HUMAN DRUG CGMP NOTES

(Volume 3, Number 3)

September, 1995

(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:

FAX FEEDBACK (Your input requested)

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MOTISE'S NOTEBOOK:

Welcome to another issue 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. 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. (For instance, this edition includes an article on injection labeling changes for USP drug products and CDER's implementation plan to phase in industry compliance with the new requirements.) Topics of special value are those that address emerging new technologies.

As a reminder, although the 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 version, 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, to update you on CGMP projects in the works, to provide you with inspectional and compliance points to consider that will hopefully be of value to your day to day activities, and to 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.

Attached 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.

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 tablet press RPMs important enough to be a factor in process validation?

References: See 21 CFR 211.110 (Sampling and testing of in-process materials and drug products), and 211.100 (Written procedures; deviations).

Yes. Tablet press speed, expressed as revolutions per minute (RPM), is indeed an important factor that needs to be controlled and addressed in tableting validation. Granulation flow characteristics will limit how fast the tableting may proceed; too fast a rate may not permit enough granulation to fall into the dies, resulting in sub-potency. Furthermore, tablet hardness is a function of compression dwell time -- too fast an RPM could mean that the granulation does not experience sufficient compression, and conversely too slow an RPM could mean excessive compression.

Contact for Further Info: Charles Ahn, HFD-325, 301-594-0098, e-mail: ahnc@fdacd.bitnet.

How long must a contract manufacturer, who performs only part of the production steps, retain records for those activities?

References: See 21 CFR 211.180(a) and (b) (General requirements)

The records retention requirements for the contractor are the same as those for the prime manufacturer, just as if the activities had been performed by the prime manufacturer. The retention time is at least one year after the expiration date of the drug product, or, in the case of some OTC drug products which are not

required to have expiration dates, three years after the last of the batch has been distributed.

The retention requirement for the contractor, therefore, means that the contractor must know what the dosage form expiration date is, or (for the above OTC products) when the last of the batch has been distributed. Where the contractor's activities are performed at some stage prior to formation of the dosage form itself (say a contract micronizer), some close communication with the dosage form producer would be needed.

It is important for the contractor's records to be available so that complete product history is maintained and, more importantly, investigations of possible problems may be conducted. The records must be kept at the contract manufacturer's facility, per 211.180(c), or else the records (or copies of them) may be kept at a different location if they can be immediately retrieved by computer or other electronic means.

Contact for Further Info: Paul J. Motise, HFD-323, 301-594-1089, e-mail: motise@fdacd.bitnet.

Gas What? (Policy Questions on Medical Gases):

1) What are the requirements for the calibration of vacuum gauges?

Reference: 21 CFR 211.68 (Automatic, mechanical, and electronic equipment).

Vacuum gauges used during the evacuation of high pressure cylinders require a daily "calibration." This simple calibration consists of an inspection of the gauge prior to the pulling of a vacuum, and with no pressure on the line. The needle should return to "zero"; if not, then an adjustment is required. If the needle cannot be adjusted and returned to zero, then the gauge should be replaced.

In addition, a firm is required to establish written calibration procedures describing their process and should document that the calibration was performed.

2) What are the labeling requirements for cryogenic home vessels?

Reference: 21 CFR 211.130(a) (Packaging and Labeling Operations)

According to 211.130(a), a firm should establish written procedures designed to assure that correct labels are used for its drug products. Until FDA's labeling requirements have been finalized, both high pressure cylinders and cryogenic home vessels are required to have adequate labeling. At the current time, we are requiring cryogenic home vessels to bear labeling similar to that applied to high pressure cylinders, but for the liquid phase. This includes bearing the statement, "Caution: Federal law prohibits dispensing without prescription" in accordance with 21 CFR §201.100(b)(1).

Please note that this requirement pertains to oxygen used for therapy, and not emergency use. So, a firm should determine when the oxygen is intended for emergency use.

Contact for Further Info: Duane Sylvia, HFD-322, 301-594-0095, e-mail: sylviad@fdacd.bitnet.

Bulk Beat (Policy Questions on Bulk Drugs)

1) What is the FDA's current policy with respect to validation of bulk pharmaceutical chemical processes?

Reference: Compliance Policy Guides 7132c.08 and 7125.38 (Process Validation Requirements for Drug Products Subject to Pre-Market Approval).

FDA expects manufacturers to be actively engaged in a validation program for all of their BPC products, although we have not insisted that validations be completed at this time. This agency policy is delineated in the referenced Compliance Policy Guides. FDA will consider withholding approval of new drug applications based on the lack of process validation when (1)

a company has not established or is not following an adequate plan to validate all BPCs; or (2) there is evidence that the process is not validated as demonstrated by repeated batch failures due to manufacturing process variability not attributable to equipment malfunction or operator error.

2) Do Warning Letters involving bulk drug GMP charges require center review or concurrence?

