HUMAN DRUG CGMP NOTES

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

Issued By: The Division of Manufacturing
and Product Quality, HFD-320
Office of Compliance
Center for Drug Evaluation and Research

Project Manager: Paul J. Motise, HFD-325

IN THIS ISSUE:

Stability)

1) Are firms required to keep analytical stability data generated by a remote lab available for FDA inspection at the manufacturer's site?

2) For finished product stability testing, is it necessary to sample from an unopened container at each test interval?

- Gas What? (Policy Questions on Medical Gases):

  1) What is the current policy on gas product yield reconciliation? I understand the Compressed Gas Association filed a citizens petition requesting exemption from this requirement.

  2) Must batch production records for compressed medical gases contain copies or specimens of all labeling used, or are alternative measures acceptable? What regulatory follow up would be appropriate if labeling/copies are required but lacking?

- What is the "EES" and how might it affect my work?

Toward The Electronic Government:

- Electronic Signature Final Rule Published 3/20/97

Attachments:

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. Thanks for your great FAX FEEDBACK and e-mail responses. 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 (FOI) Act, our intended readers are FDA field and headquarters personnel. Therefore, we can't 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 is a forum to address your CGMP questions, update you on CGMP projects, and clarify and help you apply existing policy to your day to day inspectional and compliance activities. This publication does not supplant agency 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, you can reach us by interoffice paper mail, phone at (301) 594-1089, or electronic mail.

If you would like to receive an electronic version of this document via electronic mail, let us know (see the check-off line in FAX FEEDBACK). We're also on the Internet at http://www.fda.gov/cder/cgmpnotes.htm.

Thanks!

Paul J. Motise

POLICY QUESTIONS:

Do the CGMP requirements for records retention apply to the raw data generated in support of new drug applications?

Reference: 21 CFR 211.180 General requirements, Subpart J Records and Reports, Section; 21 CFR 314.50 Content and format of an application.

Yes, if the raw data are associated with drug products which are used in tests involving human subjects, or if the drug products are

distributed to the market after NDA approval.

Additionally, it is very important to realize that we consider the raw data generated in development of the application to be part of the application and therefore the data should be retained as long as the application is in effect. The new drug regulations require "an application to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of an application that is received or other wise obtained by the applicant from any source."

Contact for further information: Nicholas Buhay, HFD-325, 301-594-0098; e-mail: buhay@cder.fda.gov

Do the CGMP regulations apply to a U.S. made cosmetic that is exported to a country where it is regulated as a drug?

Reference: Section 201(g) of the Food, Drug and Cosmetic Act; 21 CFR 210.1, Status of current good manufacturing practice regulations

No. The drug CGMP regulations apply to articles that U.S. law and regulation define as drug products. Drug CGMPs don't apply to articles that don't meet that definition, even if the articles are deemed, and regulated as, drugs outside the U.S.

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

Active Pharmaceutical Ingredients (APIs)

1) Must USP grade APIs be analyzed in accordance with USP monographs? Must manufacturers test each batch for all monograph specifications?

Reference: Compliance Policy Guide (CPG) 7132.05, October 1, 1980, Performance of Tests for Compendial Requirements on Compendial Products.

The referenced CPG addresses the issue of whether a firm is required to use the compendial methodology as a batch release test for drug products to determine compliance with monograph specifications. The CPG states that a pharmaceutical manufacturer is not required to apply compendial analytical methods as a batch release test unless the firm has made specific commitments to do so (as in an NDA or a drug master file), or where the official method is the only appropriate test. Neither the USP nor the CGMP regulations specifically requires a firm to utilize the compendial method as a batch release test. This policy also applies to API manufacturers.

CGMP, however, requires that batch release test methods be scientifically sound. Non-compendial methods can be used for batch release purposes, as long as the capabilities of these methods are shown to be equivalent to or better than the compendial test methods. However, in the event of a dispute regarding conformance of the API with USP specifications, the compendial method is the referee test.

CPG 7132.05 also establishes that in some cases, it may not be necessary for a manufacturer to test each batch for all compendial monograph specifications. The nature and extent of end product testing beyond potency should be determined by the manufacturer based on the adequacy of process validation and adequacy of in-process manufacturing controls.

2) In many countries, where it may be difficult to obtain USP reference standards, API manufacturers use secondary standards (usually production lots that are further purified and qualified in the laboratory) for analysis. Is use of such secondary reference standards acceptable for analysis of compendial articles?

Reference: USP 23, <11> Reference Standards.

Many USP tests and assays of APIs are based on comparing a test sample with a USP Reference Standard. Page 1653 of USP 23 states that "where it is directed that a Standard solution or a Standard preparation be prepared

for a quantitative determination by stepwise dilution or otherwise, it is intended that the Reference Standard substance shall be accurately weighed. . ."

