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GXP Talk Questions 75 and 76

By **Jerry Lanese and Timothy J. Fields, editors** **Nov 21, 2016 10:18 am PST**

CONTRACTOR DEVIATIONS AND ANALYTICAL REFERENCE STANDARDS

"GXP Talk" provides a forum for compliance practitioners to address issues **identified by the readers of the** ***Journal of GXP Compliance.***

"GXP Talk" is the longest-running continuing series in the Journal of GXP Compliance. A total of 76 questions on GXP topics have been discussed including questions #75-76 discussed in this issue. Previous discussions addressed a wide range of compliance activities covering essentially all sections of the US GMPs. Responses to questions and associated opinions have been contributed by representatives from multiple pharmaceutical industry and regulatory agencies. In the current format, questions and answers are presented together.

Readers are invited to participate and contribute questions, answers, and discussion for this series – please share your successful practices with others. This column succeeds when we are able to address current GXP issues submitted by interested readers. Please contact column coordinators ***Jerry Lanese*** *at jerry@lanesegroup.com or* ***Tim Fields*** *at timfields213@comcast.net with comments or submissions for publication. We welcome your questions and your opinions on questions.*

QUESTION 73
SHOULD CONTRACTOR DEVIATIONS/INVESTIGATIONS BE ENTERED INTO YOUR ORGANIZATION'S DEVIATION SYSTEM? IF THE CONTRACTOR IS NOT TRENDING DEVIATIONS/INVESTIGATIONS, WHO SHOULD?

Answer

The regular readers of this column will recognize that we have responded to similar questions that relate to contractor issues in the past. It is apparent that contractor relations and responsibilities are very important in this age of virtual organizations.

When an organization (contractee) engages with a contract manufacturer (contractor) it cannot assume that the contractor will perform all compliance-related tasks the organization and the regulators expect. The contractor may not understand the GMP environment or it may be trying to manufacture the product or material without appropriate supporting systems. There must be a document that spells out the responsibilities for each party. Typically this is not included in the business contract. Since the ultimate responsibility for assuring compliance related activities are completed lies with the organization's (contractee's) quality unit, the document is called the Quality Agreement. The Quality Agreement defines the delegation of GMP compliance-related responsibilities between an organization and its contractor.

This question focuses on a system that has been the source of a number of FDA observations – the deviation / investigation system. Who should be responsible for this system? It is important that deviations be identified, logged, and investigated. Appropriate corrective and / or preventive actions must then be implemented and verified. Since the contractor is close to the deviations and investigations, it is appropriate that it maintain the deviation / investigation system for the activities under its control. If the

contractor does not track deviations, investigations, and the resulting CAPAs, the organization (contractee) will have to do it. Wherever the responsibility lies, the roles and responsibilities and expectations for timeliness must be defined and agreed between parties. The appropriate place to document the contractee / contractor responsibilities for any system is the Quality Agreement.

What is also important, no matter who is responsible for the system, is the timely recording of the deviation, completion of the investigation and applicable CAPAs. and effective communication between the contractor and its customer.

QUESTION 74

IS IT APPROPRIATE TO QUALIFY A COMMERCIAL PRODUCT AS A HOUSE ANALYTICAL STANDARD AGAINST THE USP STANDARD AND USE THE HOUSE STANDARD AS PRIMARY/REFERENCE STANDARD?

Answer

The short answer to this question is “yes”. The use of secondary reference standards is a cost-saving practice often used by laboratories that perform a high volume of testing on a material for which high-quality commercial material and an established primary reference material are available. It is appropriate to consider the terminology used and ICH guidance on the topic.

ICH Q6A (1) states:

> *A reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test. It should have a quality appropriate to its use. It is often characterized and evaluated for its intended purpose by additional procedures, other than those use in routine testing.*

The question uses the terms USP standard, reference standard, primary standard, and house standard. The definition and use of this terminology should be clarified. As indicated in the ICH statement above, a reference standard is a substance that is prepared for use as the standard in a test. A primary reference standard is the best available for a chemical, microbiological, or physical characteristic. It is the standard on which all other standards of that material are based. In most cases, primary physical standards and some chemical primary standards are maintained by NIST (2)
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or other national standards agency. In the United States, the USP also maintains an inventory of primary standards used by the pharmaceutical industry. USP standards are primary standards for defined uses. The British Pharmacopoeia also maintains an inventory of chemical standards recognized as primary standards in Europe.

When a firm goes through the process of characterizing commercially available material against a USP primary standard for internal use as a standard, it creates its house standard. This standard may also be referred to as a secondary standard.

The ICH statement, above, states that the commercial material that will be characterized to be the house standard should have quality appropriate to its use. If the firm intends to use a commercial material as the house standard in place of a USP standard, it would not be appropriate to use a grade of the commercial material which is less than USP. The commercial material should be USP grade or better.

The minimum testing that should be performed on the proposed house standard is all of the compendial tests for the material found in the USP. The comparison test result should be within the USP specifications. The ICH statement above goes on to say that the material intended to be the house standard is characterized and evaluated for its intended purpose by additional procedures, other than those used in routine testing. It would also be appropriate to assay the candidate standard by a technique different from the compendial test. Additional impurity testing may be appropriate. Other tests should also be considered. The laboratory must be proactive and anticipate issues that may arise in its environment as it characterizes the candidate secondary standard against the USP primary standard.

REFERENCES

1.

ICH Q6A; Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances; ICH; 1999

2.

NIST; National Institute of Standards and Technology. A federal agency responsible for the maintenance of primary standards in the United States

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