Reference: Regulatory Procedures Manual, Chapter 8-10-45, Center Concurrence, (Transmittal Notice 94-2)

Yes. Since June 1, 1994, all Warning Letters with GMP charges involving bulk drug substances require CDER review and concurrence. This change was effected with a revision to the above referenced chapter.

For domestic BPC manufacturers, Districts should submit Warning Letter recommendations to CDER's Office of Compliance, Division of Manufacturing and Product Quality (HFD-320). Warning Letters to foreign BPC manufacturers are issued directly by HFD-320. More on this in future editions.

Contact for Further Info: Edwin Rivera, HFD-322, 301-594-0095, e-mail: rivera@fdacd.bitnet.

On Stability (Policy Questions on Stability Issues):

1) For injectable drugs in multi-dose containers, is the number of entries to withdraw a dose a factor in determining the expiration date?

Reference: 21 CFR 211.166 (Stability testing).

Unless the multi-dose container is labeled to yield a specific number of doses of a stated volume, there is no limit to the number of withdrawals that may be made from a multi-dose container before the drug is depleted or before the drug reaches its expiration date. The primary concern with multi-dose containers is the potential for contaminating the product during multiple penetrations through the container stopper. While the expiration dating assigned to such products would be based on the stability of the drug product, stability protocols should include requirements for the testing and evaluation of container-closure integrity. Container-closure integrity testing may include physical testing of the closure seal by use of a leak test and by monitoring the ability of the system to prevent microbial contamination. However, it does not normally include an evaluation of multiple penetrations through the container stopper. Furthermore, injectable drug products in multi-dose containers are generally formulated with an anti-microbial agent or preservative, as per the approved NDA and USP requirements.

2) How should the start of the expiration dating period be calculated for new batches of finished drug products intended for commercial distribution?

Reference: 21 CFR 211.166 (Stability testing), and 211.94 Drug product containers and closures.

The expiration date assigned to a new batch of finished drug product should be calculated from the date of release of the finished drug product, provided that the date of release does not exceed 30 days from the date of manufacture of the batch. The date of manufacture of the batch is considered to be the initial date that an active ingredient has been added to the batch during manufacturing. If greater than 30 days has elapsed between the date of manufacture and date of release of the batch, the expiration date should be calculated from within 30 days of the date of manufacture of the batch, and not the date of release.

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Special Report: CDER Compliance Implementation for New USP Injectables Labeling Requirements

BACKGROUND:

Based on a 1991 review of injectable products' nomenclature, the USP has revised General Chapter <1> INJECTIONS. Approximately 130 monograph titles will be affected. The greatest number of changes involve dropping the term "STERILE" from injectable drug titles. The nomenclature revisions became official in USP 23 on January 1, 1995.

Because the nomenclature revisions affected so many product titles, CDER believed it was unreasonable to expect manufacturers to comply with the changes by the official date. Also, concern was expressed that health care providers should be given time to be apprised of these changes. The USP agreed with these concerns and announced in the September-October 1993 Pharmacopeial Forum that there will be an extension of time for adopting the revised titles. Rather than adopting all the revised titles at once, title changes will be reproposed for supplemental revisions.

CDER in turn has prepared an implementation plan based on USP time frames which addresses both USP and non-USP products. CDER has decided to apply the USP revised nomenclature uniformly to all products to lessen confusion that could arise from having similar products with different titles.

IMPLEMENTATION PLAN:

To assist CDER reviewers and FDA field offices in applying these nomenclature revisions consistently, the following implementation plan has been established. [NOTE: CDER reviewers have been advised of this plan via an April 14, 1995, memorandum entitled "Implementation Plan for New Injection Nomenclature", from Yana Mille, Chairperson, CDER Labeling and Nomenclature Committee.]

This plan divides FDA regulated products into two categories:

1. Approved or grandfathered (pre-1938) products subject to USP monographs; and,
2. Approved or grandfathered (pre-1938) products not subject to USP monographs.

For products in these two categories, a "flag" or reminder statement should appear on the labels for a six month period alerting practitioners to the changes. This should assist practitioners in becoming familiar with these revised titles. An example of a "flag" would be: "FORMERLY STERILE (insert drug name) ".

Since the labels and labeling are being revised to comply with compendial requirements [21 CFR 314.70(d)], revised labels and labeling may be submitted with an annual report provided the change is described. However, if the firm prefers to submit revised labels and labeling as a "Special Supplement - Changes Being Effected" [21 CFR 314.70 (c)], this type of submission would be accepted since it affords the Agency an opportunity to approve the new labeling.

Category 1 Products

For USP monograph products, a revised injection title (revised established name) shall not be used until a USP Supplement, stating the revised monograph title, has been published. Firms will then have 18 months from the effective date of that Supplement to revise the labels and labeling to reflect the new title.

