HUMAN DRUG CGMP NOTES

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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:

This is the second year of our periodic memo on CGMPs for human use pharmaceuticals. Your *FAX FEEDBACK* responses are terrific and we

especially appreciate your suggested topics for coverage. In addition to *FAX FEEDBACK*, feel free to call, write or send us e-mail, as several of you have done.

As a reminder, although HUMAN DRUG CGMP NOTES 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.

However, beginning with this issue, we are making HUMAN DRUG CGMP NOTES available electronically, by two methods, to people outside FDA. First, interested persons can send electronic mail to the Internet address DOCNOTES@FDACD.BITNET. There's no need for text in the body of the message, although including a name, address and phone number will facilitate any necessary follow-up. Our system will automatically reply by sending the electronic (ASCII text file) current issue of this document to the requester. (Note that, as mentioned below, FDA'ers can receive the electronic edition via regular agency e-mail.)

Second, for savvy Internet users, is the File Transfer Protocol (FTP). The memo is available as ASCII text and WordPerfect (5.1) files. To download either of these files, connect, using FTP, to CDVS2.CDER.FDA.GOV and login as ANONYMOUS. Then enter any password. The ASCII file is HDCGMP.TXT, and the WordPerfect file is HDCGMP.WPC. For example, your commands to receive the WordPerfect file would look like this:

```
FTP CDVS2.CDER.FDA.GOV
LOGIN ANONYMOUS
<any password>
BINARY
GET HDCGMP.WPC HDCGMP.WPC
EXIT
```

(This method of distributing binary files has terrific potential and I'm certain you will be hearing more about it in the future.)

The primary purpose of this document is to enhance field/headquarters communications on CGMP policy issues and to do so in a timely manner. This issuance 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.

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

Thanks!

Paul J. Motise

POLICY QUESTIONS:

What is The Application Integrity Policy (AIP)?.

References: CPG 7150.09, Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities, Final Policy dated 7/1/91; 21 CFR

314.150 Withdrawal of approval of an application; "Points to Consider for Internal Reviews and Corrective Action Operating Plans", DHHS,PHS,FDA,OE dated 6/91

This policy describes the actions FDA takes when it finds that an NDA/ANDA applicant has compromised the government's product application review process. The AIP policy is invoked for applications pending for the affected facility or company when the agency's findings reveal: (1) a pattern or practice of submission of false or misrepresented data, which is material to approval in applications; or, (2) bribery or paying of illegal gratuities to agency employees. The agency will then ordinarily defer scientific review of all pending applications and supplements, until it conducts a satisfactory evaluation of the accuracy and reliability of the information submitted in those applications. The agency's evaluation of the firm's data is referred to as a validity assessment.

The policy provides that, as a first step, the responsible firm should hire consultants to perform audits of all impacted applications to review for false or misrepresented data. This constitutes an internal review. Additional corrective actions include:

(1) voluntary withdrawal of NDAs/ANDAs found to contain discrepancies;

(2) voluntary recall of products following the withdrawal of the NDAs/ANDAs;

(3) identification of all individuals associated with wrongful acts, and removal of those persons from activities under FDA's jurisdiction; and,

(4) submission of a written corrective action plan describing the firm's commitment to ensure compliance and to prevent future instances of wrongful acts.

FDA would then reinspect the firm to verify satisfactory completion of the internal review and corrective actions.

To protect the consumer, when we discover data discrepancies we may take administrative and/or legal actions such as: FDA-requested product recall (which is very rare), product therapeutic equivalence rating downgrade, seizure, injunction, prosecution, referral for grand jury investigation, and/or withdrawal of approval of NDAs/ANDAs containing data integrity problems.

Evidence needed to invoke the AIP policy differs greatly from a CGMP case. Investigators need evidence that shows that the firm's raw data was falsified or misrepresented when submitted to FDA in NDAs/ANDAs, post approval supplements, or annual reports. Examples include:

(1) a misrepresented pilot/biostudy batch size;

(2) stability or release testing where failing results are disregarded without investigation, and the test is repeated until passing results are obtained and only the passing results are reported;

(3) selective reporting of test results;

(4) falsified batch records; and,

(5) other false or misrepresented information submitted to the agency that may affect a reviewer's decision for approval of the application/supplement.

Investigators should suspect data integrity problems (DIPs) with NDA/ANDA submissions if they encounter any of the following:

(1) biobatch records that do not match equipment logs or raw material inventory records;

(2) raw material inventory records that do not match shipping and invoice records

from ingredient suppliers;

(3) reworks or process modifications that are not reported; or,

(4) batch sizes or formulations that are misrepresented.

