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
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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. Your FAX FEEDBACK continues to be 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, as several of you have done. We also welcome brief articles FDAers (field and headquarters) may wish to contribute. Subjects should be CGMP related, and topics addressing new technologies would be especially valuable.

Although this document is fully releasable under the Freedom of Information (FOI) Act, our intended readership is FDA field and headquarters personnel. Therefore, for now, 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 policy issues and to do so in a timely manner. This document is a forum to hear and address your CGMP policy questions, update you on CGMP projects in the works, provide you with inspectional and compliance points to consider that will hopefully be of value to your day to day activities, and clarify existing policy and enforcement documents.

We intend to supplement, not supplant, existing policy development/issuance mechanisms, and to provide a fast means of distributing interim policy.

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) 594-1089, or by electronic mail. Note that the syntax for all our Internet addresses has changed to "accountname"@cder.fda.gov, as explained elsewhere in this edition.

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).

Thanks!

Paul J. Motise

POLICY QUESTIONS:

Are ASTM or NIST test methods considered "official" like those published by the USP and AOAC?

References: 21 CFR 211.160 (General Requirements), 211.165 (Testing and Release for Distribution) and 211.194(a)(2) (Laboratory Records), all in Subpart I, Laboratory Controls; USP 23, General Notices, p. 2

No. Under the Food, Drug, and Cosmetic Act, "official" relates to "official compendium", meaning USP/NF or Homeopathic Pharmacopeia. Unfortunately, the word "official" has taken on much broader meaning in common usage -- extending to NDAs, other government agencies, and quasi-governmental organizations.

The question needs a context for a clear answer that relates to what we expect firms to do. Let's consider two facets -- the analytical method which governs determination of conformance to a standard, and the need for methods validation.

Determination of compliance involves the

measurement of a drug's conformance to a given standard or legal yardstick -- an objective way of determining compliance when there's a question. The customary hierarchy of legal yardsticks consists of: (1) methods in an approved NDA; (2) methods in the USP/NF or HP(for compendial drugs) and the AOAC (Association of Official Analytical Chemists) Book of Methods ; and (3) other scientifically sound methods. The third category is one that may be subject to debate in any dispute, even if the scientifically sound method is generated by NIST (the National Institute of Standards and Technology), ASTM (American Society for Testing and Materials), or some other organization.

Regarding methods validation, the CGMP regs, at 211.194(a)(2), relieve firms from having detailed data relating to method accuracy for methods in approved NDAs, the USP/NF, or the AOAC Book of Methods. The regulation doesn't recognize other sources and doesn't use the word "official". Relief is conditional upon having a reference to the specific method and not deviating from the method.

A related question follows.

Can a company use an older (not updated) version of an official method, or must it use the most updated version?

Reference: (See references for above question)

Here again, we need context for clarity.

In resolving issues of conformance to an "official standard" (broadly meaning NDA or compendial), the current version of the analytical method is the method that FDA will use to determine compliance.

From a compliance point of view, all compendial products (most ANDA products or NDA products which have become compendial) must meet, at any point in their shelf lives, the standards set forth in the revision of the compendia that was current at the time the drugs were manufactured.

Monographs published in the current revision of the compendia supersede all earlier revisions. Thus, a firm which cites a USP monograph as a test method in its application (ANDA products) or firms whose products subsequently become compendial (NDA products) should be mindful of this and update their methods accordingly.

In the context of lot to lot release testing, firms should use the approved methods they've committed to use, per their approved applications. While this statement may seem to be at "odds" with the paragraph above, the following indicates that it is not. The process used by the USP to revise its contents -- the Pharmacopeial Forum (PF) -- is a gradual one. The PF is the medium used by the USP to publicize proposed monograph revisions and provide opportunities for firms or other interested parties to comment on the proposed revisions. Generally, firms are active (and are encouraged by the agency to be) participants in this process, which usually precludes any problems. Firms may use any scientifically sound method, but should be aware that in the event of a dispute the current method (what you can call the "official method") will govern.

