HUMAN DRUG CGMP NOTES

(Volume 5, Number 4)

December, 1997

(A Memo on Current Good Manufacturing Practice Issues on Human Use Pharmaceuticals)

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Office of Compliance
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file format as the firm's original records.

2) How can investigators confirm that persons who use electronic signatures have filed the requisite legal equivalence certification per part 11?

3) Will FDA certify or approve electronic recordkeeping services or products as complying with part 11?

Attachments:

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FAX FEEDBACK (Your input requested)

MOTISE'S NOTEBOOK:

Welcome to another edition of Human Drug CGMP Notes, our periodic memo on CGMP for human use pharmaceuticals. This edition completes 5 years of the notes and, with your support, we'll continue. Your FAX FEEDBACK responses are great and we especially appreciate your suggested topics for coverage. You need not, however, limit the dialog to FAX FEEDBACK. Feel free to call, write, or send us e-mail. We also welcome brief articles FDAers may wish to contribute. Subjects should be CGMP related and would be especially valuable if they address emerging new technologies.

As a reminder, although the document is fully releasable under the Freedom of Information Act, our intended readership is FDA field and headquarters personnel. Therefore, we cannot extend our distribution list for the paper edition to people outside the agency. The primary purpose of this memo is to enhance field/headquarters communications on CGMP issues in a timely manner. This document is a forum to hear and address your CGMP questions, update you on CGMP projects, and provide you with inspectional and compliance points to consider that we hope will be of value to your day to day activities, and to clarify existing policy and enforcement documents. This publication supplements, not supplants, existing policy development/issuance mechanisms.

Appended to each edition of the memo is a *FAX FEEDBACK* sheet to make it easier for us to communicate. In addition to FAX (at 301-594-2202), you can reach us by interoffice paper mail, using the above address, by phone at **(301) 594-0098** (note this change from prior editions), or by electronic mail.

If you would like to receive an electronic version of this document via electronic mail, see the check-off line in *FAX FEEDBACK*.

Thanks!

Paul J. Motise

POLICY QUESTIONS:

Do the CGMP regulations require equipment to be labeled with calibration dates? Do the regulations distinguish critical from noncritical equipment for this purpose?

Reference: 21 CFR 211.67, Equipment cleaning and maintenance; 211.68(a), Automatic, mechanical, and electronic, equipment; 211.160(b)(4), General requirements [Laboratory Controls]; 211.105 Equipment identification.

No and no. The CGMP regulations do not require that each piece of equipment bear status labeling as to its state of calibration or maintenance. However, per 211.67, 211.68, and 211.160, equipment must be calibrated and/or maintained according to an established schedule, and records must be kept documenting such activities.

The regulations do not distinguish critical from noncritical equipment for calibration and maintenance purposes. However, the need for calibrating a given piece of equipment depends on its function. In general, things that measure materials warrant calibration. In addition, the 1978 preamble to the CGMP regulations states that 211.68(a) is intended to control equipment

having an effect on product quality. Prudence dictates this be interpreted broadly. Equipment not requiring calibration/maintenance need not be tracked or included in the firm's calibration/maintenance program.

During an inspection a firm should be able to document when a specific piece of equipment was last calibrated/maintained, the results or action, and when its next calibration/maintenance is scheduled. The absence of such documentation is a CGMP deviation. While the absence of a calibration/maintenance tag is not objectionable, the presence of a calibration/ maintenance tag alone should not be assumed to satisfy regulatory demands, and the supporting documentation should be audited. The firm should also be able to support its decision to not include a particular piece of equipment in the calibration/maintenance program.

Don't confuse use of calibration tags with the CGMP requirement, at section 211.105, that major equipment be identified with a distinctive number or code that is recorded in batch records. This identification requirement is intended to help document which pieces of equipment were used to make which batches of drug product.

Contact for further information: Brian Hasselbalch, HFD-325, (301)594-0098: e-mail: hasselbalchb@cder.fda.gov

If a USP drug product meets USP specifications, but fails a firm's internal, more stringent, lot release specifications, and the lot is released for distribution, should investigators note this on the FDA-483?

Reference: 21 CFR 211.165(f) General requirements [Subpart I, Laboratory Controls] and 211.192, Production record review.

Before deciding on whether or not the situation should be reported on an FDA-483, be sure to determine how the firm intends to apply the internal specification. If the more stringent specification functions as an alert limit, and not a hard and fast lot release criterion, then the failure should not be recorded on the FDA-483. On the other hand, if the firm has committed itself (e.g., in a new drug application, or otherwise) to the specification as a lot release condition, then the item should be included on the FDA-483, because as a matter of CGMP, the firm did not adhere to its established release specifications.

The lot should be rejected, per section 211.165(f), if it fails the hard and fast release specification.