We generally recommend use of official reference standards for analysis of compendial articles. However, use of secondary reference standards is acceptable if each lot's suitability is determined prior to use by comparison against the current official USP reference standard and each lot is requalified periodically in accordance with a written protocol. The protocol should clearly address the receipt, storage, handling and use of primary reference standards, the purification of secondary standards, and their qualification against USP reference standards.

Contact for further Information: Edwin Rivera, HFD-322, 301-594-0095; e-mail: rivera@cder.fda.gov

Is nonviable particulate monitoring under static rather than dynamic conditions acceptable for routine monitoring of aseptic processing areas?

References: 21 CFR 211.160(b), General requirements (Subpart I Laboratory Controls); 211.113, Control of microbiological contamination; 1987 Guideline on Sterile Drug Products Produced by Aseptic Processing.

No. Sampling an environment for particulates during static (at rest) times is of minimal utility in assessing actual processing conditions. On the other hand, operational (dynamic) monitoring performed throughout aseptic processing is needed. Here's why.

Aseptic processing operations are designed to exclude living microorganisms, endotoxins, and particulates from the finished product. It is generally accepted that monitoring of particulate concentration in classified (environmentally controlled) areas during operations serves as a direct indicator of changes in local air quality while indirectly indicating the increased potential for the introduction of microorganisms to the monitored area.

Occasional static monitoring during periods of no operation to ensure particulate levels remain well below an area's classification level would be useful as a facility maintenance parameter. However, firms should obtain data from dynamic monitoring (during operations) as a routine batch control. Firms should monitor frequently throughout manufacturing, and in proximity to the work surfaces and exposed product or container/closures. For example, in class 100 areas, samples should be taken about one foot away from the work surface. Many firms now have the capability to monitor nonviables continuously; however, failure to monitor continuously is not objectionable.

High levels of particulates generally represent a departure from processing norms, indicating, for example, unusual personnel activity which challenges the intended cleanroom design parameters. It is therefore important that the Quality Control unit investigate such "particulate excursions."

Finally, when qualifying a cleanroom, firms conduct studies to establish the room's air classification. Although the classification studies include assessment of particulate levels under static conditions, the final classification should be derived from data generated while equipment is in place and operations are ongoing.

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

Laboratory Issues

1) Is it acceptable for a manufacturer to replace faulty or out of calibration instrumentation with "spare/backup" instruments that have been previously calibrated but stored at a remote location?

Reference: 21 CFR 211.160(b)(4), General requirements, Subpart I, Laboratory Controls.

Yes, provided the replacement instruments remain within calibration, meet established specifications, and haven't been stored longer

than the established calibration interval.

The heart of the issue is equipment suitability. Let us assume that the spare instrument is, first of all, the same make and model as what it is supposed to replace, thus ensuring that performance characteristics of the two are the same and the analytical method at hand is not modified. If that's the case, then the spare instrument may be stored anywhere storage conditions don't adversely affect its performance (reliability, accuracy and precision).

Before any lab instrument is put into use, the CGMP regulations require that the firm ensure it is within calibration specifications. If the "spare" instrument may drift out of calibration during storage, as might be the case if it has moving parts, then we would expect the firm to recalibrate the instrument before putting it into service. Remember that some instruments are so delicate that just moving them from one place to another causes them to go out of calibration.

Finally, section 211.160(b) of the CGMP regulations requires firms to calibrate laboratory instrumentation at appropriate intervals according to a written program. If the storage period for the "spare" in question exceeded that interval, we would expect firms to re-calibrate the instrument prior to use.

> 2) The USP states that a balance needs a Measurement Uncertainty (MU) that doesn't exceed 0.001. Would a balance having an MU of 0.00149 meet the specification? What if a firm's numerical analysis SOP states to round from one number past the reported value (i.e., drop the nine and round based on the four)?

Reference: 21 CFR 211.160(b)(4) as in the question above; USP 23 <43> Weights and Balances, page 1680.

USP 23 states ±0.1% accuracy and gives an example of 50 mg ± 50 ug as acceptable. The above question reflects that clarification is needed in two areas, 1) the meaning of significant figures, and 2) measurement uncertainty.

For a number 0.001 to be significant at 0.001, the uncertainty of the final digit is ±.0005; i.e. the actual figure has a potential true value of anywhere from 0.0005 to 0.0015. The MU of 0.00149 cited would meet the specification because it falls within the limits stated. The final 2 digits of 49 given in the question may or may not be significant. The USP gives the minimum acceptable limits of precision; greater precision is acceptable. However, this leads to the question of the meaning of the final 2 digits given. If they are not significant figures, then they should not be reported. It's a little like giving a person's height to 1/64 inch, but taking the measurement using a yardstick graduated in inches. You may have confidence in that measurement to within ±½ inch, no more. For more precision, another measuring device capable of greater accuracy would be needed.