Contact for Further Info: Monica Caphart, HFD-325, 301-594-0098, e-mail: caphartm@cder.fda.gov

Would pharmaceutical industry "teams" be compatible with drug CGMP regulations (e.g., regarding a q.c. unit's role, team approval of its own work, and product release)?

Reference: 21 CFR 211.122 (Responsibilities of quality control unit)

No, not if team implementation effectively usurps or countermands the function of the quality control unit. Overall responsibility of the quality control unit, especially with regard to approving specifications and releasing product for distribution, is clearly stated in the regulations.

Investigators who encounter "teams" in a

pharmaceutical manufacturing facility should pay careful attention to the function of, and authority granted to, such units and the net effect that team autonomy may have on established standards and product quality.

For example, be wary of teams that may decide to implement production methods, analytical methods, or product specifications that differ from those in approved new drug applications.

Keep in mind the "so what" of team implementation. The existence of teams, per se, would not be a legitimate 483 observation because in some cases team implementation may not be at odds with the CGMP regulations and may, in fact, be beneficial. For instance, the quality control unit itself may theoretically be structured as a team. Production units may also include teams that could legitimately recommend process improvements to the q.c. unit (which ultimately evaluates and approves or disapproves of the suggestions). Production unit teams should not, however, independently put those changes into effect in the absence of q.c. unit review and approval.

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

On Stability (Policy Questions on Stability Issues):

1) For expiration dates that fall after the year 2000, does FDA require or recommend the year to be expressed as 4 digits in order to avoid ambiguity?

Reference: See 21 CFR 211.137(a) and (d), (Expiration Dating)

There is no codified requirement for expressing the expiration date in any specific format, but we recommend using 4 digits for the year 2000.

As it is common practice for companies to use the month and last two digits of the year to specify an expiration date on drug product labels, some companies have been using the designation "00" to specify an expiration date in the year 2000. We have received inquiries that suggest that it may not be apparent to consumers that "00" is intended to represent the year 2000. Therefore, we now recommend that the designation for the year 2000 and beyond not be abbreviated on drug product labels.

2) How long may a firm store in-process/intermediate powder blends and triturations, sustained-release pellets/beads, and tablet cores, absent separate stability studies, before using them in the finished drug products?

Reference: 21 CFR 211.110 (Sampling and testing of in-process materials and drug products); and 211.111 (Time limitations on production)

For such intermediate/in-process materials that are known to be chemically and physically stable, a holding period of up to approximately 30 days (under appropriate storage conditions), before use in manufacturing a finished drug product, is generally acceptable without conducting stability studies to verify the holding periods.

However, for unstable materials, or for such materials held for longer than approximately 30 days before use in manufacturing a finished drug product, stability studies should be conducted according to an approved stability protocol to verify the holding periods. The stability studies should include evaluations of the in-process/intermediate materials up to the time of their use in manufacturing a finished drug product, and should include long-term monitoring of finished product batches manufactured with the in-process/intermediate materials.

In the latter case, until appropriate stability data is generated, the expiration date assigned to finished product batches should be calculated based on the date of manufacture/release of the in-process/intermediate material, rather than on that of the finished product.

Contact for Further Info: Barry Rothman, HFD-325, 301-594-0098, e-mail:

rothmanb@cder.fda.gov

Gas What? (Policy Questions on Medical Gases):

1) What are the requirements for modifying the zero step of the calibration procedure for Servomex (R) oxygen analyzers?

Reference: 21 CFR 211.160(b)(4) (General requirements); and 211.165(e) (Testing and release for distribution); Subpart I (Laboratory Controls)

The Servomex (R) Oxygen Analyzer instruction manual states that the analyzer zero step (zeroing) is to be checked once a week, after transportation, or if the instrument has undergone a temperature change of 10 degrees C/18 degrees F or more.

It has been our experience that these instruments are usually placed in a room that is well ventilated, and in many instances open to the outside environment when filling operations are underway.

Thus, the analyzer would be expected to be exposed to temperature fluctuations of 10 degrees C/18 degrees F or more during a 24 hour period.

