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GXP Talk: Invitation to Participate

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Editor's Note:

The following summarizes a listing of questions and answers regarding GXP compliance issues published in "GXP Talk" in the Journal of GXP Compliance during the last 10+ years. Many of these questions addressed validation issues. Readers of the Journal of Validation Technology are also invited to submit questions to be addressed in this ongoing feature. Also see GXP Talk Question #77 in this journal addressing application of cleaning validation to laboratory equipment cleaning.

INTRODUCTION

"GXP Talk" provides a forum for discussion of compliance issues identified by readers of the Journal of GXP Compliance (JGXP).

"GXP Talk" is the longest running continuing series in JGXP. A total of 77 questions on GXP topics have currently been discussed since series introduction in 2006. See question #77 published in this issue. Previous discussions have 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 industries and regulatory agencies. In the current format, questions and answers are presented together.

Readers are invited to participate ad contribute questions, answers, and discussion for this series – please share your successful practices with other readers. 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, Rich Poska at richposka@gmail.com, or Melissa Carella at melissa.carella@cbinet.com with questions, comments, or submissions for publication. We welcome your input.

PAST QUESTIONS

GXP Talk has addressed a broad range of compliance questions in past publications. The following lists all previously published questions:

1. We are assessing our Annual Product Review Program. Who should read the Annual Product Review? What action is required? Published in the Journal of GXP Compliance (JGXP), Volume 10, #3, 2006.
2. We are a medical device firm and, therefore, subject to 21 CFR 820. We are also registered to ISO 9000. Both the regulation and the standard require an audit program. Can the requirement for both be

satisfied within one SOP? JGXP Vol 10, #4, 2006.

3. We are entering instrumental data directly into a validated LIMS; that data is processed within the LIMS using a validated macro; the results are maintained in the LIMS and then reported on a Certificate of Analysis to Quality Assurance. Is a second review by the laboratory required? What should be included in that review? What data or records should be reviewed by Quality Assurance? JGXP Vol 10, #4, 2006.
4. If you realize that a record such as a validation report, calibration report, or environmental report requested by a regulatory agency investigator has not been completed, what should you do? Should you show the data or reports that have not been reviewed or approved? JGXP Vol 11, #1, 2007.
5. With regard to process validation, at what point during development or process transfer of the drug product do you challenge the extremes of the process parameters, such as time, speed, pressure, or temperature? JGXP Vol 11, #1, 2007.
6. Are continuous improvements or process improvements subject to change? JGXP Vol 11, #2, 2007.
7. Will FDA inspect the Information Technology Department in the same way they would inspect the production area? JGXP Vol 11, #2, 2007.
8. We have a product that has a label requiring room temperature storage and a stability sample at 40°C 75% RH gave an out-of-specification (OOS) result for the assay. The result was confirmed. Do we have to inform the FDA and file a Field Alert? JGXP Vol 11, #3, 2007.
9. Where in the cGMPs is there a requirement to meet customer requirements? Is this necessary to comply with cGMPs? JGXP Vol 11, #3, 2007.
10. How much do GMPs apply to development activities? What developmental activities can FDA investigators inspect during a site or pre-approval inspection? JGXP Vol 11, #4, 2007.
11. How are ICH Guidelines established in the United States? Where are they published? Which guidelines take precedence, FDA or ICH? JGXP Vol 11, #4, 2007.
12. What should virtual pharmaceutical companies expect FDA will inspect during a routine surveillance or compliance audit? JGXP Vol 12, #1, 2007.
13. The terms accountability and responsibility are frequently used in quality standards and guidances but are not defined by any major document. It is not clear whether these terms are synonymous with no difference in meaning or whether there are significant or subtle differences in meaning. How are these terms to be interpreted or applied within a standard or an internal policy or procedure? JGXP Vol 12, #1, 2007.
14. It is an expectation of FDA that investigations be completed in a "timely" manner. Procedures for some firms require that investigations be completed within 20 days. What is the current regulatory expectation for completion of an investigation? JGXP Vol 12, #2, 2008.
15. Are the ICH guidelines "stricter" than US GMPs or FDA requirements? Will the industry move to the ICH, changing the role of the FDA? JGXP Vol 12, #2, 2008.
16. We hear the agency is interested in PAT (Process Analytical Technology) and continuous production. How do the batch-oriented regulations apply to traceability and record-keeping in the continuous production environment? How do you decide what is a batch? JGXP Vol 12, #3, 2008.
17. The medical device GMPs are called a Quality System Regulation and the FDA has recently published its guidance "Quality System Approach to Pharmaceutical CGMPs." Why is there no common regulation that defines a Quality System applicable to drugs, devices, and even other items regulated by FDA? JGXP Vol 12, #3, 2008.
18. Because design of a drug is much less complex than design of a device, does design failure modes effects analysis (FMEA) really appl to pharmaceuticals? Would you separate out each component of a design FMEA (i.e., packaging, formulation, etc.)? JGXP Vol 12, #4, 2008.
19. If a firm changes name, how critical is it if standard operating procedures (SOPs) to be under the new name? Is it a violation of the GMPs to keep using SOPs under the old name? JGXP Vol 12, #4, 2008.
20. Human errors such as raw data entries, transcription errors, and wrong dates constitute violations to an SOP on record keeping that requires accurate, clear, and legible data. Too often the corrective action is training, and often this is not effective. What other options are available for corrective actions? JGXP Vol 12, #5, 2008.
21. Can accelerated testing be used as a substitute for long-term stability testing? JGXP Vol12, #5, 2008.

