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

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IN THIS ISSUE:

MOTISE'S NOTEBOOK:

Welcome to another edition of Human Drug CGMP Notes, our periodic memo on CGMP for human use pharmaceuticals. Your FAX FEEDBACK responses are still great and we especially appreciate your suggested topics for coverage. In addition to using FAX FEEDBACK, feel free to call, write, or send us e-mail, as several of you have done. 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.

Although this 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 and to do so in a timely manner. This document is a forum to hear and address your CGMP questions, update you on CGMP projects in the works, provide you with inspectional and compliance points to consider that we hope will 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.

To receive an electronic version of this document via electronic mail, address your e-mail request to **motise@cder.fda.gov**. Place **"Subscription Request"** in the subject field, and in the body of your message type **"SUBSCRIBE Human-Drug-CGMP-Notes"**. To discontinue this service, send the same message, but use the word UNSUBSCRIBE instead of SUBSCRIBE (see FAX FEEDBACK).

Thanks!

Paul J. Motise

Policy Questions:

What types of inspectional findings suggest data integrity problems that may be material to the approval of an application?

References: CPG 7150.09; General Policy Fraud, Untrue Statement of Material Fact, Bribery and Illegal Gratuities, and Points to Consider for Internal Reviews and Corrective Action Operating Plans, dated June 1991.

In order for a data integrity issue to be of significance, it must be considered "material" to the approval of the application. Generally, information is considered material if it influences an agency decision.

The following inspectional observations often suggest data integrity problems associated with an application. If your inspection finds problems that appear to fall into one of these categories, the problems should be thoroughly investigated and documented. If the inspectional findings demonstrate a pattern and practice of unreliable data submissions, that may be cause for invoking the Application Integrity Policy. If it is determined that the false submissions were intentional, that may be cause for criminal prosecution.

1. Inconsistencies in dates or times.
    a. Using a raw material prior to receipt
    b. Using equipment that wasn't available
    c. Assaying a product prior to the manufacture of the product
    d. Two different products in the same equipment at the same time

2. Data reporting.
    a. Creating acceptable test results without

actually performing the test
b. Using acceptable records which relate to one batch while altering the records so that the records appear to relate to a bio-batch or stability batch
c. Discounting failed results without an investigation, retesting and reporting only passing results
d. Reporting unrealistic results (results that look too good or results subjected to unrealistic storage conditions, e.g. accelerated conditions for 2 years)
e. Back dating stability test records to meet the required test interval commitments (testing at 6 months but reporting the data as a 12 month result)
f. Failing to submit annual reports or excluding specific lots from the stability program in order to avoid submitting failed results to the agency. (Also check for field alert reports.)
g. Manipulating the analytical procedure to obtain more favorable results
h. Selecting samples for analysis based on appearance (even film coat, bottles with visibly consistent fill volume)

3. Inaccurate/untrue information relative to the production of the bio-batch or stability batches.

a. Multiple batch records for the same lot
b Misrepresenting the batch size
c. Misrepresenting the container/closure
d. Misrepresenting the quality/source of the active ingredient
e. Creating batch production records that are not contemporaneous with the manufacture of the product
f. Excluding from the submission, in-process test records which show the product fails to meet specifications
g. Failure to supplement significant process changes which might affect bio-availability and are made to correct product failures (e.g., add lubricant to blend)

Contact for Further Information: Bruce W. Hartman, HFD-324, 301-827-0062; e-mail: hartmanb@cder.fda.gov.

What types of failures must a batch of new drug product exhibit to trigger a field alert report?

References: 21 CFR 211.192, Production record review, and 21 CFR 314.81(b)(1), Other postmarketing reports, Reporting Requirements, NDA-Field alert report.

21 CFR 211.192 requires a thorough investigation of, among other things, a failure of a batch to meet any of its specifications. This is required whether or not the batch has been distributed. The meaning of distribution here is distribution of the batch in whole or in part.

21 CFR 314.81(b)(1) requires the submission within three working days in a Field Alert Report (FAR) of information concerning any failure of a distributed batch to meet any of the specifications established in an application. This is required when the drug product is both the subject of any type of application and when the batch has been distributed, in whole or in part.

For both of the above requirements, a failure includes any test result which falls outside of an established specification, and which has not been invalidated (e.g., found to be laboratory error). (A failure also includes other developments which are not discussed here).

The required FAR should be submitted within the three day time period after the information becomes known or after distribution, whichever occurs later. An initial report should be filed while any investigation is ongoing and which extends beyond the three day period. The FAR, initial and follow-up as necessary, is required even though a batch may have been released after consideration of the failed test result which falls outside of an established specification along with all data which may be generated by the investigation and the information in the drug product production and controls records reviewed and approved in accordance with 21 CFR 211.192.

