

# HUMAN DRUG CGMP NOTES

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(A Newsletter 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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## COMMENTS FROM THE DIVISION DIRECTOR:

By way of introduction, this is the first issue of a periodic newsletter on CGMPs for human use pharmaceuticals. The purpose of the document is to enhance field/headquarters communications on CGMP policy issues and to do so in a timely manner. We hope to use this newsletter as a forum to hear and address your CGMP policy questions, to let you know what CGMP projects are in the works so you may respond to industry inquiries as to "what's cooking", to provide you with inspectional and compliance points to consider that will hopefully be of value to your day to day inspectional activities, and to clarify existing policy and enforcement documents.

Each issue of HUMAN DRUG CGMP NOTES will be published as needed. I want to stress that this newsletter is intended to supplement, not supplant existing policy development/issuance mechanisms. HUMAN DRUG CGMP NOTES will provide a fast means of distributing interim policy and addressing questions.

Most importantly, I want this communication to foster the flow of information to and from the field. Don't hesitate to ask a question or present your views. You may not be the only person who has the very same question on a particular issue. Your input will help us to develop robust practical policy in the human drug CGMP arena. Therefore, please feel free to contact us with your questions and comments. You may send your input to our Policy and Guidance Branch, HFD-323, by interoffice paper mail, using the above address, by phone at (301) 295-8089, by FAX at (310) 295-8202, or by VAX electronic mail at BARR::A1::FDACD, or MOTISE::A1::FDACD.

*Paul F. Vogel*

## **POLICY QUESTIONS:**

### ***Which antibiotic monograph prevails, CFR or USP?***

CGMP Issue and Reference: Suitability of Standards and Specifications; See 21 CFR 211.160 and 211.165

CHI-DO recently posed the above question while conducting an inspection. The answer is that the CFR monograph prevails if there is any conflict between a USP and CFR antibiotic monograph.

If the USP monograph includes additional requirements not addressed by the CFR monograph, such as dissolution, then we would expect those tests to be performed as well.

CDER has been working for some time on a proposal to eliminate all of the antibiotic CFR monographs. We don't anticipate publication of a proposal soon. In the meantime, be guided by the above policy.

Division Contact for Further Info: Tony Lord, HFD-325, (301-295-8098)

### ***Is lack of a Product Development Report reason to withhold application approval?***

No! Recently, the Center has received a number of recommendations from the field to withhold application approval based, in part, on the lack of Product Development Reports. In addition, presumably because of these field recommendations, some firms have submitted such reports to headquarters review units (Offices of Drug Evaluation I and II, Office of Generic Drugs, Pilot Drug Evaluation Staff). These reports vary in their organization and contain data which is generally already available in other parts of the application, which confounds and delays the application review.

There are no regulations or other agency policies requiring product development reports. While much

of the development data is necessary, there is no requirement for a formal approved report which summarizes such data. The lack of such a development report at a firm is not an appropriate reason for recommending that application approval be withheld even though it may be a useful tool for the firm and the investigator conducting the pre-approval inspection. Firms should be told that if they do prepare such reports, they should not make them part of the official application, nor would they supplant any portion of the application.

CDER is preparing additional guidance for industry and the Field in the pre-approval area. In the interim, continue reporting manufacturing process problems you encounter during pre-approval inspections.

## **PROBLEM EMERGING?**

### ***Item: Finished Vials and Pre-Filled Syringes Subjected to Post-Production Ethylene Oxide Sterilization***

We have received reports that some firms are assembling convenience kits that consist of finished drug products packaged in vials and pre-filled syringes, and medical devices. The kits are then subjected to ethylene oxide sterilization. The primary purpose of the exposure is, of course, to sterilize the devices. However, at the same time, finished packaged drugs undergo stressful conditions that may adversely affect their integrity and stability, conditions which their original producers had not envisioned.

We need to know if you have encountered this kind of operation and if there were any problems (e.g., container/closure failures, product discoloration, precipitates or other signs of stability failures) you detected with the drug products that were exposed to the ethylene oxide.

