGMP through routine auditing.	AHI Comment: An audit does not assure continual CGMP compliance.
AHI	Page 8	Lines 300-302	If the Owner uses Contracted Facilities for the storage and routine testing for stability and reserve samples, the Quality Agreement should delineate the frequency of testing and timely communication of the results.	AHI Comment: Test frequencies are too much detail to include in the Quality Agreement; it should just state that a protocol will be prepared and approved by the contractor and Owner.
AHI	Page 8	Lines 310-314	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, investigation records, annual reports, and any other documents/records related to the product manufactured or services provided by the Contracted Facility.	AHI Comment: Standard Operating Procedures are normally not approved by the Owner. Additionally, the Owner never gets to sign off on validation documents related to common facility / equipment such as pharmaceutical water or multiple use production tanks. The Owner also will not sign off on laboratory records. They are reviewed and approved by the Contracted Facility under their GMP responsibilities.

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AHI	Page 9	Lines 327-337	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 brought into the line, train, or facility: testing procedures: major manufacturing equipment: shipping methods; lot numbering scheme: container closure systems; tamper evidence features: key personnel; and product discontinuation. 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 reports.	AHI Question: Please clarify; the following text seems to indicate that the Contracted Facility (CF) should inform the Owner of all products they are manufacturing in the facility and when they are discontinued: *"**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 brought into the line, train, or facility:** testing procedures: major manufacturing equipment: shipping methods; lot numbering scheme: container closure systems; tamper evidence features: key personnel; **and product discontinuation**."* From experience, the product list of a CF is not routinely disclosed and is generally considered confidential. Maybe the intent is not to reveal what is produced rather than reveal any changes. If this is the case it should be expressed accordingly. AHI Comment: Regarding Line 329: *"…additional products brought into the line, train, or facility..."* As Owners we would request this; however, Contract Facilities may have different ways to manage additions to their facility. This kind of notification may not be explicit, for instance it could be included in a cleaning validation plan; and details of the products will likely be high level at best due to confidentiality agreements. This is too much detail. Notification of any and all changes that have a potential to impact the quality or regulatory compliance of the product should be sufficient.

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AHI	Pages 9-11	Lines 348-456	V. Illustrative Scenarios	AHI Recommendation: AHI recommends the case studies reflect problems specifically related to not having a Quality Agreement in place and not to deviations from the GMP regulations. In several instances the examples mention that the Quality Agreement is irrelevant because the facility was in violation of the CFR. An example for a pertinent case study would be as follows: *"A Contracted Facility making an API becomes aware (by some means, maybe a Quality Agreement) that a non-GMP starting material vendor has tweaked the manufacturing process to improve yield. The material still meets incoming acceptance criteria (no use testing performed), but the method did not pick up the formation of low levels of a new impurity that forms as a result of the "tweak"; the impurity subsequently reacts with the API penultimate starting material to yield a new impurity in the API, which is not rejected well during purification and happens to fall above the VICH threshold for ID. The Owner was never informed of the tweak and there was no use testing required because it was not covered in a Quality Agreement with the Contracted Facility. In this case, there are no deviations from GMPs, but a Quality Agreement could have avoided the hassle of having to deal with another impurity."*
AHI	Pages 9-10	Line 372-374	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.	AHI Recommendation: There seems to be a typo. We recommend to delete *'but'* and leave in *'and'.*
AHI	Page 11	Lines 460-461	Written Quality Agreements are not explicitly required under existing CGMP regulations and do not relieve either party of their responsibilities under CGMP regulationss or under the Act.	AHI Recommendation: There seems to be a typo. We recommend removing the extra *'s'* from *'regulationss'*.