

HUMAN DRUG CGMP NOTES

(Volume 1, Number 3)

September, 1993

(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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NOTE FROM THE DIVISION DIRECTOR

The wide-ranging issues discussed in this edition demonstrate the characteristic dynamism and evolution of the GMP and preapproval program areas. Here is a brief preview of 3 of many issues being addressed:

Bulk Pharmaceutical Chemicals (BPCs):

Although BPCs are required to be manufactured in conformance with GMPs, there are no regulations. FDA and the industry are increasing their focus on this important area. We are presently developing regulations (or an industry guideline) to describe minimum requirements, and we will be seeking your perspective and that of the industry. In the interim, continue to be guided by the general concepts described in the finished pharmaceutical regs (21 CFR Part 211). As with any inspectional observation, significance depends on the potential for adverse impact on the product. What may be significant for a dose form product may not be significant for a BPC, where the raw materials, manufacturing processes, and degree of control afforded by adequate testing are often different. As with any GMP issue, there are many situational factors that must be considered to determine significance. That's what makes our jobs so challenging! Please let us know if you have any questions or comments in this evolving area.

Process Validation: Nobody argues anymore about the importance of process validation. However, we are sensing that some may be misinterpreting FDA's expectations, by extending the concept to everything (and to the "nth degree"), without sufficient consideration of feasibility, practicality, and, most importantly, contribution to assuring the quality of the product. Therefore, we have begun the process to develop a series of industry guidelines that will describe appropriate approaches and examples of expectations for types of products ... e.g. tablets, capsules, oral liquids, semi-solids, sterile products, etc. This is a major effort which will require the collective efforts of

all of us and the industry.

Routine Collection of Biosamples ... FDA recently published the final rule clarifying the 1991 interim regulation that requires all bioequivalence laboratories to retain samples of the test articles used to demonstrate the bioavailability/bioequivalence of important preapproval batches. The interim and final rules assure the availability of samples that are required to be collected routinely at both the manufacturer and biolab in connection with preapproval inspections. Additional guidance for you and the industry is under development now, and will be available soon. In the interim, please contact William Crabbs if you have any questions.

That's enough for now. We continue to appreciate your enthusiasm and program support.

Paul Vogel

MOTISE'S NOTEBOOK:

This is the third issue of a periodic memo on CGMPs for human use pharmaceuticals. Judging from your response via FAX FEEDBACK, I am pleased that our prior editions were so well received. We especially appreciate your suggested topics, which, starting with this edition, we will cover in this publication.

Many people outside of FDA have acquired copies of the memo, given us their feedback and asked to be put on our distribution list. Though pleased at the wide interest, we must stress that, although the document is fully releasable under the Freedom of Information (FOI) Act, our intended readership is FDA field and headquarters personnel. For now, we cannot extend our distribution list to people outside the agency. Again, our purpose 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.

This document is intended 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 new integrated e-mail addressing system, address the message to the last name of the contact, such as BARR, or MOTISE).

Speaking of 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).

Much has happened since our last edition -- some administrative, like changed phone numbers, and some things more significant like publication of new regulations and inspectional guides. Here's what's happening.

Thanks!

Paul J. Motise

POLICY QUESTIONS:

How many and, what size, pilot stability batches for Antibiotic NDA/AADA Pre-Approval Inspections do we expect?

References: See 21 CFR § 211.166 (Stability

testing), and Office of Generic Drugs Policy and Procedure Guide #35-92 and #22-90.

An exhibition batch (used to generate bioequivalence and stability data) must be representative of the product to be marketed. For AADAs the batch is compared to the innovator's product -- the Antibiotic NDA exhibition batch is compared to the product used in pivotal clinical trials.

For AADA finished drug products and AADA bulk drug substances produced by chemical synthesis, stability data (and bioequivalence data if required) must be generated on at least one batch which is at least 10% of the proposed commercial batch size (100,000 dosage units for solid oral dosage forms). For bulk drug substances produced by fermentation, stability data must be provided on three production scale batches, at least two of which should be generated by different starter cultures.