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

Laboratory Issues

1) Now that both my lab and the USP have run out of Prednisone dissolution calibrator tablets, how can I perform my scheduled USP dissolution apparatus calibration?

References: 21 CFR 211.160(b)(4), General requirements (Subpart I, Laboratory Controls), and USP 23, Section <711>, Dissolution.

The CGMP regulations require calibration of laboratory instruments at suitable intervals in accordance with an established written program.

Firms that have committed themselves, via approved new drug applications or their own internal standard operating procedures, to perform USP dissolution tests must calibrate the USP dissolution test apparatus according to the USP.

The USP dissolution apparatus suitability test requires use of two different USP Dissolution Calibrator tablets, one a non-disintegrating type, the other a disintegrating type. The calibrator tablets are supplied only by the USP. The current disintegrating calibrator tablet is Prednisone Lot K. The non-disintegrating calibrator tablet is Salicylic Acid Lot M.

Unfortunately, the USP has run out of Prednisone Lot K Calibrator Tablets and we don't expect the new Lot L to be ready for distribution until early 1997.

Until the new Calibrator Lot L is available, it is acceptable for firms to calibrate their USP dissolution apparatuses using only the Salicylic Acid calibrator tablets. Laboratories that run out of Prednisone Lot K Calibrator tablets must document when their supplies expired.

When the new Lot L becomes available, it is an acceptable practice for laboratories to calibrate their apparatuses using both disintegrating and non-disintegrating tablets at their next scheduled calibration time. It is not necessary to perform an interim calibration using only the disintegrating calibrator tablets as soon as they become available.

As an alternative, a firm may extend its calibration interval if such extension is justified and approved by the quality control unit. We expect that such justification would take into account analytical findings which demonstrate that tableting operations and the dissolution test equipment are in a state of control, frequency of apparatus use, and maintenance history of the apparatus.

Note that where firms follow the above it would not be appropriate for investigators to cite as an objectionable observation, on an FDA-483, the failure to perform adequate dissolution test apparatus calibration because of the use of only the Salicylic Acid calibrator tablets.

Contacts for Further Info: Robert Rippere, HFD-354, 301-594-0104, e-mail: rippereb@cder.fda.gov; and Paul Motise, HFD-325, 301-594-1089, e-mail: motise@cder.fda.gov.

Gas What? (Policy Questions on Medical Gases):

1) Are scuba diving tanks of air regulated as medical gases?

Reference: Federal Food Drug and Cosmetic Act, Section 201(g), Definitions

No. Scuba diving tanks hold compressed breathing air, which is not a medical gas, but is, along with fittings and the regulator, regulated by the Consumer Product Safety Commission (CPSC). Empty tanks are regulated by the Department of Transportation which addresses cylinder specifications and hydrostatic testing.

You should forward any complaints you receive regarding scuba tanks to the CPSC, Office of Compliance, 4330 East West Highway, Room 613.11, Bethesda, MD 20814. The CPSC general phone number is 301-504-2706 or 301-504-0580.

Division Contact for Further Info: Mike Verdi, HFD-322, 301-594-0095; e-mail:

verdim@cder.fda.gov.
CPSC Contact: Jay DeMarco, 301-504-0608, ext. 1353.

On Stability (Policy Questions on Stability)

1) Can it be assumed that USP chromatographic assay methods are stability-indicating?

Reference: 21 CFR 211.166(a)(3) Stability testing, 211.165(e) Testing and release for distribution, 211.194(a)(2) Laboratory records

No. While frequently assay methods utilizing chromatography are stability-indicating, clearly such is not always the case. Furthermore, publication in the USP does not mean the method is stability-indicating. USP23 acknowledges this in <1151> "Pharmaceutical Dosage Forms," which states, "Monograph assays may be used for stability testing if they are stability-indicating..." Where use of a stability-indicating assay method is required, the user of the method must have data generated from the testing of his/her product, showing that the method distinguishes the active ingredient from its degradation product(s).

2) Is it acceptable to place an expiration date on a bottle cap instead of the bottle label?

Reference: 21 CFR 211.137(d), Expiration dating, and 201.17, Drugs; location of expiration date

No. The expiration date must appear on the immediate container (except when single-dose containers are in individual cartons, in which case the expiration date may be placed on the individual carton instead of the immediate product container). A bottle cap is part of the immediate container closure system, but is not the immediate container itself.

If the expiration date were to be placed on the bottle cap, there would be a greater chance of mix-up at the end user (or pharmacy dispensing) level because many bottle caps fit either bottles of different lots of the same product, or different products.

Division Contact for Stability Matters: Barry Rothman, HFD-325, 301-594-1089, rothmanb@cder.fda.gov.