Division Contact: Paul Motise, HFD-323, (301-295-8089)

## **IN THE WORKS:**

*Where are the revised CGMP labeling regulations?*

Answer: A draft final rule has cleared the agency but appears to be impacted by the administration's moratorium on new regulations. In the Federal Register of June 23, 1989, the agency published a proposed rule to amend certain labeling provisions of the CGMP regulations. The proposal specifies conditions for the use of gang-printed or cut labeling, exempts from labeling reconciliation requirements manufacturers that employ 100 percent drug product label inspection systems, and requires firms to identify filled drug product containers that are not immediately labeled (bright stock). Our work on the final rule is complete and we are optimistic that the final rule will publish soon. Until new rules are in effect, the existing regulations govern.

Division Contact for Further Info: Paul Motise, HFD-323, (301-295-8089)

*Status of the third copy drug application regulations?*

In order to address certain fraudulent practices found during investigations of the generic drug industry, a proposed rule was published in the Federal Register on 1/28/91 which would require submission of an extra review copy of the chemistry and manufacturing controls sections of drug applications. The third copy will be used by FDA investigators during pre-approval inspections to audit application commitments against applicants' actual manufacturing practices. The final rule has cleared the agency but appears to be impacted by the moratorium on new regulations.

In the interim, during inspections continue to rely upon the firm's copy of the application. Of course, should evidence indicate data integrity problems, contact HFD-324 (301-295-8098) to request a headquarters copy from CDER to assist during your inspection.

Division Contact for Further Info: William Crabbs, HFD-323, (301-295-8089)

*Status of GMP revisions under the Retrospective**Review?*

A proposed rule was published in the Federal Register on February 12, 1991 which provided for more flexibility and discretion in the ways in which drug manufacturers could meet CGMP regulations while maintaining those requirements necessary to assure drug product quality. The proposed amendments: 1) exempt IND drugs from expiration dating requirements under specified conditions, 2) allow more latitude in defining "separate or defined" areas, 3) allow annual examinations of a representative number of reserve samples and batch records in lieu of every batch, and 4) allow more latitude in conducting input/output verification of automatic, mechanical and electronic equipment. The division completed review of public comments and prepared a draft final rule which is in the initial steps of the clearance process. Until a final rule becomes effective, current requirements remain in effect; however, the significance of any deviation will be evaluated in the context of the proposal and the adequacy of the alternative system used.

Division Contact for Further Info: William Crabbs, HFD-323, (301-295-8089)

*Bioretention sample regulation status?*

Under the preapproval inspection program, investigators collect samples of the test articles used to demonstrate bioequivalence in support of an NDA/ANDA; samples are collected from both the manufacturer and the biolab.

To ensure the availability of samples, on 11/8/90, FDA published in the Federal Register an interim rule (regulation) that requires biolabs to retain samples of the test articles, effective immediately. A final rule cleared the agency but appears to be impacted at OMB by the prior administration's moratorium on new regulations.

Interim guidance, for your use during inspections, will be issued shortly.

Division Contact for Further Info: William Crabbs, HFD-323, (301-295-8089)

*Electronic Signatures and Electronic Records, what's in store?*

Answer: In the Federal Register of July 21, 1992, FDA published an advance notice of proposed rulemaking on electronic identification/signatures. The notice requested comments on how the agency might accept signature alternatives within the context of three kinds of current and future electronic records: documents maintained by the industry, submitted to FDA, and created and maintained by the agency itself. Discussed were seven key areas of consideration involved in that effort, and the ongoing work of the agency's task force and working group on electronic identification/signatures. The original comment period deadline of 10/19/92 was extended to 12/18/92 by a Federal Register notice of 10/21/92. The issues extend well beyond drug CGMPs. However, until the agency can resolve those issues and publish appropriate regulatory changes, keep in mind the current agency position that the drug CGMP regulations do not anticipate nor permit alternatives to handwritten signatures whenever the regulations require documents to be signed, initialed, approved or endorsed. Although CDER and this division are playing a key role in this project, all centers, general counsel, and ORA are actively working on policy/regulations development. This subject will likely get much attention in the pharmaceutical industry in the near term. We will keep you posted on major developments.

Division Contact For Further Info: Paul Motise, HFD-323, (301-295-8089)

*Guidelines and Inspectional Guides Under Development:*

Guideline on Repackaging of Solid Oral Dosage Form Drug Products: The draft was made available to the public by Federal Register notice of 10/15/92; comments due by 12/14/92. The guideline provides information on certain practices and procedures required by the CGMP regulations for repackaging solid oral dosage form drug products, with a focus on testing, labeling control, stability studies and

expiration dating, reserve samples, and penicillin cross-contamination.