We expect the exhibition batch to be made in accordance with CGMPs, using equipment, processes, procedures the same as, or equivalent to, what is anticipated for commercial batches.

Caution: One large batch cannot be represented as three separate and distinct batches.

Division Contact for Further Info: Bruce W. Hartman, CSO, HFD-324, (301-594-0098).

What CGMPs apply to a drug warehouse?

References: 21 CFR Parts 210/211 (CGMP Regulations) and 205 (Guidelines For State Licensing of Wholesale Prescription Drug Distributors).

While Section 501(a)(2)(B) of the Act (the "CGMP" section) applies to anywhere drugs are manufactured, processed, packed, or held (including warehouses), the CGMP regulations (21 CFR Parts 210 and 211) only apply to drug

manufacturers' warehouses. The storage and recordkeeping requirements issued under the Prescription Drug Marketing Act, codified under Part 205.50 of the CFR, describe the "CGMPS" FDA believes should be followed by wholesalers that store prescription drugs. FDA stated, in the Preamble to Part 205 (Federal Register of September 14, 1990), that wholesalers who stored their prescription drugs in compliance with the requirements of 21 CFR 205.50 would be considered by the Agency to meet their CGMP obligations under Section 501(a)(2)(B) of the Act.

Contacts for Further Info: Call Margaret O'Rourke, HFD-334, (301-594-0107) re: Part 205, and Paul Motise re: Parts 210/211.

Must a firm conduct stability studies when repacking solid/liquid oral dosage forms into unit dose containers?

Reference: CPG 7132b.10, (Unit Dose Labeling for Solid and Liquid Oral Dosage Forms) Attachment B

Solid and liquid oral dosage form drug products may be repackaged into unit dose containers without conducting stability studies to support the expiration dates used, provided the following conditions are met:

- a. The unit dose container complies with the Class A or Class B standards described in the twenty second edition of the United States Pharmacopeia, General Tests, Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets.
- b. The expiration date does not exceed six months; and
- c. The six month expiration period does not exceed 25 percent of the remaining time between the date of repackaging and expiration date shown on the original manufacturer's bulk container of the drug repackaged, and the bulk container has not

been previously opened.

This policy only applies to solid and liquid oral dosage forms in unit dose containers. All requirements on other dosage forms and other types of packages apply.

Division Contact for Further Info: Barry Rothman, HFD-325, (301-594-0098).

In conducting in-process tablet weight checks, during a tableting operation, is it acceptable to weigh ten tablets at a time, or must ten individual tablets be weighed?

Reference: 21 CFR 211.110(a)(1), Sampling and testing of in-process materials and drug products.

In-process check weighing of 10 tablets to arrive at an average, for purposes of tablet press (punch cam) adjustment, is current practice and acceptable.

The above, pre-supposes that the tableting process itself has already been validated. During validation, it would be proper to weigh individual tablets to determine if the range of weights is sufficiently narrow to show the process is in control. If the validation runs show a weight range that is consistently narrow, then production run in-process checks of 10 tablets to derive an average, is justified.

Individual tablets may be checked (e.g. for content uniformity) during end product testing.

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

POLICY EMERGING:

Item: Metrification of Federal Standard 209E (Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones, 9/11/92); Clarification.

In Vol. 1, No. 2 of the Human Drug CGMP Notes, we said it is not acceptable to qualify a clean room in Metric units by performing a mathematical conversion of the English values.

There were two original purposes for this statement. First, was to prevent people from playing "mathematical games"; obtaining a failing result in the English system, then using some rounded off conversion factor and suddenly obtaining passing results. As the finally issued version of FS-209E uses a fairly accurate conversion factor of 3,530 particles per cubic meter for Class 100, this concern has been largely mitigated in this country, at least with respect to people "shopping around" within the Class Limits Chart. The French, however, proposed using 4,000 as their class limit; so there could be some problem in portions of Europe. The second reason was to assure that the number of sampling locations used was properly based upon the system used. In theory, based upon how "sloppy" a conversion factor was used, an insufficient number of sampling points could be used.

