

# Client Alert

May 2013

## FDA Issues Draft Guidance Recommending Utilization of Robust Quality Agreements in Contract Drug Manufacturing Arrangements

On May 28, 2013, the US Food and Drug Administration (FDA) published a draft guidance entitled “Contract Manufacturing Arrangements for Drugs: Quality Agreements.”<sup>1</sup> The draft guidance describes FDA’s views on defining, establishing and documenting the responsibilities of parties that are involved in the contract manufacturing of drugs that are subject to current good manufacturing practice (cGMP) requirements. In the draft guidance, FDA recommends that such parties — referred to by the draft guidance as “Owners” and “Contracted Facilities” — utilize quality agreements to assure drug quality, safety and efficacy. To be considered for any final version of the guidance, comments should be submitted by July 29, 2013.<sup>2</sup>

### Background

Companies that introduce drugs into interstate commerce are responsible for ensuring that they are not adulterated or misbranded, irrespective of whether the company itself manufactures the drugs or the drugs are manufactured by a contract manufacturing organization (CMO).<sup>3</sup> This requirement arises initially from the new drug application (NDA) approval process. Among other things, an NDA for a new drug must include “a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packaging of such drug.”<sup>4</sup> This means that an NDA must include “the name and address of each manufacturer of the drug product,” including “each contract facility involved in the manufacture, processing, packaging, or testing of the drug product and identification of the operation performed by each contract facility.”<sup>5</sup> FDA’s approval of an NDA is premised in part on the agency’s determination that the “methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product ... comply with the current good manufacturing practice regulations.”<sup>6</sup> If the drug is not manufactured by the CMO in a manner that

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<sup>1</sup> FDA, Draft Guidance for Industry, *Contract Manufacturing Arrangements for Drugs: Quality Agreements* (May 2013), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm> [hereinafter *Draft Guidance*].

<sup>2</sup> FDA, Notice, *Draft Guidance for Industry on Contract Manufacturing Arrangements for Drugs: Quality Agreements; Availability*, 78 Fed. Reg. 31,943, 31,943 (May 28, 2013).

<sup>3</sup> See Federal Food, Drug, and Cosmetic Act (FD&C Act) § 301(a). The draft guidance emphasizes that “[b]ecause the Agency considers contractors an ‘extension of the manufacturer’s own facility,’ both Owners and Contracted Facilities are responsible for ensuring that their products are not adulterated or misbranded.” *Draft Guidance* § III.A.

<sup>4</sup> FD&C Act § 505(b)(1)(D).

<sup>5</sup> 21 C.F.R. § 314.50(d)(1)(ii)(a)-(b).

<sup>6</sup> *Id.* § 314.125(b)(13). To inform this determination, FDA may conduct a preapproval inspection of the manufacturing facility (including any CMO facility) where, according to the NDA, the drug is to be manufactured. See *id.* § 314.125(b)(12).

ensures and preserves the drug's identity, strength, quality and purity, then FDA may withdraw its approval of the NDA.<sup>7</sup>

Other provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) require that drug companies work "to establish and maintain quality oversight of contracted manufacturing operations and the materials produced under contracted manufacturing arrangements."<sup>8</sup> Under Section 501(a)(2)(B) of the FD&C Act, a drug is deemed to be adulterated if

the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with *current good manufacturing practice* to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

The most recent amendment to the FD&C Act states that, for purposes of Section 501(a)(2)(B), "current good manufacturing practice" means "the implementation of *oversight and controls* over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products."<sup>9</sup> Thus, under the FD&C Act, a drug company that uses a CMO to manufacture its drugs may itself violate cGMPs if the company fails to conduct adequate oversight of and establish effective controls over the CMO to assure that CMO complies with cGMPs.<sup>10</sup>