22. Is it appropriate to have a written procedure (i.e., standard operating procedure [SOP]) for change control or to have procedures for each case (e.g., facilities, process, cleaning method)? JGXP Vol 13, #1, 2009.
23. Is it possible to extend a product's shelf life (i.e., after shelf life expiration) if recontrol in the user's lab produces results within specifications? JGXP Vol 13, #1, 2009.
24. Our dilemma is whether secondary reference standards need to be qualified against a United States Pharmacopeia (USP) reference standard or not. In our case, a finished product testing laboratory was releasing material using a "USP grade" material as a secondary standard. There was no testing of this material, but they were taking the purity from the certificate of analysis. I have done qualification of secondary standards before, and the methods utilized required that the method utilized required that the lot of raw material, to be utilized as the secondary standard, was qualified as the secondary standard. The simplest scenario here would be that a drum of X, which is USP grade, is utilized in a manufacturer of a drug product. The laboratory does not want to use a USP reference standard of X every time for testing of a finished batch. Therefore, they take a sample of the USP grade material X from the drug and want to use it as a secondary standard. What testing should be done? JGXP Vol 13, #2, 2009.
25. What should be done during an Annual Product Review? How much time do you encompass in one report? Do you consider batches from the year before and end user reports coming in after the year? JGXP Vol 13, #2, 2009.
26. If a company is in the stage of manufacturing a prototype drug product (delivery device and formulation), should one assume that all aspects of GMP should be implemented because, even though you do not have a product and have not begun manufacturing operations, you in fact have a prototype product that will be used by your contract labs to conduct clinical studies? JGXP Vol 13, #3, 2009.
27. What degree of testing is required for primary packaging components? JGXP Vol 13, #3, 2009.
28. What is the return on investment (ROI) for quality assurance (i.e., how do you sell quality assurance activities to management)? JGXP Vol 13, #4, 2009.
29. Will registration to International Organization for Standardization (ISO) 901 prepare a pharmaceutical firm for the transition to a pharmaceutical quality system as outlined in ICH Q10? JGXP Vol 13, #4, 2009.
30. How far should change control go when a supplier changes (for example) his ingredients? JGXP Vol 14, #1, 2010.
31. When the source of water feed is a municipal water company, is it necessary to do regular analytical testing for quality of water supplied? Why is the Certificate of Analysis (CoA) from the water company not enough to justify use of it to make Purified Water or Water for Injection (WFI)? JGXP Vol 14, #1, 2010.
32. What is exempt or not exempt from US FDA investigations during an audit? JGXP Vol 14, #2, 2010.
33. Ten years from now, what will be the impact of process analytical technology (PAT) on the following: **Validation of a product step (costing and labeling) Registration strategy for new parameters Collaboration with FDA? Will other agencies (European Union) follow and adopt? JGXP Vol 14, #2, 2010.**
34. If we have a robust system for annual product review and conclude every year that the process is still valid, is it necessary to perform a formal revalidation every three years? JGXP Vol 14, #3, 2010.
35. Does FDA expect standard operating procedures (SOPs) to be reviewed on a regular basis? Would it be acceptable to write in the SOP that procedures should generally be reviewed every three years? Who should be responsible for the review? JGXP Vol 14, #3, 2010.
36. I have cited the use of deviations and exceptions in the past relative to validation protocols and find myself in the position of defining use and application of each term relative to validation studies. Can you help me with this? JGXP Vol 14, #4, 2010.
37. For a Water for Injection (WFI) system that has online total organic carbon (TOC) and conductivity analyzers, can an organization change existing procedures that require the sampling and testing of every use port on a daily basis and use reduced sampling and testing of the WFI system? JGXP Vol 14, #4, 2010.
38. Is there a suggested frequency or time for performing verification of a preventative action after

