HUMAN DRUG CGMP NOTES

(Volume 3, Number 1)

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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. This begins our third year. Your FAX FEEDBACK responses are still excellent and we especially appreciate your suggested topics for coverage. We've revised FAX FEEDBACK to enable us to better respond to your particular questions on a given topic. 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. Also welcome are 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 readership is FDA field and headquarters personnel. Therefore, for now, we cannot extend our distribution list to people outside the agency. The primary purpose of this communication 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 we hope will 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.

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 the Policy and Guidance Branch, HFD-323, by interoffice paper mail, using the above address, by phone at (301) 594-1089, or by electronic mail (under the agency e-mail system, address your message to the last name of the contact, such as Rutledge, or Motise.)

FDA staffers may receive an electronic version of this document via electronic mail, by letting us know (see the check off line in FAX FEEDBACK). Thanks!

Paul J. Motise

POLICY QUESTIONS:

What kinds of USP dissolution test failures are significant enough to be noted on Forms FD-483 ?

References: See 21 CFR 211.165(a), Testing and release for distribution.

Routine failure of manufactured batches of a product to pass USP Dissolution tests at Stage 1 is not significant enough to be noted on Forms FD-483; neither is occasional failure of individual dosage units at Stage 2. A batch does not fail the USP Dissolution Test until it fails at Stage 3. However, frequent failures at Stage 2 are significant when other batches of the same product have Stage 3 failures, and therefore should be noted on Forms FD-483..

CDER requires submission of test data for twelve dosage units in every new drug application, or supplement thereto, that requires dissolution test information. CDER and the USP define the dissolution test at Stage 2 (twelve units tested). We anticipate that manufacturers should have to test at Stage 2 routinely, and that there will be occasional failures of individual dosage units at Stage 2. That is why the USP Acceptance Table in Chapter <771> provides for a third level of testing (24 units). CDER and the USP consider Stage 1 (six units tested) to be a bonus situation in which, because all of the dosage units tested dissolved so well, we permit manufacturers to do less than the expected amount of testing on the batch.

CDER has been working with the USP for some time to upgrade many USP Dissolution tests that have low tolerances, long test times, and/or high apparatus speeds. Several upgraded tests that have been published in Pharmacopeial Forum have drawn criticism from a number of pharmaceutical manufacturers because the upgraded test would be likely to require companies to do Stage 2 testing--which would

precipitate Form FD-483 observations that would not be warranted.

Contacts for Further Info: Monica Caphart, HFD-325, 301-594-0098, and Bob Rippere, HFD-335, 301-594-0104.

Is pressure sensitive labeling on a roll considered to be cut labeling?

References: See 21 CFR 211.122(g), Materials examination and usage criteria.

No, not unless peeled off the roll prior to being brought to the labeling line. Some misinformation appears to have been circulated in the pharmaceutical industry that FDA considers pressure sensitive labeling to be cut labeling -- this is not correct. Pressure sensitive labeling on a roll is roll labeling which does not require 100% verification, unless a firm wants to eliminate reconciliation, in which case 100% verification must be performed. However, if any type of labeling is received on rolls but is removed from the rolls by peeling them off or cutting off individual pieces prior to being brought to the labeling line, then we consider the pieces to be cut labeling.

Is it acceptable for two employees to verify correctness of hand applied labeling inserts by inspecting the insert bar codes or bleed lines (for correct alignment)?

Yes, as long as the firm can document adequate (representative) sampling and inspection (proofing) of the incoming lot of inserts to ensure that the correct inserts had been received. Bar codes on the inserts could also be scanned using hand or pen type scanners as long as the equipment is able to create an electronic record of the number of pieces scanned and this information is archived so that it can be checked against the packaging records during inspections.

Contact for Further Info on above labeling issues: Anthony Lord, HFD-322, 301-594-0095.

Would FDA disapprove a pharmaceutical plant because it was located next to a landfill site?

Reference: 21 CFR Part 211, Subpart C, Buildings and Facilities, generally.

Not necessarily. More important than a facility's proximity to sources of contamination is the adequacy of measures the firm takes to prevent such contamination from adversely affecting drug product quality. It would be far from prudent to locate a pharmaceutical establishment alongside a land reclamation facility (which conjures up visions of such potential sources of contamination as rodents, insects, birds, and ground water toxic leachates). The task of protecting the drug product and production environment from such contamination would be challenging, but not insurmountable. Field investigators who encounter such a situation should, of course, pay close attention to how the firm isolates production operations from potential contaminants. However, in the absence of demonstrated routes of contamination, we would not disapprove of the facility based solely on its proximity to the landfill.

Division Contact for Further Info: Paul J. Motise, HFD-323, 301-594-1089.

Gas What? (Policy Questions on Medical Gases):

1) What is the significance of the air liquefaction statement? Is further testing required if this statement is not available?

Reference: 21 CFR 211.165(f), Testing and release for distribution.

The United States Pharmacopeia XXIII Oxygen monograph states that if the air liquefaction statement is present then a firm is exempt from performing the carbon dioxide and carbon monoxide impurities testing.