Category 2 Products

For those products which are not subject to USP monographs, firms will have 18 months from the effective date of USP 23 to revise the affected labels and labeling. In other words, revised labels and labeling should be in place by July 1, 1996. The changes to be made are as follows:

1. The term "STERILE" is eliminated from the titles of injectable products. [NOTE: The term "STERILE" will not be removed from appropriate monograph titles for WATER that are intended for

direct administration, such as *STERILE WATER FOR INJECTION*.]

2. For established names of injectable products, the following USP classification system should be used in determining the product's title:

   a. LIQUIDS

      (1) Title for liquid preparations that are drug substances or solutions thereof:
      [**DRUG**] **INJECTION**
      (2) Title for liquid preparations of solids suspended in a suitable liquid medium:
      [**DRUG**] **INJECTABLE SUSPENSION**
      (3) Title for liquid preparations of drug substances dissolved or dispersed in suitable emulsion medium:
      [**DRUG**] **INJECTABLE EMULSION**

   b. SOLIDS

      (1) Title for dry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for Injections:
      [**DRUG**] **FOR INJECTION**

      (2) Title for dry solids that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Injectable Suspensions:
      [**DRUG**] **FOR INJECTABLE SUSPENSION**

Contacts for Further Info: Meade North, HFD-335, 301-594-0104, e-mail: northm@fdacd.bitnet, and Yana Mille, HFD-611, 301-594-0340, e-mail: milley@fdacd.bitnet.

Toward The Electronic Government:

PDF format added to electronic editions of Human Drug CGMP Notes

We've added another format to the electronic editions of this newsmemo, the Adobe® (PDF (portable document format). Look for the letters PDF in the CDER Internet Gopher (address gopher.cder.fda.gov) and FTP (File Transfer Protocol) server (address cdvs2.cder.fda.gov) directories that have the name Human Drug CGMP Notes.

PDF files may be viewed or printed using Adobe's widely available Adobe Acrobat® Reader 2.0, which is distributed for different PC platforms. Adobe distributes the reader free of charge via many on-line services.

Use of multi-platform electronic file readers and printers along with their respective common document formats permits people who have different computer systems to nonetheless view, read, and print electronic documents in a form that closely matches the layout, fonts, and styles of the original document; graphics are also preserved. Thus, if you don't use (for example) WordPerfect as your word processor, you won't be restricted to using the plain vanilla ASCII (American Standard Code for Information Interchange) format to view and print electronic documents. For instance, graphics in this newsmemo, which don't appear in the ASCII edition, will appear in the PDF format.

Use of PDF format files is also being explored by other parts of CDER as a means of exchanging electronic documents.

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DOC ID CNOTES95.w60

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Aseptic Processing	John W. Levchuk	594-0095
	Edwin Rivera	"
	Tony Lord	"
Biotechnology	Walter Brown	594-1089
Bulk Drugs	Edwin Rivera	594-0095
CGMP Guidelines	Paul Motise	594-1089
Civil Litigation Guidance	Nick Buhay	594-0098
Clinical Supplies/IND CGMP	Paul Motise	594-1089
	Bruce Hartman	827-0062
Computer Validation	Paul Motise	594-1089
	Charles Ahn	594-0098
Content Uniformity	Monica Caphart	594-0098
	Russ Rutledge	594-1089
Criminal Litigation Support	Nick Buhay	594-0098
Data (Application) Integrity	Bruce Hartman	827-0062
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Dissolution	Monica Caphart	594-0098
	Russ Rutledge	594-1089
Electronic Records/Signatures	Paul Motise	594-1089
CGMP for Pharmacies	John Levchuk	594-0095
Inspection (For Cause) Assignment Preparation	Randall Woods	827-0062
Labeling Controls (CGMP)	Tony Lord	594-0098
Laboratory Issues	John Levchuk	594-0095
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Medical Gases	Duane S. Sylvia	594-0095
NDA/ANDA Pre-Approval Inspections	Bruce Hartman Randall Woods	827-0062 "
Penicillin Cross Contamination	Duane S. Sylvia	594-0095
PET Radiopharmaceuticals (CGMP)	John Levchuk	594-0095
Process Validation (Non-Sterile Dosage Forms)	John Dietrick	594-0098
Process Validation (General)	Paul Motise	594-1089
Recycling Plastic Containers	Paul Motise	594-1089
Repackaging	Tony Lord	594-0095
Salvaging	Paul Motise	594-1089
Stability/Expiration Dates	Barry Rothman	594-0098
Sterile Facility Construction (Clean Rooms)	Tony Lord	594-0095
Sterilization Validation	John W. Levchuk Edwin Rivera	594-0095 "
Topical Drugs	Randall Woods	827-0062
Videoconferencing	Russ Rutledge	594-1089

FAX FEEDBACK

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FROM: _____

AT: _____ MAIL CODE: _____

PHONE: _____ FAX: _____

E-MAIL ADDRESS: _____
To receive the electronic version of HUMAN DRUG CGMP NOTES via E-mail, check here _____, or send an e-mail request to docnotes@fdacd.bitnet.

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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