A balance exhibiting a reading of 0.001 thus has a potential uncertainty range of 0.0005 to 0.0015. The mass used for calibration should be traceable to a national standard or a mass with an uncertainty statement. Traceable means an unbroken chain of measurements relating to a national or other acceptable standard. For the US, the national standard weights are stored under controlled conditions at the National Institute of Standards and Technology (NIST) in Gaithersburg, MD.

Generally, an electronic balance has linearity and precision compared with internal weights, and calibration is done with a traceable standard. The accuracy is often compared to traceable reference standards kept with the balance on a daily or weekly basis, and certified biennially. While the USP may specify an accuracy of 0.1%, throughout the pharmaceutical industry you generally find the balances in use capable of greater accuracy.

Common practice is to weigh a pharmaceutical sample on a transfer vessel (a weighing boat or weighing paper), transfer the sample to the preparation vessel (volumetric flask, beaker etc.), then weigh the empty transfer vessel. The difference in weights is the sample weight. It is important to note that this differential weighing tends to cancel any gross errors in the balance accuracy, as determined by the calibration with

the reference weight. That is, balance weight errors will be of the same magnitude on the same side of the ± uncertainty.

Contact for further information: Russ Rutledge, HFD-325, 301-594-0098, e-mail: rutledgec@cder.fda.gov

On Stability

> 1) Are firms required to keep analytical stability data generated by a remote lab available for FDA inspection at the manufacturer's site?

Reference: 21 CFR 211.22, Responsibilities of quality control unit; 211.180(c) General requirements, Subpart J Records and Reports.

No. The CGMP regulations require that firms retain and make available during an FDA inspection all analytical data generated in the course of QC and stability testing. However, firms are not required to keep the data at the manufacturing site if the testing is performed at another location. Consequently, there are times when it is necessary to inspect an outside testing facility to audit pertinent analytical data as well as the testing facility's CGMP controls. If the testing is being conducted by a contract lab, the manufacturer is responsible for assuring the adequacy of the lab as well as for evaluating and performing appropriate follow-up to the test results.

> 2) For finished product stability testing, is it necessary to sample from an unopened container at each test interval?

Reference: 21 CFR 211.166, Stability testing; February, 1987, Guideline For Submitting Documentation For The Stability Of Human Drugs And Biologics.

Except for large containers, a random sample should be collected from an unopened container at each interval. For solid-oral dosage form products which are packaged in large containers intended for repackaging, samples may be taken from an opened container, although more than one container should be sampled during the stability study. Because in large containers dosage units near the closure may have different stability properties from dosage units in other parts of the container, it may be necessary to collect separately identified samples from different parts of the container to ensure the samples accurately represent any stability differences. Lastly, firms should have written SOPs specifying their sampling protocols.

Contact for further information: Barry Rothman, HFD-325, 301-594-0098, e-mail: rothmanb@cder.fda.gov

Gas What? (Policy Questions on Medical Gases):

> 1) What is the current policy on gas product yield reconciliation? I understand the Compressed Gas Association filed a citizens petition requesting exemption from this requirement.

Reference: 21 CFR 211.103, Calculation of yield; 211.184(c), Component, drug product container, closure, and labeling records.

The Compressed Gas Association filed a citizens petition requesting that medical gases be exempt from the requirements for yield reconciliation. On May 11, 1995, the agency concurred with the CGA based on the amounts of product loss through evaporation from storage tanks, large cryogenic dewars, the filling operations, and the filling of large amounts of industrial product from the same storage tanks.

The agency will publish a notice in the Federal Register proposing to amend the CGMP regulations accordingly. The notice will include an interim enforcement policy that will apply the exemption. However, existing requirements remain in effect until the notice is published.

> 2) Must batch production records for compressed medical gases contain copies or specimens of all labeling used, or are alternative measures

acceptable? What regulatory follow up would be appropriate if labeling/copies are required but lacking?

Reference: 21 CFR 211.188(b)(8), Batch production and control records.

Batch production records for compressed medical gases must contain copies or specimens of all labeling used, per 21 CFR 211.188(b)(8). Photographs or photocopies of large labeling that would be awkward to physically append to the records may be used in place of original labeling. It's important to have labeling, or accurate copies thereof, to enable investigations and problem resolution in the event of mix ups. Although additional labeling controls may contribute to preventing mix-ups, such controls are not substitutes for including labeling specimens or copies in the batch records.