In The Works

Compliance Date for Cut Labeling Controls Extended to August 1, 1997

In the Federal Register of July 19, 1996, 61 FR 37679, FDA extended to August 1, 1997 the compliance date for labeling controls for items of cut labeling other than the immediate container label, under 21 CFR 211.122(g).

We are taking this action to afford industry sufficient time to purchase necessary equipment or take other steps necessary to comply with certain provisions of the final rule, published in the Federal Register of August 3, 1993 (58 FR 41348), and to provide additional time for FDA to consider any revisions to the final rule itself.

We will publish in the Federal Register our determination as to whether § 211.122(g) will be retained as currently codified or whether it will be revised. The compliance date for the remainder of § 211.122(g) as it applies to immediate container labels, was August 3, 1994. Note that under § 211.125, a waiver of labeling reconciliation is conditioned on a 100-percent examination for correct labeling performed in accordance with § 211.122(g)(2).

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

Comment Period For 5/3/96 Proposed Rule CGMP Changes Extended to September 30, 1996

In the Federal Register of July 29, 1996, 61 FR 39372, FDA extended the comment period for the 5/3/96 proposed rule (61 FR 20104) regarding CGMP changes from August 1 to September 30, 1996.

FDA is taking this action in response to a request from the Nonprescription Drug Manufacturers Association (NDMA) to extend the comment period. NDMA asked for more time to permit the nonprescription drug industry to prepare and submit comments to the agency.

Division Contact For Further Info: John Dietrick, HFD-325, 301-594-0098; e-mail: dietrickj@cder.fda.gov.

Status of CGMP Guidance for Bulk Pharmaceuticals

The initial draft of a CGMP guidance document for bulk pharmaceuticals (i.e., active pharmaceutical ingredients) was circulated for comment within the agency in March 1996. This is a joint project with the Centers for Veterinary Medicine, and Biologics Evaluation and Research. We've reviewed the internal agency comments and are making the appropriate changes. FDA intends to make the draft document available for public comment by publication of a notice of availability in the Federal Register. Several public workshops, both in the U.S. and abroad are planned during the comment period. We cannot at this point predict the exact outcome and dates when these activities will occur. However, project has a high priority both within CDER and the agency.

Division Contact For Further Info: Edwin Rivera, HFD-322, 301-594-0095; e-mail: rivera@cder.fda.gov

Toward The Electronic Government:

CDER Internet WEB Site Launched

CDER has launched a significant WEB site on the Internet. A part of the overall FDA WEB site (home page address: http://www.fda.gov) the site is now up, running, and loaded with useful and timely information. The CDER page address is http://www.fda.gov/cder.

The site is constructed of four main categories:

(1) *About CDER*, which includes organizational charts, personnel listings, telephone directories, the center's history and the CDER mission statement;

(2) *Drug Information*, where you'll find new drug approval letters, approved final printed labeling, the Orange Book, a drug/device product approval list, drug quality reporting system forms, a data standards manual, MedWatch reporting forms, the National Drug Code and an Inactive Ingredient Guide (purged of non-releasable data);

(3) *Regulatory Guidance*, including industry guidance documents, relevant Federal Register Notices, CDER's Manual of Policy and Procedures, selected excerpts from the Code of Federal Regulations -- such as the CGMP regulations in hypertext -- and HUMAN DRUG CGMP NOTES; and,

(4) *What's Happening*, where postings announce upcoming public meetings and events, and such publications as News Along the Pike.

To connect to the CDER home page directly, point your browsers to: http://www.fda.gov/cder.

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DOC ID CNOTES96.4pd

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Civil Litigation Guidance	Nick Buhay	594-0098
Clinical Supplies/IND CGMP	Paul Motise Bruce Hartman	594-1089 827-0062
Computer Validation	Paul Motise	594-1089
Content Uniformity	Monica Caphart Russ Rutledge	594-0098 594-1089
Criminal Litigation Support	Nick Buhay	594-0098
Data Integrity Case Development	Bruce Hartman	827-0062
Electronic Records/Signatures	Paul Motise	594-1089
Facility Reviews	Russ Rutledge	594-1089
Foreign Inspections	John Dietrick	594-0095
Inspections/ Investigations (For Cause)	Randall Woods John Singer	827-0065 827-0071
Labeling Controls (CGMP)	Paul Motise	594-1089
Laboratory Issues	Monica Caphart Russ Rutledge	594-0098 594-1089

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Recycling Plastic Containers	Paul Motise	594-1089
Repackaging	Barry Rothman	594-0098
Salvaging	Paul Motise	594-1089
Stability/Expiration Dates	Barry Rothman	594-0098
Sterile Facility Construction (Clean Rooms)	Michael Verdi	594-0095
Topical Drugs	Randall Woods	827-0062
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Videoconferencing	Russ Rutledge Paul Motise	594-1089 “
Water Quality	Michael Verdi Rick Friedman	594-0095 "

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:
_____
_____