### **The Draft Guidance**

The draft guidance emphasizes that drug companies should mitigate the risk associated with outsourcing the manufacturing of their drugs by entering into robust quality agreements with their CMOs. In the draft guidance, FDA acknowledges that "the CGMP regulations do not explicitly require Owners and Contracted Facilities to document their respective responsibilities in contract manufacturing arrangements," but then states (1) that cGMP regulations "require that Quality Unit responsibilities and procedures be in writing" and (2) that "implementing a written Quality Agreement facilitates compliance" with this cGMP requirement.<sup>11</sup> It seems likely, therefore, that the practical effect of FDA's current thinking is that the agency, in most circumstances, will view the absence of a quality agreement — or the absence of an adequate quality agreement — to be tantamount to a violation of cGMPs.<sup>12</sup>

After emphasizing that drug companies should utilize quality agreements in their arrangements with CMOs, the draft guidance describes in detail the elements of a robust quality agreement. According to

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<sup>7</sup> See *id.* § 314.150(b)(2).

<sup>8</sup> *Draft Guidance* § III.A.

<sup>9</sup> FD&C Act § 501 (emphasis added), amended by Food and Drug Administration Safety and Innovation Act, Pub. L. 112-144, tit. VII, § 711 (2012); see also *Draft Guidance* § III.A..

<sup>10</sup> Cf. Warning Letter from Paul J. Teitell, District Director, Cincinnati District, FDA, to Charles J. Kubicki, Owner, Pristine Bay, LLC d/b/a Vianda (Apr. 26, 2013) (stating that "a firm that contracts with other firms to conduct certain dietary supplement manufacturing, packaging, and labeling operations for it is responsible for ensuring that the dietary supplement is not adulterated for failure to comply with dietary supplement CGMP requirements, regardless of who actually performs the dietary supplement CGMP operations"); Warning Letter from Kirk Sooter, District Director, Philadelphia District, FDA, to Judy A. Hannan, President, Entrenet Nutritionals, Inc. (May 8, 2013) (stating that dietary supplement company cannot "contract out its ultimate responsibility to ensure that the dietary supplement it places into commerce ... is not adulterated for failure to comply with dietary supplement CGMP requirements").

<sup>11</sup> *Draft Guidance* § IV (citing 21 C.F.R. § 211.22(d)).

<sup>12</sup> See *id.* § IV.A (stating that during inspections "FDA routinely requests and reviews evidence of Quality Agreements (or the lack of Quality Agreements)").

FDA, a quality agreement “is a comprehensive written agreement that defines and establishes the obligations and responsibilities of the Quality Units of each of the parties involved in the contract manufacturing of drugs subject to CGMP.”<sup>13</sup> As for its elements, a quality agreement “should track the basic subparts of the CGMP regulations ... to ensure coverage of all applicable CGMP responsibilities.”<sup>14</sup> Accordingly, most quality agreements will contain the following sections:

- Purpose/scope.
- Terms (including effective date and termination clause).
- Dispute resolution.
- Responsibilities, including communication mechanisms and contacts.
- Change control and revisions.<sup>15</sup>

The draft guidance states that the “most critical elements” of a quality agreement are the sections covering (1) the responsibilities of the drug company and the CMO and (2) change control.

With regard to the “responsibilities” provisions of a quality agreement, the draft guidance discusses in detail the following:

- Quality Unit responsibilities: This section “should define in detail the CGMP responsibilities of each party .... In particular, this section ... should be clear with respect to **product release**. Owners are ultimately responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.”<sup>16</sup> In addition, this section should:
  - Establish “a **communication plan** regarding both verbal and written correspondence between the Owner and Contracted Facility.”
  - Provide “for Owners to **evaluate and audit** Contracted Facilities to ensure CGMP compliance.”
  - Institute procedures for responding to “**regulatory inspections** (e.g., pre-approval inspections, routine surveillance, or for-cause),” including outlining “the parties’ respective obligations on reporting inspectional observations and findings, as well as Agency actions.”<sup>17</sup>
- Facilities and equipment: This section should (1) “identify the **specific site(s)** at which manufacturing operations will be performed” and (2) “indicate which party will be responsible for carrying out validation, qualification, and maintenance activities for any relevant **equipment or equipment systems**.”<sup>18</sup>
- Materials management: This section “should indicate who is responsible for setting specifications for **raw materials**; auditing, qualifying, and monitoring **suppliers** of those materials; and conducting required **sampling and testing**.”<sup>19</sup>

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<sup>13</sup> *Id.* § IV.A.