In addition to the appropriateness of lot release, you should also consider whether or not the firm investigated the failure of the lot to meet either the alert or release specifications. If no investigation was conducted, this should be included on the FDA-483. As specified in 211.192, failure of a batch to meet any of its specifications must be thoroughly investigated, and the investigation must include conclusions and follow up.

Contact for further information: Brian Nadel, HFD-325, (301)594-0098: e-mail: nadelb@cder.fda.gov

Does the 211.170(b) double sample size exemption for reserve samples of sterile drug products mean firms don't have to keep enough samples to run even one sterility test?

Reference: 21 CFR 211.170(b), Reserve Samples.

No. This section states that firms don't have to keep twice the quantity of reserve samples to perform sterility and pyrogen testing. That means firms must still keep sufficient quantity to perform one such sterility and pyrogen test. The sample size must also, per this section, be twice as large as needed to perform other tests.

Once a container closure system has been validated, the sterility characteristic of a drug product would not be expected to change over time. In addition, in many cases, keeping twice the sample size needed to run sterility tests, in addition to samples for other tests, would not be justified by the benefits of keeping the extra units.

Furthermore, the sensitivity limits of sterility testing are such that the tests are not likely to detect low levels of contaminated units within a given lot.

Accordingly, should sterility failures be suspected for distributed lots, reserve sample testing would be of less value in confirming the problem than thorough investigation of the relevant production and control records for the affected lot.

Contact for further information: Paul J. Motise, HFD-325, 301-594-0098; e-mail: motise@cder.fda.gov

Has FDA identified an appropriate microbiological specification for monitoring critical surfaces in an aseptic area used to make sterile drug products?

Reference: June, 1987 "Guideline on Sterile Drugs Produced by Aseptic Processing"

Yes. Product, container, and closure contact surfaces are known as "critical surfaces." Microbiological monitoring of critical surfaces should yield zero colony forming units (CFUs). Firms often express this action limit as <1 CFU. FDA's 1987 "Guideline on Sterile Products Produced by Aseptic Processing" states:

> "Equipment surfaces which contact sterilized drug product or sterilized container/closure surfaces should, of course, be sterile. It is just as important in aseptic processing to properly validate sterilization processes applied to these equipment surfaces as it is to validate such processes for the drug product and container/closures."

This standard can also be found in international publications such as the European Union's "Manufacture of Sterile Medicinal Products" (Annex I to the European Union Guide to Good Manufacturing Practice).

Contact for further information: Richard L. Friedman, HFD-322, 301-594-0095; e-mail: friedmanr@cder.fda.gov

If two contract labs test the pH on samples from the same lot, but arrive at different conclusions, one within specifications and the other out-of-specifications (OOS), would it be appropriate for the manufacturer to ignore the OOS result and use the in-spec result for batch release purposes?

Reference: 21 CFR 211.160, General requirements [Laboratory Controls]; 211.194, Laboratory records.

No. It should not be assumed that the OOS result is incorrect and the in-spec result is accurate. There is an equal possibility that either is the probable true value. Assuming that 1) the solution tested is identical for both laboratories, 2) the analysts followed the correct analytical method, and 3) analysts made no technical errors in performing the analysis, further information would be needed to ascertain which result should be considered reliable. For example, the information might take into account:

> (1) the maintenance status of the pH meter (e.g., was it calibrated in accordance with SOPs?; was the probe in good working order?); and,
> (2) the solution(s) used in the calibration (e.g., were they current and appropriate?; did they bracket the specification range?).

In this situation the above information for both labs should be compared. In addition, the analysts should be interviewed to ascertain if there was a possibility the sample was contaminated or mishandled.

Acceptance of one result over the other without an investigation could be considered "selective reporting". It would be advisable to look for a reasonable cause for the discrepancy rather than ignore the undesired result. The OOS result may very well be the true value. However, if contamination of the sample or other lab error is a probability, then the result could be invalidated with the above information as justification. In such a case resampling would be indicated, and the retest results would substitute for the original.

Contact for further information: Russ Rutledge,

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Gas What? (Policy Questions on Medical Gases):

1) Has the "zero" calibration step, that uses room air, for the Servomex Model 570A oxygen analyzer been discontinued? If so, when should a firm implement the revised calibration procedure?

Reference: 211.160(b)(4), General requirements and 211.165(e), Testing and release for distribution, [Subpart I - Laboratory Controls].

Yes. The procedure known as the "U.S. Instruction Manual for Servomex Model 570A Oxygen Analyzer" (Addendum) has been discontinued, through a joint effort between the Servomex Company and FDA, effective October 9, 1997, Rev. 5. Servomex intends to notify its customers regarding this change.

Therefore, any firm using a Servomex Model 570A and calibrating the analyzer via the Addendum needs to stop using this method immediately and begin calibrating the analyzer according to the original or new manual.

Calibration using the Addendum would be an appropriate FDA 483 item because the method is not scientifically sound.