implementation? Should corrective action and preventive action (CAPA) remain open until verification is complete? JGXP Vol 15, #1, 2011.

39. What are the minimum requirements for issuance of the batch record to the production floor? JGXP Vol 15, #1, 2011.
40. The US FDA almost always reviews the complaint system during a site inspection. Both the device and pharmaceutical industry receive a wide range of feedback about their products. What constitutes a complaint? JGXP Vol 15, #2, 2011.
41. We have raw material inspection sheets used in the warehouse by quality control (QC) technicians that enter the incoming name, lot number, and other relevant information. They then examine the certificate of analysis and draw samples. The samples and inspection sheets are then delivered to the QC laboratory. We are in the habit of putting lab results (e.g., appearance, solubility, viscosity, ID) on that sheet (not in the lab notebook). Is that permissible? JGXP Vol 15, #2, 2011.
42. How can we guarantee the stability of a reference standard, and how often should we retest it? JGXP Vol 15, #3, 2011.
43. Does the pharmaceutical industry spend too much on full compliance and aiming for no FDA 483s from an inspection when a few fda-483s will not close you down? JGXP Vol 15, #3, 2011.
44. With which system does an FDA investigator begin an inspection? JGXP Vol 15, #4, 2011.
45. An intermediate is out-of-trend, but within specifications, for a known impurity. However, it is known that if taken through the next step, the batch will fail the specification for this impurity. Can this batch of intermediate be mixed with a low impurity batch in the next stage to ensure that the next stage will meet specifications, or should it be reprocessed? JGXP Vol 15, #4, 2011.
46. In reading through references about sampling, I find reference to pooled samples and composited samples. What is the difference between the two? JGXP Vol 16, #1, 2012.
47. Does the US FDA investigator always highlight a possible 483 during an inspection or can they write up a 483 on a report without bringing it to the attention of the firm? JGXP Vol 16, #1, 2012.
48. What is the advantage or disadvantage of an external audit for a small company? JGXP Vol 16, #2, 2012.
49. Is change control only the need to have procedures to track changes? We have change control for many things, but different procedures for things like SOP changes, cleaning procedure changes, raw material, and component changes? JGXP Vol 16, #2, 2012.
50. Where do we put the first calibration of a recently installed laboratory instrument? Is it part of qualification? JGXP Vol 16, #3, 2012.
51. How far should change control extend? For example, should change control include a change of ingredients by a supplier outside the company? JGXP Vol 16, #3, 2012.
52. In the annual product review, if a lot is manufactured but not released, do we include the reason? JGXP Vol 16, #4, 2012.
53. Can pharmaceutical companies be forced to change outdated equipment used in manufacturing? JGXP Vol 16, #4, 2012.
54. In equipment qualification protocols, can we include documents or forms that can be used for recording data gathered during execution of the protocol? JGXP Vol 17, #1, 2013.
55. In the view of FDA, should customer complaints be handled as deviations? JGXP Vol 17, #1, 2013.
56. In the FDA 2011 Guidance on Process Validation and during discussions on meetings on process validation, we are told that we can no longer assume that three batches constitutes process validation. How many batches will be required for process validation? JGXP Vol 17, #3, 2013.
57. When performing a supplier audit of a non-International Organization for Standardization (ISO) company, can we only hold the organization accountable to 21 CFR 210 and 211 and ICH-approved standards? JGXP Vol 17, #3, 2013.
58. How does US FDA determine appropriate training / qualification of personnel? JGXP Vol 18, #1, 2014.
59. How does one handle an out-of-specification (OOS) result for temperature land humidity in a stability chamber? JGXP Vol 18, #1, 2014.
60. It has been said that people changes fall under change control. If operator A and B are qualified, how is this change control? JGXP Vol 18, #2, 2014.

