

HUMAN DRUG CGMP NOTES

(Volume 2, Number 3)

September, 1994

(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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DIVISION SUBJECT AREA CONTACTS

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(Your input requested)

Division Director's Notes:

By way of introduction, I've recently become the Director of the Division of Manufacturing and Product Quality. I look forward to working with you to meet the challenges, and realize the opportunities, that face us, as we are all asked to do more with less. Despite shifting priorities and shrinking resources, I assure you that the CGMP program area remains vitally important in the agency's overall drug quality assurance responsibilities.

More than most rules, the CGMP regulations are dynamic. For example, changes are on tap for labeling controls, reserve samples, batch record reviews, and computer systems. We are committed to keeping the CGMP regulations current, and issuing timely and valuable policy and guidance. We will also take advantage of new technologies and innovations, such as videoconferencing and electronic distribution of documents, to enhance field/CDER communication and policy development. Human Drug CGMP Notes is but one mechanism to reach those goals. Your feedback is critical to our mutual success, and I encourage your input into this and other projects.

Douglas I. Ellsworth

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-

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 continue to be excellent and we especially appreciate your suggested topics for coverage. You need not, however, limit the dialog to conveyance by FAX FEEDBACK. Feel free to call, write or send us e-mail, as several of you have done.

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 will hopefully be of value to your day to day activities, and to clarify existing policy and enforcement documents.

Since our prior edition, we have begun the process of obtaining department approval for converting this memo into a true newsletter. Upon receiving such approval we will be able to accept "subscription requests" from anyone outside of the agency. The process takes time, but we have taken the first steps. Until we have the approval, the document remains an in-house issuance.

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

1089, or by electronic mail (under the integrated e-mail system, address the message to the last name of the contact, such as CRABBS, or MOTISE.)

If you would like to receive an electronic version

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of this document via electronic mail, let us know (see the check off line in FAX FEEDBACK).

Thanks!

Paul J. Motise

POLICY QUESTIONS:

Can manufacturers use Millipore's "Matrix Approach" to validate a product/filter combination as sterilizing?

References: See 21 CFR 211.113, Control of microbiological contaminants

Yes. CDER has performed an intensive evaluation of Millipore's matrix procedures and reports. We have concluded that their matrix system is scientifically sound and acceptable. It compares the product to be evaluated with products in a database that have actually been tested for bacterial retention. This is not the only approach that can be used. For example, products can be grouped and the worst case product from each group can be tested for bacterial retention, or each product can be tested for bacterial retention. All of these methods will meet the CGMP validation requirement for filter bacterial retention.

The key requirement is that the drug manufacturer must have a report that shows the characteristics of the product in question and the products, from the database, used to show that the filter will sterilize the product. They must also have a copy of the test methods used to actually test the products or to test the products in a database.

Division Contact for Further Info: Dr. John Levchuk, HFD-322, 301-594-0095.

The new drug application will normally state the proposed production batch size. Any change in the manufacturing process or batch size before approval of the application requires an amendment which provides the blank documentation for the new batch size. If and when the application is approved, the approval will be for the amended batch size. Process

Does a manufacturer need to test each drug product for filter extractables?

References: See 21 CFR 211.65, Equipment Construction.

NO. Drug manufacturers do not have to test sterile drug products for filter extractables. In most cases the extractables cannot be detected because the drug product interferes with the test methods and the quantities present are very low. The level of extractables from current sterilizing filters is very low, i.e. approximately 13-15 mg per 10 inch cartridge. Accounting for dilution by the drug product, the quantities are in the parts-per-million range. This does not mean that the drug manufacturer does not need to have information concerning filter extractables. They must have data showing the identity, quantity and toxicity of the extractables. They should also have the methods and solvent systems used to obtain the amount of extractables per filter. This information can be supplied by the filter manufacturer.

Division Contact for Further Info: Dr. John Levchuk, HFD-322, 301-594-0095.

What's Required of a firm that decreases its proposed scale-up batch size prior to NDA/ANDA approval because it can't meet its established specifications for full scale production? Are new stability studies required?

References: 21 CFR 211.166, Stability testing; 21 CFR 314.60, Amendments to an unapproved application.

validation must then be performed on the final approved production batch size prior to commercial distribution.

Tentative expiration dates are approved on the basis of stability testing on the biobatch and any other batches available. Full shelf life stability studies must then be done on the first three

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production batches (in this case, the final approved scale-up batch size) to confirm the tentative expiration date.