Calibration of the analyzer zero step at weekly intervals may be appropriate if a manufacturer can document that the instrument had not been moved and that the temperature of the area where the analyzer is kept did not fluctuate more than 10 degrees C/18 degrees F. The use and retention of 24 hour temperature recording charts would be acceptable documentation.

If a manufacturer is unable to supply such documentation, we will continue to consider it a major CGMP violation if the analyzer is not calibrated daily, or more often, when cylinders of Oxygen USP are being filled.

Additionally, before we would even consider accepting monthly calibration of the analyzer zero step, we would require validation data to support a firm's contention that monthly calibration is appropriate. Such data should include 24 hour temperature charts and daily zero step calibration checks for at least one (1) year.

Please note that each individual facility would be required to perform its own oxygen analyzer validation study.

2) Are the new digital readout Servomex(R) 244 oxygen analyzers acceptable for oxygen analysis?

Reference: 21 CFR 211.165(e) (Testing and release for distribution)

FDA does not approve or disapprove laboratory instrumentation. However, we are aware that the manufacturer of Servomex (R) analyzers has instituted a major modification to the Servomex 244 oxygen analyzer (OA) that merits further validation before it can be acceptable.

The firm implemented several internal changes and converted the analyzer from an analog to a digital read-out but did not validate USP methodology equivalency.

Servomex(R) is developing validation data and is expected to send it to us upon completion. In the meantime, absent data that demonstrate USP equivalency, the 244 OA with a digital readout would not be acceptable for the analysis of medical gases, especially Oxygen USP.

Firms which use the digital 244 oxygen analyzer are required under the above reference to demonstrate USP method equivalency.

Nevertheless, the analog 244 OA remains an acceptable analyzer, when used in conformance with applicable CGMP requirements, for analysis of medical oxygen.

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

Should sterile drug process inspections continue to focus on sterile filtration validation?

Reference: 21 CFR 211.113(b) (Control of microbiological contamination)

Yes. We want to clarify any apparent confusion regarding inspectional coverage in light of a review division policy regarding sterilization filtration validation. CDER has announced that supplements submitted to applications approved prior to March 31, 1995, in which the filters and filtration conditions have not changed, will not prompt review divisions to revisit sterilizing filtration validation issues--unless specific safety concerns have arisen.

This policy applies strictly to drug application review. There is no change in inspectional audit points, and, more importantly, CGMP requirements. 21 CFR 211.113 states that any sterilization process must be validated. In addition, 21 CFR 211.63 and 211.65 require that equipment used in processing of a drug product be suitable for its intended use and not adversely affect the identity, quality, strength, purity, or safety of a drug product.

For aseptically processed products which employ sterile filtration as the sole means of rendering the drug product free of microorganisms, it is particularly critical to validate the efficacy of the filtration process. If any validation task is contracted to a sterilizing filter vendor, it remains the sterile drug product manufacturer's ultimate responsibility to ensure that worst-case formulation and processing parameters are adequately studied, evaluated, and documented. Final conclusions by responsible personnel must also be documented by the firm. This data should be available during current drug pre-approval inspections and for already marketed products produced by sterile filtration.

As stated in FDA's Sterile Drug Products Produced by Aseptic Processing (1987) guideline, if a product grouping or bracketing strategy is used, the firm should be prepared to support its applicability to the particular drug product studied.

Information Contact: Richard Friedman, HFD-324, 301-594-0095, e-mail: friedmanr@cder.fda.gov

Data Integrity Report:

COA Transcriptions, and Lab Work Misrepresentations

A practice observed during some inspections of finished drug manufacturers is the transcription of test results from the supplier's Certificates of Analysis (COAs) for raw materials to the manufacturer's own lab books. When this occurs, any observer (e.g., FDA Investigators) can be misled to believe that the manufacturer performed these lab tests when, in truth, this may not be the case.

Investigators who observe this practice should request proof that the tests were performed by the company, in the form of actual lab equipment printouts, chromatographs, or original notes.