Let's look at it another way; there are four (4) required tests listed under the oxygen monograph. They are the identification test, the

carbon dioxide impurity test, the carbon monoxide impurity test and the assay. As long as the air liquefaction statement is available either by a letter from the supplier or by a certificate of analysis, then the identification and the assay are the only tests required.

2) Has the odor test been eliminated from the prefill inspections, due to concerns over pathogenic contamination or other dangerous compounds?

Reference: 21 CFR 211.84(d)(3), Testing and approval or rejection of components, drug product containers, and closures; 211.94(b&c), Drug product containers and closures; and, 211.113(a), Controls of microbiological contamination.

No. The Compressed Medical Gases guideline, page 5 and 6, states that since the containers and closures for medical gases are reused over and over again, they require special considerations, i.e., inspections, prior to filling. Therefore, an odor test of each cylinder to detect foreign odors is required. Of course, the odor test should not be performed on anesthetic gases such as nitrous oxide, or on carbon dioxide.

At the present time, we are unaware of any problems and have received no reports of medical gases becoming contaminated with pathogens. However, if this is a problem or a major concern, then a medical gas manufacturer would be required in accordance with 21 CFR 211.113, Control of Microbiological Contamination, to establish written procedures designed to prevent objectionable microorganisms in the drug product.

Division Contact for Further Info: Duane Sylvia, HFD-322, 301-594-0095.

Published In Final:

CGMP revisions; retrospective review, final rule, 1/20/95, effective 2/21/95.

Reference: 60 FR 4087, No. 13, 1/20/95.

The changes to the CGMP regulations include: clarifying the degree of discretion provided to manufacturers to determine whether separate or defined areas of production and storage are necessary, clarifying the standard used to determine the degree of scrutiny necessary to check the accuracy of the input to and output from computer systems, exempting investigational new drug products from bearing an expiration date, permitting the use of a representative sampling plan for examination of reserve samples, and clarifying the manufacturer's responsibilities regarding batch records during the periodic evaluation of drug product quality standards. The revisions come as a follow up to the 2/12/91 (56 FR 5671) proposed rule, as part of the agency's ongoing retrospective review, and are expected to provide regulatory relief while maintaining product quality.

Division Contact for further info: Paul J. Motise, HFD-323, 301-594-1089. Contact for docket and FR info: Howard P. Muller, Jr., HFD-362, 301-594-1046.

Toward The Electronic Government:

Human Drug CGMP Notes; 1995 Cumulative issues to be posted to Internet FTP server.

Beginning with this volume, we will post cumulative issues of Human Drug CGMP Notes to CDER's Internet FTP (File Transfer Protocol) Server (address: CDVS2.CDER.FDA.GOV). Each edition will be posted in WordPerfect 5.1 and ASCII (American Standard Code For Information Interchange) formats. The file names will appear in the format "HDCGMPxx.myy" where "xx" will appear as "w5" for WordPerfect 5.1, or "as" for ASCII text, and "myy" will represent the date, where "m" will be "1" through "9" for months January through September, "o", "n" and "d" represent October, November and December, and "yy" will be the last two digits of the year, respectively. Thus, this edition in WordPerfect format, for example, will

be posted as "HDCGMPW5.395".

Division Contact For Further Info: Paul J. Motise, HFD-323, 301-594-1089.

Focus On: Media Fill Contamination Rate

References: 21 CFR 211.113(b), Control of microbiological contamination; and Guideline on Sterile Drug Products Produced by Aseptic Processing; PDA Journal of Pharmaceutical Science & Technology, Sept./Oct. 1994, Vol 48, No. 5, letter to the editor by Kunio Kawamura, Ph.D., Takeda Chemical Industries

The performance of media fill runs is a standard industry practice for the purpose of:

- simulating aseptic assembly operations of sterile product without actual product fill;

- prompting the need for evaluation of the assembly operation when positive contaminated units result during a media fill run;

- identifying environmental and human caused operational deficiencies and any other causes for discrepancies and their correction;

- validating the aseptic assembly process.

Recent industry and FDA discussions have focused on the question of media fill contamination rates and the adequacy of statistical methods for determining acceptable sterility assurance levels (SALs). This is based on the percentage of filled media units that are found to be contaminated.

FDA's Guideline On Sterile Drug Products Produced By Aseptic Processing references a media fill contamination rate of .1% in two separate instances. Currently, contamination rates >.1% are expected to prompt industry to:

- investigate thoroughly records of the processes, equipment, environment and personnel associated with the failed media fill;

- identify the causes and correct the problems; and,

- revalidate with three additional media fill runs.

However, the result of a media fill contamination rate <.1% (even as low as the incidence of one contaminated unit out of any number of units) in a media fill should be regarded by an aseptic operator as sufficient reason to:

- investigate (e.g. speciate and identify the possible origins of the organisms in the contaminated unit(s), considering potential developing trends over many media fills, etc.)