Decreasing the proposed production batch size is not a problem in itself. We would, however, expect the district to investigate the change and the failed batches to determine if the batch instructions in the amended application would yield an acceptable product, i.e., earlier scale-up problems are resolved.

Division Contact for Further Info: John Dietrick, HFD-325, 301-594-0098.

Are UPC bar codes acceptable for automated labeling verification?

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

The revised CGMP regulations do not specify what automated system or bar code symbology firms must use. The goal is to have a unique code (for scanners) or area (for machine vision systems) for a specific drug product on the labeling which can be reliably verified by automated systems. When the revisions were first proposed, low density bar codes were already in use by a number of firms for labeling verification. At that time, the UPC (Universal Product Code) was not considered to be a practical bar code to use for verification since the equipment available could not reliably scan the high density UPC barcodes at packaging line speeds of 200 to 300 containers per minute. In fact, the equipment available in the early 1980's was not always reliable even with low density bar codes.

However, equipment available today can reportedly read UPC bar codes at high packaging line speeds. If that is demonstrated to

What size reserve samples should repackagers maintain? What reserves should be examined as part of an annual review?

Reference: 21 CFR 211.170(b) Reserve samples.

be correct, we would have no objection to the use of the UPC bar code to verify labeling. One drawback to using the UPC code is that it cannot be changed to reflect major revisions of the labeling. Therefore, a firm using UPC codes to verify labeling must have adequate procedures to control and remove from use obsolete labeling because the UPC bar code will be the same on current and obsolete labeling. If you inspect firms that use high density bar codes such as the UPC or Code 128, evaluate the firms' controls over the labeling and bar code printing because these high density codes require high resolution printing, such as photo-lithography.

Division Contact for Further Info: Anthony Lord, HFD-322, 301-594-0095.

When USP Compendial drug monographs list multiple identification tests, must a firm perform all tests, or will one test suffice?

Reference: 21 CFR 211.84(d), Testing and approval or rejection of components, drug product containers, and closures.

All of the USP identity tests must be conducted and the component must conform to all the identification test specifications for the article to be deemed USP. The reason why some monographs include multiple identification tests (usually listed as tests A, B, etc) is that each test individually is insufficient to provide the necessary assurance of specificity. (The same requirement holds true for dosage form monographs that have multiple identity tests.)

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

Manufacturers (repackagers included) must maintain reserve samples of all batches manufactured. Each sample must consist of at least twice the amount necessary to perform all analyses. Unlike stability study samples, which may reveal only a general trend of a given product, reserve samples are needed to provide quick and specific, although less analytic,

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indications of problems of individual lots. Thus, a reserve sample should be:

1. large enough to provide all necessary analytic testings in investigations;
2. representative of an actual retail configuration; and,
3. examined periodically for visible deterioration.

In general, repackers should set aside at least two full retail package units from each batch to satisfy the reserve and periodic examination requirements.

Division Contact for Further Info: Charles Ahn, HFD-325, 301-594-0098.

Gas What? (Policy Questions on Medical Gases):

1) Is the Pressure Differential Method an acceptable, alternate method for the testing of nitrous oxide?

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

Yes, this is an acceptable testing methodology for the determination of strength/potency of nitrous oxide. However, an identification test must be performed concurrently to preclude the presence of carbon dioxide which will provide the same results as nitrous oxide.

2) Are check valves, i.e., double block and bleed, acceptable and effective at preventing contamination of the incoming product?

Reference: 21 CFR 211.110(a), Sampling and FDA is partially extending, by one year, the effective date of the new labeling control requirements and is reopening the administrative record on the scope of a provision of the final rule. The affected sections are 211.122(g) as applied to cut labeling other than the immediate container label, and the corollary waiver of labeling reconciliation per section 211.125(c).

This action is being taken in response to two citizen petitions from a total of five trade associations. The delay will allow us to further assess the availability of equipment necessary for compliance with the regulation for items of

testing of in-process materials and drug products

Check valves should not be used in the manufacture of medical gases, unless a validation study has been performed.

A recent inspection found a large firm utilizing several check valves which are designed to prevent the back flow of a gas back into a supply line. According to the valve manufacturer, these valves are maintenance free. Realizing that these valves are mechanical, the investigator did not believe this claim and requested the firm's validation study proving that these valves function as required. The firm did not have a study and proceeded to perform a validation of these valves to demonstrate their acceptability. Consequently, the firm's validation study showed that these valves were malfunctioning, and could allow a foreign gas to contaminate (back flow) the incoming supply lines.

