VIRTUAL QUALITY ASSURANCE: SPONSOR RESPONSIBILITIES

Robbi Freisem

About The Author

Ms. Freisem is a subject matter expert in GXP Quality Assurance providing our clients with an effective CMC quality system management through drafting individual standard operating procedures. Her technical background is in drug substance manufacturing, small molecule and biologic API's, sterile manufacturing, plant design, and technology transfer. She is a proficient negotiator of Quality Agreement and coordinating regulatory interactions with a CMO. Her capabilities include investigation remediation, lot release oversight, inspection preparation assistance, and site inspections providing extensive knowledge of ISO and cGMP requirements.

Today's drug development business model relies heavily on outsourcing. There is a tendency for small, 'virtual' pharmaceutical companies to rely solely upon the quality control/quality assurance (QC/QA) units within third party contract manufacturing organizations (CMOs) to perform the quality functions.

While many CMOs have well-functioning QA operations, there are several recent examples where Drug Product Sponsors, in addition to the CMOs, have received warning and even cease and desist letters from the FDA and/or EMEA.

When a CMO fails to provide compliant cGMP operations, it can have potentially devastating consequences; including, the injunction of clinical materials, withholding approval of requests for export certificates, and/or approval of pending drug applications listing the facility. For product development companies operating on aggressive clinical timelines with limited resources any of these consequences could disrupt/end a clinical program and damage a company's business interests

As the holder of the IND, NDA, BLA or ANDA, the Sponsor is responsible; regardless of who actually manufactures the drug or any contract, supply agreement or quality agreement that is signed by the CMO.

Consider the following case:
The FDA Warning Letter 10-ALT-15, to the President of River's Edge Pharmaceuticals, LLC dated May 20, 2010. River's Edge is the Sponsor of the Drug Product, and FDA describes River's Edge as "an own-label distributor that has entered into agreements with contract manufacturers to manufacture all products."

The FDA letter then cites them for significant cGMP violations; including:

1. The failure to establish "scientifically sound and appropriate specifications, standards, sampling plans, and test procedures" [21 C.F.R. § 211.160(b)]
2. The failure to fulfill "its responsibility to approve or reject all procedures or specifications impacting on the identity, strength, quality and purity of the drug product" [21 C.F.R. § 211.22(c)].
3. "Your quality control unit has not fulfilled its responsibility nor exercised its authority to approve or reject all drug products manufactured, processed, packed, or held under contract by another company [21 C.F.R. § 211.22(a)]." The final sentence of this section specifically states this requirement as the responsibility of the Sponsor's quality control unit.

The cGMP Violations portion of the FDA Warning Letter concludes:
"... [W]e are concerned about your firm's fundamental understanding of what is required by your [quality control unit] and the regulatory expectations for a firm

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that enters into agreements with contract manufacturers to manufacture all drug products. Although you have agreements with other firms that may delineate specific responsibilities to each party (e.g., quality control responsibilities), you are ultimately responsible for the quality of your products. Regardless of who manufactures your products or the agreements in place, you are required to ensure that these products meet predefined specifications prior to distribution and are manufactured in accordance with the [Federal Food, Drug, and Cosmetic] Act and its implementing regulations, including CGMP regulations..."

So how can a virtual company establish a basic Quality unit that fulfills cGMP requirements?

Establish three components within your organization:

1. A basic set of policies and Standard Operating Procedures (SOPs) for directing the Sponsor responsibilities for oversight.
2. A system to document changes made to any policies, procedures, protocols, specifications, Quality Agreements and other regulated activities.
3. Sponsor Quality Assurance review of both records, test methods and validations, product specifications, and other activities related to the oversight of drug manufacture and control independent of the contractor.

Virtual companies can fulfill these responsibilities using a Quality Assurance consultant as long as that individual is independent of the CMO and has the authority to reject nonconforming batches.

Even during clinical phases of drug development the holder of the IND is responsible for the quality and safety of the drug product. The Quality unit of the CMO does not hold the ultimate responsibility for conformance of study drug.

Contact Us

DS InPharmatics LLC
P.O. Box 532
Harleysville, PA 19438

Tel: 1-855-805-8402
Fax: 1-800-934-5753
Email: solutions@dsinpharmatics.com

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