61. How are International Conference for Harmonization (ICH) guidances published into law in the United States? Where are ICH guidances published? What takes precedence, FDA or ICH guidances? JGXP Vol 18, #2, 2014.
62. Are changes made under programs for continuous improvements or process improvements subject to validation? JGXP Vol 18, #3, 2014.
63. Which guidelines should be used for auditing equipment suppliers? Generally, these suppliers are ISO certified. JGXP Vol 18, #3, 2014.
64. Can product groupings be used in biological manufacturing cleaning validation? JGXP Vol 18, #4, 2014.
65. When is an unexpected result considered a discrepancy or a deviation? JGXP Vol 18, #4, 2014.
66. If we receive a raw material from a supplier and it does not meet specifications, should the event be captured in our deviation system, the supplier's deviation system, or tracked in some separate system? JGXP Vol 19, #1, 2015.
67. The most cited FDA observation is not following procedures. How does an organization eliminate or justify human error such as not following procedures? JGXP Vol 19, #1, 2015.
68. The GMPs require that non-sterile products be free of objectionable organisms. What is an objectionable organism? JGXP Vol 19, #2, 2015.
69. Do we need to validate test methods for raw materials, intermediates, and in-process materials? If yes, which of the characteristics should be evaluated? JGXP Vol 19, #2, 2015.
70. What are the regulatory requirements and expectations for process improvements in the pharmaceutical industry? JGXP Vol 19, #3, 2015.
71. Biological products are more Variable than small molecule products. So how can one Validate the biological process as required by FDA? JGXP Vol 20, #1, 2016.
72. If a raw material does not meet specifications, should it be captured in the site deviation system, the supplier's deviation system, or other deviation system? Who should investigate the deviation, the firm or the supplier? JGXP Vol 20, #1, 2016.
73. In the FDA 2011 Guidance on Process Validation and during discussions on meetings on process validation, we are told that we can no longer assume that three batches constitutes process validation. How many batches will be required for process validation? JGXP Vol 20, #2, 2016.
74. When performing a supplier audit of a non-International Organization for Standardization (ISO) company, can we only hold the organization accountable to 21 CFR 210 and 211 and ICH-approved standards? JGXP Vol 20, #2, 2016.
75. Should contractor deviations/investigations be entered into your organization's deviation system? If the contractor is not trending deviations/investigations, who should? JGXP Vol 20, #6, 2016.
76. Is it appropriate to qualify a commercial product as a house analytical standard against the USP standard and use the house standard as the primary reference standard? JGXP Vol 20, #6, 2016.
77. Cleaning methods for pharmaceuticals are developed and Validated for use in the cleaning of manufacturing equipment. Are these same methods required to be used in the analytical laboratory for cleaning glassware, tubing, and other analytical equipment? Must these laboratory cleaning methods also be validated?

JGXP Vol 23, #1, 2019.

FUTURE Q&A – WE NEED YOUR HELP

The Q&A reported in GXP Talk over many years have been very well received by readers, and publication of suggested new topics have been repeatedly requested. Several new Q&A suggested by readers are currently in progress by authors. We need your help to continue the success of GXP Talk. This feature will be most useful when the compliance community submits questions or topics for discussion. Please contact column coordinators Jerry Lanese at jerry@lanesegroup.com, Rich Poska at richposka@gmail.com, or Melissa Carella at melissa.carella@cbinet.com with comments, questions, or other input.

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