We would not object to use of a particle counter designed to sample one cubic foot of air and convert this precisely into the equivalent number of liters.

We would object to "juggling" the numbers; developing a sampling plan for the number of sampling locations based upon one system using "sloppy" conversion factors, collecting sample volumes based upon another system, again with "sloppy" conversion factors, then converting that number using "sloppy" conversion factors into a number to be read against a limit to determine compliance with a specific Class. This was intended to be the "thrust" of the last edition's article.

Division Contact: Robert Sorensen, CSO, HFD-322, (301-594-0095)

Update on Recycled Plastics in Drug Product Containers

Reference: 21 CFR § 211.94 Drug product containers and closures.

Potential problems attendant to use of recycled material in plastic container closure systems is receiving more attention. Two broad categories of "recycled" material are "regrind" (i.e., tailings and scrap plastic attendant to production of bottles from otherwise virgin starting materials), and "post consumer" plastics (which are washed, ground and melted for incorporation with virgin material to produce new containers). Several states are mandating post consumer recycle content in pharmaceutical containers and several others are considering such a move.

Potential problems include drug contamination from leachables, adverse changes in product stability, and adverse changes in performance characteristics of the plastic containers. The Office of Generic Drugs has initiated a study to determine the affects of using "regrind", and letters to several container producers have been issued. In addition, the Office of Compliance has initiated a surveillance program to obtain more information from a sampling of container makers.

For now, during your inspections, be aware that plastic containers received by drug producers may be made up, in whole or in part, of recycled material. It is important for pharmaceutical producers to know if, when, and to what extent recycled material is present, so they may evaluate the potential impact, consistent with CGMP requirements regarding container/closure suitability. We'll keep you posted on developments.

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

PUBLISHED IN FINAL:

The following CGMP related documents have been published in final form:

Retention of Bioavailability and Bioequivalence Testing Samples; Final Rule: Federal Register of 4/28/93, pg. 25918. (Field Contact: William Crabbs, HFD-323, 301-594-1089, Industry Inquires to: Marilyn L. Watson, HFD-360, 301-594-1038).

Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; Revision of Labeling Controls; Final Rule: Federal Register of 8/3/93, pg 41348. The final rule, effective August 3, 1994, defines gang-printed labeling, specifies more restrictive conditions for use of gang-printed labeling and cut labeling, exempts drug manufacturers that employ automated 100% labeling inspection systems from the labeling reconciliation requirement, and requires manufacturers to identify filled containers that are set aside and held in an unlabeled condition for future labeling operations. The changes are intended to reduce the frequency of drug product mislabeling and associated recalls.

Even though the rule will not be fully effective until August of '94, we expect it to generate considerable interest among pharmaceutical firms, resulting in inquiries during inspections or calls to district offices. We plan to provide additional guidance on these revisions in future editions of HUMAN DRUG CGMP NOTES.

(Contact: Paul Motise, HFD-323, 301-594-1089, or Tom Kuchenberg, HFD-362, 301-594-1046).

The following inspectional guides were issued in July 1993 by the Division of Field Investigations, with input from HFD-320: (Primary contact is the issuing division. Additional guidance is available from HFD-320 according to subject area, per the attachment on division specialists).

Guide To Inspections of High Purity Water

Systems

Guide To Inspections of Microbiological Pharmaceutical Quality Control Laboratories

Guide To Inspections of Lyophilization of Parenterals

Guide To Inspections Of Validation of Cleaning Processes

Guide To Inspections of Pharmaceutical Quality Control Laboratories

TOWARD THE ELECTRONIC GOVERNMENT:

CDER Field Office Service Expanded to Electronic Orange Book

The Field can now access a new on-line database called the "Orange Book/Rx Query. The service is in addition to three other CDER systems already available to districts (Imports Quick Lookup, Drug Quality Reporting, and Library Electronic Reference Network). The Orange Book/Rx Query enables you to retrieve information about approved NDAs and ANDAs by ingredient name, NDA number, applicant name, and other criteria.