<sup>14</sup> *Id.* § IV.B.

<sup>15</sup> *Id.*

<sup>16</sup> *Id.* § IV.B.1.a. (emphasis added); *see also id.* (stating that final product release of finished goods for distribution “cannot be delegated to a Contracted Facility under the CGMP regulations or any terms of the Quality Agreement”).

<sup>17</sup> *Id.* (emphases added).

<sup>18</sup> *Id.* § IV.B.1.b. (emphases added).

<sup>19</sup> *Id.* § IV.B.1.c. (emphases added).

- Product-specific terms: This section should “provide **specific terms** related to the particular product or products involved,” including:
  - 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.
  - Provisions for drug company personnel (“person in the plan”) in the CMO’s facility.<sup>20</sup>
- Laboratory controls: This section should address the “adequate **laboratory facilities**” that each of the Quality Units of the parties to the quality agreement should have “available to them for testing and approval (or rejection) of drug products” and include “[p]rocedures delineating controls over sampling and testing samples.”<sup>21</sup>
- Documentation: This section “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.” It also should “specify how records and documentation required by the applicable CGMP regulations will be made available for immediate retrieval, and how copies will be made and maintained under a certification or controlled copy procedure.”<sup>22</sup>

With regard to change control, the draft guidance states that “[c]hanges may be initiated by either party for many reasons and should be discussed and addressed in the Quality Agreement.”<sup>23</sup> In particular, quality agreements should provide that the CMO must provide to the company for which it is manufacturing drugs notice of changes related 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.
- Product discontinuations.

Likewise, quality agreements should require each party to the contract manufacturing arrangement to notify the other of the following events that may initiate changes:

- Investigations into manufacturing deviations and out-of-specification results.

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<sup>20</sup> *Id.* § IV.B.1.d. (emphases added).

<sup>21</sup> *Id.* § IV.B.1.e. (emphases added).

<sup>22</sup> *Id.* § IV.B.1.f. (emphases added).

<sup>23</sup> *Id.* § IV.B.2.

- 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.
- Adverse event reports.

Finally, quality agreements should identify “the types of changes for which Owner review and approval must be obtained before implementation and those changes that can be implemented with notification only.”<sup>24</sup>

### **Illustrative Scenarios**

The draft guidance concludes by providing “hypothetical scenarios” that illustrate some common problems in contract manufacturing arrangements — and FDA’s “thinking regarding possible resolution of the problems.”<sup>25</sup> The lessons of the illustrative scenarios are twofold and can be summarized as follows:

1. Quality agreements do not exempt CMOs from cGMP requirements related to the operations they perform, regardless of whether the quality agreement specifically discusses those cGMP requirements.
2. Drug companies are not relieved of their responsibility to ensure the quality and safety of the drugs they introduce into the marketplace simply because a quality agreement allocates responsibility for a particular activity to the CMO.

Notwithstanding these lessons, drug companies and CMOs should “implement written Quality Agreements as a tool to delineate responsibilities and assure the quality, safety, and effectiveness of drug products.”<sup>26</sup>

### **How We Can Help**

Hunton & Williams’ food and drug practice has extensive experience advising clients on drug manufacturing matters. If you need assistance negotiating and drafting quality agreements or have questions about current good manufacturing practice requirements, please contact us.

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<sup>24</sup> *Id.*

<sup>25</sup> *Id.* § V.

<sup>26</sup> *Id.*