Accordingly, it would be appropriate to include in an FDA 483 the observation that batch production records lacked copies or specimens of all labeling used. The appropriateness of pursuing further actions, such as issuance of warning letters, would have to be assessed in the context of all inspection findings, the potential public health risks and the firm's compliance history.

Contact for further info: Duane Sylvia, HFD-325, 301-594-0095.

What is the "EES" and how might it affect my work?

Reference: Establishment Evaluation System User's Guide, Center for Drug Evaluation and Research, August 27, 1996.

EES, the Establishment Evaluation System, is an Oracle® client/server application system used to process Establishment Evaluation Requests (EERs). An EER is a step in the new drug review process in which there's an assessment of a firm's CGMP compliance and application commitments relating to chemistry.

EES is designed to automate the submission, tracking, and evaluation procedures associated with processing an EER. By allowing users to share information electronically, EES improves communication and planning between CDER and ORA, who share responsibility for processing and monitoring an EER.

Several field district offices (including, NWJ, PHI, BLT, CIN, ATL and LOS), several CDER review divisions, and CDER's Office of Compliance have been using the EES. This includes:

1 - initiation of EERs by review divisions when the life cycle of a pending application reaches that stage;

2 - determination, where possible, of the acceptability of drug manufacturing and testing facilities based on a profile review;

3 - requests for the District Offices to determine the need for physical facility visits, when necessary, in order to determine compliance with CGMPs;

4 - assignment of preapproval inspections when necessary;

5 - electronic communication of subsequent District Office recommendations; and,

6 - CDER/OC's evaluation of the District Office recommendation, and concurrence or non-concurrence.

We expect the remaining districts and review divisions will be coming on line in the next two months. Then all agency components involved in the drug review process will be able to access real time records generated during processing of each pending application.

By providing real time processing and evaluation of data and information, EES streamlines communications and eliminates lag times previously caused by paper mail systems. EES will maximize efficiency of communication among various FDA components that are responsible for evaluating establishments.

Contact for further information: Randall Woods,

HFD-324, 301-827-0062; e-mail: woodsr@cder.fda.gov

Toward The Electronic Government:

Electronic Signature Final Rule Published 3/20/97

Reference: Federal Register, 62 FR 13430, March 20, 1997.

21 CFR Part 11; Electronic Records; Electronic Signatures, known as the e-sig rule, has now published in final and is scheduled to go into effect on August 20, 1997. The final rule Federal Register notice and related documents are posted to our Internet site at http://www.fda.gov/cder/esig/part11.htm. You can also get there by following the "What's New" links on the CDER home page (http://www.fda.gov/cder) and the agency home page (http://www.fda.gov).

The purpose of the rule is to accept and promote new technologies and permit industry and FDA to benefit from the efficiencies of electronic recordkeeping while maintaining our ability to protect and promote the public health.

Guidance and training for field investigators will be forthcoming. However, in the near term keep the following in mind during your CGMP inspections when you encounter electronic records:

(1) Be flexible. While it is vital that we still be able to audit and copy electronic records, try to interpret and implement Part 11 liberally, affording people the benefit of the doubt as much as possible. We don't want to inadvertently erect barriers to electronic recordkeeping. Be prepared to meet with firms to resolve Part 11 implementation questions. HFD-320 is prepared to participate in CGMP related discussions, as needed.

(2) Part 11 is not retroactive. Electronic records created or modified before the effective date of Part 11 will be held to acceptability standards that were in place at that time. For CGMP purposes, electronic signatures were not acceptable substitutes for handwritten signatures or initials -- evaluate on a case by case basis the significance of using those electronic signatures in place of handwritten signatures.

(3) Current systems will not be grandfathered. Existing electronic recordkeeping systems may have to be modified to conform with Part 11 once the rule goes into effect. Part 11 will apply to electronic records that are created, modified or maintained after the effective date.

(4) Be prepared to discuss with firms those file formats and media (e.g., disk or tape) that you can manage. This is important so that firms can meet the requirement that their systems be able to generate accurate and complete copies of records in electronic form that we can review and copy.

(5) Firms do not have to await FDA acknowledgment or review of their 11.100(c) certifications (regarding the legally binding equivalency of electronic and handwritten signatures) before they implement electronic records and electronic signatures.

We are gathering a collection of frequently asked questions about Part 11 and will publish them along with the answers when we've reached a critical mass. Feel free to send us questions you receive from industry.

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

P. Motise 6/1/97
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FAX FEEDBACK

TO: Paul Motise, HUMAN DRUG CGMP NOTES, HFD-325
FAX: 301-594-2202 (Phone 301-594-1089)

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