We expanded district access to enhance information exchange between CDER and the Field, realizing that, as part of their enforcement activities, investigators need to quickly and easily determine the approval status of particular applications. The electronic Orange Book meets that need and has several advantages over the paper version. First, information is substantially more up-to-date than in the supplemented paper document. Second, your search criteria is not limited to "active ingredient". You can, for example, obtain a listing of all applications currently approved for one particular company -- not possible with the paper Orange Book.

To obtain direct access to the CDER on-line

databases, see your local data manager.
We hope Field districts will benefit from this
enhanced access to information.

Division Contact for Further Info: David Doleski,
HFD-324, (301-594-1060)

P. Motise 9/1/93
DOC ID CNOTESC.993

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

(Note: All phone numbers are in area code 301, unless otherwise noted.)

Applications Integrity Policy	Bradford Williams	594-0098
Aseptic Processing	John W. Levchuk	594-0095
	Robert L. Sorensen	"
	Edwin Rivera	"
Bulk Drugs	Edwin Rivera	594-0095
CGMP Guidelines	Paul Motise	594-1089
Civil Litigation Guidance:		
Non-Sterile	Bradford Williams	594-0098
Sterile	Terry E. Munson	594-0095
Clinical Supplies	Paul Motise	594-1089
Computer Validation	Paul Motise	594-1089
Content Uniformity	Tony Lord	594-0098
	Charles Ahn	"
Criminal Litigation Support	Nick Buhay	410-962-8054
Data (Application) Integrity	Bruce Hartman	594-0098
	Tony Lord	"
	LuAnn Summy	"
Dissolution	John Dietrick	594-0098
Electronic Records/Signatures	Paul Motise	594-1089
Foreign Drug EIs (Compliance)	Jerry Kirk	594-1089

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General Microbiological	Terry Munson	594-0095
GMPs Pharmacies	John Levchuk	594-0095
Labeling Controls (CGMPs)	Tony Lord	594-0098
Laboratory Issues	Bradford Williams	594-0098
LAL/Pyrogens	Terry Munson	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 Randy Woods	594-0098 594-0098
Particulates in Parenterals	Terry E. Munson	594-0095
Penicillin Cross Contamination	Duane S. Sylvia	594-0095
PET Radiopharmaceuticals (CGMPs)	John Levchuk	594-0095
Pharmaceutical Water Systems	Terry Munson	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	William Crabbs	594-1089
Salvaging	Paul Motise	594-1089
Stability/Expiration Dates	Barry Rothman	594-0098
Sterile Facility Construction (Clean Rooms)	Robert Sorensen	594-0095
Sterilization Validation	John W. Levchuk Robert Sorensen Edwin Rivera	594-0095 " "

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Supplements	William Crabbs	594-1089
Tamper-Resistant Packaging	Duane S. Sylvia	594-0095
Topical Drugs	Randy Woods	594-0098
Water Systems	Terry E. Munson	594-0095

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: _____

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).

<p>I found this issue of HUMAN DRUG CGMP NOTES to be [check as appropriate]:</p> <p>__ not very; __ somewhat; __ very; __ extremely informative, and</p> <p>__ not very; __ somewhat; __ very; __ extremely useful to my inspectional/compliance activities.</p>
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Please have the HFD-320 information contact person get in touch with me regarding:

Antibiotic Pilot Stability Batches ____	Recycled Plastics ____
Metrics and 209E ____	Electronic Orange Book ____
In-Process Tablet Weight Checks ____	Unit Dose Stability ____
Warehouse CGMPs ____	Other _____

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