The revised calibration procedure discussed under Section 6.0, “Calibrating the Model 570A,” and under Section 3.3, "Calibration for Oxygen U.S.P. Verification" (new section), in the new manual calls for the use of high purity nitrogen with a minimum potency of 99.9% for the "zero" step, and oxygen with a minimum potency of 99.2% for the "span" step. This method is scientifically sound.

2) Has there been any change regarding the use of production lots as reference standards, as identified in the December 1994, edition of Human Drug CGMP Notes?

Reference: 21 CFR 211.194(c), Laboratory Records.

No. Gases filled by the firm should not be used to calibrate oxygen analyzers because they are not normally of the same purity, nor tested to the same precision and accuracy, as what is supplied specifically for calibration purposes. Reference standards or calibration gases should be obtained from a specialty gas manufacturer or a supplier of standards. Any reference standard should be accompanied by a valid certificate of analysis which should be maintained on file.

Contact for further info: Duane Sylvia, HFD-325, 301-594-0095, e-mail: sylviad@cder.fda.gov

Toward The Electronic Government:

1) When investigators make copies of electronic batch production records, under 21 CFR Part 11, must the copies be in the same file format as the firm’s original records.

Reference: 21 CFR Part 11; Electronic Records; Electronic Signatures; Sections 11.10(b), Controls for closed systems and 11.30, Controls for open systems.

No. Part 11 only requires that persons be able to generate electronic (and human readable) copies that are accurate and complete. Electronic copies can be accurate and complete without being in the same computer file format as the original. The rule advises firms, however, to consult with the agency if there are any questions regarding our ability to review and copy electronic records.

Accordingly, during your inspections, if you encounter an electronic batch production record that is not in a file format you can copy for off-line review, you’ll need to work with the firm to ensure that the conversion file used for the copy you can use preserves the record content and integrity of meta data (data, such as time stamps, that describe a file), so as to be both accurate and complete.

When you make and maintain electronic copies

of electronic records, keep in mind the need to establish copy authentication and maintain integrity of your files, just as you would when you copy paper records. Guidance and training will be forthcoming in this area. In the meantime, consider, for example:

(1) using digital signature software to authenticate your copy file; signature verification would detect any post-signing record changes;

(2) obtaining from the firm an affidavit confirming that your copy is accurate and complete; and,

(3) placing the disk or tape holding your electronic copy in a container under official seal, and documenting a chain of custody for the container in a manner similar to official samples.

2) How can investigators confirm that persons who use electronic signatures have filed the requisite legal equivalence certification per part 11?

Reference: 21 CFR Part 11; Electronic Records; Electronic Signatures; Section 11.100(c); Field Management Directive (FMD) 146, Electronic Records: Electronic Signature Certification.

FMD 146, which was issued to the field October 22, 1997, provides detailed instructions regarding this aspect of part 11. Investigators should first check the ORA Intranet site (http://www.ora.fda.gov:8000/) for a listing of persons who have filed the certification. Note that this site is accessible only from internal FDA computers. ORA/ORO will update the site periodically. Therefore, if the establishment you are inspecting claims to have filed the certification, but confirmation does not appear in the ORA listing, you should call the ORA contact (Charles Ahn at 301-827-5637) to determine if the filing had, in fact, been made, but simply had not yet been posted.

Keep in mind, too, that 11.100(c) certifications are intended to be high level in nature, in order to minimize the number of submissions. That means a single corporate certification may cover multiple facilities at different locations. In such cases, we would not expect each facility at each different location to have filed a separate certification.

3) Will FDA certify or approve electronic recordkeeping services or products as complying with part 11?

Reference: Federal Register of March 20, 1997, 62 FR 13429, Notice of Final Rulemaking, 21 Code of Federal Regulations (CFR) Part 11, Electronic Records; Electronic Signatures, comment paragraph 5.

No. FDA doesn't certify or approve electronic signature/record products or services. Although we've met with representatives of electronic recordkeeping product/service vendors and developers (and we continue to meet with developers and users to learn about the technology and help people adopt trustworthy and reliable systems) FDA has not, and cannot, endorse any particular product or service. Because compliance with part 11 involves a collection of system controls (some administrative) that no one product can embody, it would be inappropriate for someone to represent a product or service as ensuring full compliance with the rule. Persons will have to perform their own evaluations, comparing for themselves product/service features against relevant part 11 requirements.

Contact for further information: Paul J. Motise, HFD-325, 301-594-1089, e-mail: motise@cder.fda.gov

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DOC ID CNOTESD7.w60

1997 HUMAN DRUG CGMP NOTES Subject Index

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FAX FEEDBACK

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I found this issue of HUMAN DRUG CGMP NOTES to be [check as appropriate]:

__not very; __ somewhat; __ very; __ extremely informative, and

__not very: __ somewhat; __ very; __ extremely useful to my inspectional/compliance activities.

Here's my question regarding _____
_____
_____

Future editions of HUMAN DRUG CGMP NOTES should address the following CGMP questions/issues:
_____
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