Division Contact For Further Info: Gayle R. Dolecek, HFD-323, (301-295-8089).

Validation Documentation Inspection Guide: This guide, initiated by Ron Tetzlaff while on detail to HFD-323, describes some common validation elements and GMP concepts for FDA inspections of validation documentation systems. It is intended to aid FDA personnel in determining whether validation documentation systems are adequate to assure the quality of drug products. The guide will include information about validation concepts and principles along with a description of documents and data that should be covered during inspections. Record keeping systems and validation strategies will be highlighted along with some of the manufacturing and control operations to be covered. Look for finalization in a few months.

Division Contact for Further Info: William Crabbs, HFD-323, (301-295-8089)

Solid Dosage Form Manufacturing Inspection Guide: This document, initiated by Robert Sharpnack, is intended to provide guidance in conducting inspections of tablet and capsule manufacturing with emphasis on validation activities. It will describe equipment, activities, and terminology relevant to the manufacture of both types of dosage forms. This document is in the first draft stage of development.

Division Contact for Further Info: William Crabbs, HFD-323, (301-295-8089)

Guide To Inspection of Topical Drug Products: This guide, initiated by the Mid-Atlantic Region, addresses selected facets of topical drug production, including potency, active ingredient uniformity, physical characteristics, microbial and chemical purity, and cleaning validation. Transdermal products are also covered. Headquarters will soon publish a final guide appropriate for field-wide use.

Division Contact for Further Info: Paul Motise, HFD-323, (301-295-8089)

**SPEECHES/PUBLICATIONS AVAILABLE:**

To obtain copies of the following speeches and publications, all on current subjects and all having been reviewed and approved for policy by CDER's Office of Compliance, call HFD-323 (301-295-8089):

*Speeches:*

Aseptic vs. Terminal Sterilization, David Barr, Parenteral Drug Association, Sept. 1992

Drug Substances, David Barr, American Association of Pharmaceutical Scientists, February 1992

Drug Substances, Gayle Dolecek, International Society of Pharmaceutical Engineers, October 1992

Efforts to Streamline the Approval Process, Gayle Dolecek, Drug Information Associates, November 1992

Current FDA Perspectives on Label Control, Anthony Lord, PackExpo, November 1992

CDER Perspectives on Process Validation for Solid Dosage Forms, Anthony Lord, Non-Prescription Drug Manufacturers Association (NDMA), October 1992

FDA Views on Pharmaceutical Water, Anthony Lord, NDMA, October, 1992

Finding A/NDA Fraud, Anthony Lord, FDA Drug School, October, 1992

FDA Considerations on Electronic Identification/Signatures, Paul Motise, Parenteral Drug Association, September, 1992

Manufacturing and Validation, Paul Vogel, Generic Drug Advisory Committee, April, 1992

Update on Compliance Issues, Paul Vogel, National Association of Pharmaceutical Manufacturers/National Pharmaceutical Alliance (NAPM/NPA), October 1992

CGMP for Clinical Supplies, Paul Vogel, Drug Information Association, October, 1992

FDA Guidelines and Inspectional Guides, Paul Vogel, NDMA, October 1992

FDA's New Warning Letter, Paul Vogel, University of Georgia College of Pharmacy, March, 1992

Symptoms vs. Root Causes of Problems, Paul Vogel, NDMA, October, 1992

Trends In Drug Product Quality, Paul Vogel, NDMA, October, 1992

Retain Samples, Brad Williams, Pharmaceutical Manufacturers Association, April 1992

Legal Responsibilities of the Drug Laboratory, Brad Williams, ASQC/FDA, February, 1992

*Publications:*

Preapproval Inspections, David Barr, Food and Drug Law Journal, Vol 47, No. 4, 1992

Validation of Legal Reference Methods of Analysis for Pharmaceutical Products in the USA, Tom Layloff/Paul Motise, Pharmaceutical Technology, June 1992

FDA Considerations on Electronic Identification/Signatures, Paul Motise, Pharmaceutical Technology, November 1992

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