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

CGMP REVISIONS:

New Labeling Controls - Some Cut Labeling Requirements Put on Hold:

Reference: 59 Federal Register 39255, 8/2/94, Final rule; partial extension of compliance date; reopening of administrative record, and 58 FR 41349, 8/3/93, Final Rule.

labeling other than immediate container labels, and to address concerns about the scope of a particular provision of that rule.

The action means that firms may continue to follow current labeling controls for items of cut labeling **other than the immediate container label**, such as inserts and shipping cartons -- for those other items of labeling, firms will have until August 4, 1995 to abide by the provisions of 211.122(g). The provisions went into effect on August 3, 1994 for **immediate container labels**, however.

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The action also means that firms will have to continue to maintain strict reconciliation for items of cut labeling **other than the immediate container label**, even where 100% automated verification systems are used.

Division Contact for Further Info: Paul J. Motise, HFD-323, 301-594-1089; HFD-362 Contact: Tom Kuchenberg, 301-594-1046.

TOWARD THE ELECTRONIC GOVERNMENT:

Aseptic Conference Proceedings Transcript on CDER Internet FTP Server

On October 12 & 13, 1993, FDA held an open meeting on the proposed rule requiring Terminal Sterilization on drugs purporting to be sterile (56 FR 51354, 10/11/91, Use of Aseptic Processing and Terminal Sterilization in the Preparation of Sterile Pharmaceuticals for Human and Veterinary Use). The meeting was intended to give industry a public forum to make formal presentations to FDA regarding various aspects of aseptic processing versus terminal sterilization. FDA wanted to be sure it received current information to aid in proceeding with this proposal.

A court transcription service recorded the meeting, transcribed it and forwarded the text to us for editing.

We mailed the edited transcripts to meeting attendees.

For those who did not attend the meeting, the document is available via the Freedom of

Information Act in either paper form or on a disk as two WordPerfect (TM) 5.1 files.

The WordPerfect (TM) files are now also available, at no cost, on CDER's Internet FTP server. To obtain the file use the following commands:

```
FTP CDVS2.CDER.FDA.GOV
LOGIN ANONYMOUS
<any password>
BINARY
GET ASEPCN12.W51 ASEPCN12.W51
GET ASEPCN13.W51 ASEPCN13.W51
EXIT
```

Division Contact for Further Info: (Aseptic Conference itself) Russ Rutledge; (Internet FTP Server) Paul J. Motise, both at HFD-323, 301-594-1089.

P. Motise 8/5/94
DOC ID CNOTESW6.994

DIVISION OF MANUFACTURING AND PRODUCT QUALITY, HFD-320 SUBJECT CONTACTS

Applications Integrity Policy	John Dietrick	594-0098
Aseptic Processing	John W. Levchuk	594-0095
	Edwin Rivera	"
	Tony Lord	"

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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
	Bruce Hartman	"
Computer Validation	Paul Motise	594-1089
Content Uniformity	Tony Lord	594-0095
	Charles Ahn	594-0098
Criminal Litigation Support	Nick Buhay	594-0098
Data (Application) Integrity	Bruce Hartman	594-0098
	LuAnn Summy	"
Dissolution	John Dietrick	594-0098
Electronic Records/Signatures	Paul Motise	594-1089
CGMP for Pharmacies	John Levchuk	594-0095
Labeling Controls (CGMP)	Tony Lord	594-0098
Laboratory Issues	John Levchuk	594-0095
	Monica Caphart	594-0098
Lyophilization	John Levchuk	594-0095
Medical Gases	Duane S. Sylvia	594-0095

**DIVISION OF MANUFACTURING AND PRODUCT QUALITY, HFD-320
SUBJECT CONTACTS (Continued)**

NDA/ANDA Pre-Approval Inspections	Bruce Hartman	594-0098
	Randy Woods	594-0098
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

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Process Validation (General)	Paul Motise	594-1089
Recycling Plastic Containers	Paul Motise	594-1089
Repackaging	William Crabbs	594-1089
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 "
Supplements for Sterilization Validation	William Crabbs	594-1089
Tamper-Resistant Packaging	Duane S. Sylvia	594-0095
Topical Drugs	Randy Woods	594-0098
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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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.

Please have the HFD-320 information contact person get in touch with me regarding:

- | | |
|-------------------------------------|-------------------------------------|
| Sterilizing Filters _____ | Batch Scale-up Issues _____ |
| Labeling Verification Systems _____ | Compendial Test Requirements _____ |
| Medical Gases _____ | Aseptic Conference Transcript _____ |
| CGMP Labeling Control Changes _____ | Reserve Samples _____ |
| Other _____ | |

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