We would regard the integrity of such a practice to be highly suspect under the following circumstances:

1. The company has no raw data (i.e., lab records, instrument printouts, etc.) showing that it actually did the tests. In such an instance, there is no proof that the identity test is being done and a periodic check of the supplier's test results would also be missing. This is also a serious CGMP deficiency since these tests are required under 21 CFR 211.84(d)(2). Such a transcription (from a supplier's COA to the recipient's books) makes it look like the company did the tests to fulfill the CGMP requirement when, in fact, the lack of raw data (i.e., the evidence) indicates they did not. This is a data integrity problem.

2. Another strong indication by which investigators can tell that a company may not be performing tests required under 21 CFR 211.84(d)(2), for which they have recorded data

that give the appearance of performance, is if the test results observed in the company's lab book are identical to those on the COA. If you had this condition plus the condition in 1 (i.e., no raw data at all), then this would be both a serious CGMP deficiency and a data integrity problem in that a company would be falsifying records, trying to make it look like it is meeting CGMPs.

However, the transcription of results from a supplier's COA to a finished manufacturer's own lab records would have less significance, as a potential data integrity problem, if a company was transcribing results from a COA and could also show you that it was actually doing the identity test and periodic validation of the supplier's test results on the COA. Again, proof would be in the form of bona fide lab records/equipment printouts showing that the manufacturer actually did the identity test and periodic check of the supplier's test results.

Different results (between the COA and the company's own results) for the same test would also add to the credibility of the claim that they are doing their own identity tests and periodic checks of a supplier's results.

Transcription, per se, of COA results is not a CGMP deviation provided the manufacturer's notebook clearly identifies the results as having been copied.

Contact for Further Info: Randal Woods, HFD-324, 301-827-0063, e-mail: woodsr@cder.fda.gov

Toward The Electronic Government:

CDER Gets New Internet Addresses

CDER's Internet electronic mail (e-mail) is no longer tied to BITNET. The syntax for our new e-mail addresses is: accountname@cder.fda.gov

For example, to send e-mail to Brian Hasselbalch, address it to: hasselbalchb@cder.fda.gov

If you're familiar with Internet, you'll find this new syntax to be more consistent with typical Internet addresses, than our prior BITNET address.

Keep in mind that this change also means you must use a different address when you send e-mail to our DOCNOTES account to receive the ASCII edition of HUMAN DRUG CGMP NOTES. The new address is: DOCNOTES@cder.fda.gov

Human Drug CGMP Notes Now on FAX-On-Demand Service

Human Drug CGMP Notes is now available on CDER's FAX-on-Demand Service.

All 1995 issues have been posted, and we'll do so for future editions, as another efficient way of increasing our readership.

To access the service, simply dial (long-distance) 1-800-342-2722, or (locally) 301-827-0577, and follow the instructions. The system will ask if you'd like a list of available documents or if you wish to select a particular document directly. (Each document is assigned a number.) Then you'll be asked to enter your FAX number using your telephone's keypad. If you experience any difficulty, please try again after a short pause.

The March, June, September and December 1995 editions have document identification numbers 3002, 3003, and 3004, and 3005, respectively.

Other CDER documents, such as NDA guidelines, and Office of Generic Drugs Policy and Procedure Guidelines are also available.

Contacts For Further Info:
Regarding Fax-On-Demand: Rynetta Little (e-mail: little@cder.fda.gov) or Pam Winbourne (e-mail: winbourne@cder.fda.gov), HFD-008, both at 301-594-1012; Regarding Internet e-mail: Paul J. Motise, HFD-325, 301-594-1089, e-mail: motise@cder.fda.gov

P. Motise 11/20/95 DOC CNOTES4P.d95

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FAX FEEDBACK

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

FROM: _____

AT: _____ MAIL CODE: _____

PHONE: _____ FAX: _____

E-MAIL ADDRESS: _____
To receive the electronic version of HUMAN DRUG CGMP NOTES via E-mail, check here _____.

This FAX consists of this page plus _____ page(s).

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 for: _____ on the subject of:

_____
_____
_____

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

_____
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_____