- evaluate results to determine the need for an expanded investigation to identify contamination causes and make corrections if possible.

Although the Guideline On Sterile Drug Products Produced By Aseptic Processing states that FDA recognizes the scientific and technical limits of validation, it should be noted that there are also limits in the degree of confidence with which one can state that observed contaminated units in any media fill represent the true contamination rate. Although the degree of confidence in perceiving the true contamination rate increases as the total number of units in a media fill increases, it must also be recognized that there can never be absolute certainty that an observed incidence of even one contaminated unit is the actual number of such units in any given media fill. Some media fills, statistically, will not accurately represent the true contamination rate. The guideline associates a 95% confidence probability with a media fill run totaling 3000 units. Therefore, the chances are that in 20 media fill runs, one of the runs will not accurately represent the true contamination rate.

In summary, true values of the contamination rate of any media fill can only be known to a degree of probability. It is thus never definitely known whether the result (i.e. contamination rate) of any particular media fill is actually a true value or not. To err on the side of patient safety would be for each contaminated unit to be investigated and corrective action taken if necessary.

Division Info. Contact: Randall Woods, HFD-324,
301-827-0062

P. Motise 3/1/95
DOC ID CNOTESW6.395

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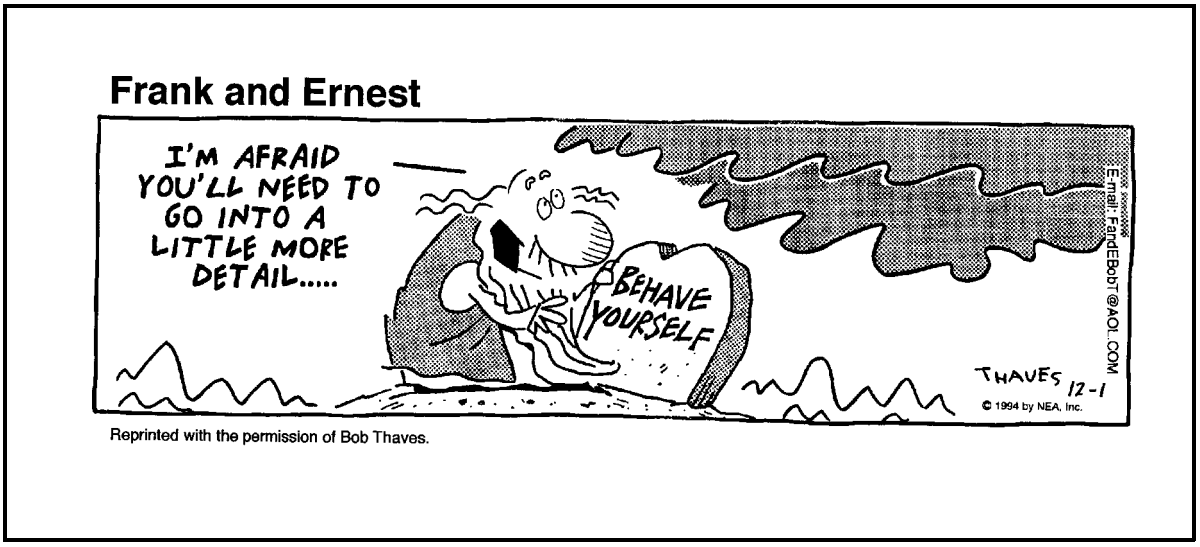
Our special thanks to Mr. Bob Thaves for allowing us to reprint one of his delightful takeoffs on the lighter side of regulation.



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DIVISION OF MANUFACTURING AND PRODUCT QUALITY, HFD-320
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Applications Integrity Policy	John Dietrick	594-0098
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:		
Non-Sterile	John Dietrick	594-0098
Sterile	Tony Lord	594-0095
Clinical Supplies/IND CGMP	Paul Motise	594-1089
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Computer Validation	Paul Motise	594-1089
Content Uniformity	Tony Lord	594-0095
	Charles Ahn	594-0098
Criminal Litigation Support	Nick Buhay	594-0098
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Dissolution	Monica Caphart	594-0098
Electronic Records/Signatures	Paul Motise	594-1089
CGMP for Pharmacies	John Levchuk	594-0095
Inspection (For Cause) Assignment Preparation	Randall Woods	827-0062
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	Monica Caphart	594-0098
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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	William Crabbs	594-1089
Salvaging	Paul Motise	594-1089
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Sterile Facility Construction (Clean Rooms)	Tony Lord	594-0095
Sterilization Validation	John W. Levchuk Edwin Rivera	594-0095 "
Supplements for Sterilization Validation	William Crabbs	594-1089
Topical Drugs	Randall Woods	827-0062
Videoconferencing	Russ Rutledge	594-1089

FAX FEEDBACK

TO: Paul Motise, HUMAN DRUG CGMP NOTES, HFD-323
FAX: 301-594-2202 (Phone 301-594-1089)

FROM: _____

AT: _____ MAIL CODE: _____

PHONE: _____ FAX: _____

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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:
_____
_____
_____