Adequate investigational coverage of any application for data integrity problems requires painstaking cross checking of equipment logs, cleaning logs, inventory records, and other general records. One method of finding discrepancies is to request a list of all past and present employees and their dates of employment. Then compare the list to signatures on batch records, test results, or R&D records. Investigators should also verify that the reported equipment was available at the firm during production dates, and that equipment capacity was adequate for the batch size manufactured. Keep in mind that absence of discrepancies in any one set of records is not conclusive that DIPs do not exist, because that one set may have been falsified.

Division Contact for Further Info: LuAnn M. Summy, CSO, HFD-325 (301-594-0098)

Is it an acceptable label checking operation to compare part numbers on dispensed and master labeling instead of performing an actual PHYSICAL COMPARISON of the entire labeling? The firm reviews labeling when it is received from the printer.

References: See 21 CFR . 211.122(a), Materials examination and usage criteria, and 211.130(c), Packaging and labeling operations.

Yes, provided the labeling is reviewed upon receipt from the printer and an affirmative association is made between the unique part number and the correct labeling. This assumes that the part number is printed on the labeling. In this case, the labeling may be checked, for example, by automated equipment that identifies the part number. Automated equipment that checks for labels on a line does not necessarily have to check for all details of the labeling -- a bar code reader essentially checks for a correct number that uniquely identifies the labeling. We still require that there be checks of finished products for errors in packaging/labeling -- usually a visual spot check, in which case more than the part number would be identified.

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

Is a firm right when it claims that it doesn't need a physical label specimen in the master record because including the specimen inhibits the move toward computerized batch records?

References: 21 CFR . 211.186(b)(8), Master production and control records.

The firm is wrong! The master production and control record must contain either labeling specimens OR **copies** of labeling. True copies may well be electronic, (e.g., a scanned image of the endorsed master labeling) and may thus become part of an electronic master record. Therefore, we disagree that this CGMP requirement inhibits the move toward computerized batch records. Even if it did, that fact would not justify a departure from the regulations, considering the option a firm has to petition FDA to change the regulations.

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

What clean room classification is required for environments which house aseptic processing isolation chambers ?

Reference: 21 CFR . 211.42(10), Design and

construction features; and, Guideline on Sterile Drug Products Produced by Aseptic Processing.

Isolation chambers are used to aseptically assemble drug products within highly contained, high quality environments in which humans are not a potential source of contaminants.

We encourage use of isolation chambers. The need to maintain the integrity of the environments within such chambers is obviously critical. Integrity breeches would permit entry of contaminants from the unit's surrounding environment.

Although we believe it is necessary to monitor and validate the environmental quality of the rooms housing such chambers, FDA has published no formal FDA policy on air quality for the rooms housing isolation chambers. However, new drug application reviewers have been calling for controlled environments that meet class 10,000 conditions for the rooms. Until more formal policy is established, we consider this level of air cleanliness to be prudent and acceptable, though not strictly a CGMP requirement.

Division Contact for Further Info: Terry Munson, HFD-322, (301-594-0095).

Considering that process validation is a CGMP requirement, will CDER withhold NDA/ANDA approvals if validation has not been completed, or is found to be problematic during the pre-approval inspection?

Reference: 21 CFR 211.100, Written procedures; deviations; CP 7346.832, Pre-Approval Inspections/Investigations and CPG 7132c.08, Process Validation Requirements for Drug Products Subject to Pre-Market Approvals.

The referenced compliance program, and compliance policy guide state that districts should recommend withholding approval of an application if the firm has attempted to validate the process and the inspection identifies either data of questionable validity or data that demonstrates the process is not valid and the firm has not committed to making appropriate changes.

Process validation is generally considered a field responsibility to be addressed post-approval. CDER will not withhold approval of an application if process validation has not been attempted or if a validation protocol is not available or, if a protocol is available, but does not adequately test all process parameters. CDER will concur with a withhold recommendation if validation has been attempted and significant data integrity issues are documented or if the process cannot be validated. If the firm uses a scientifically sound protocol and the results of the effort do not assure the production of products which reliably meet predetermined specifications, this can be indicative of a process which has flaws and cannot be validated. On occasions when this occurs, withholding approval is appropriate until the filed process is revised.

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

TOWARD THE ELECTRONIC GOVERNMENT:

A ***Using E-mail to Send Binary Files to CDER Staff***

E-mail can convey binary files not only from field district office to field district office (via Banyan), but also from the field to CDER staff via the interconnected Banyan to ALLINONE mail system.

The ability to send binary files via e-mail has great potential to make our work more productive and efficient. For example, a regulatory document (such as a warning letter,

or draft injunction decree) could be e-mailed to your correspondent in native word processing format (such as Word Perfect), such that your CDER correspondent can edit it as appropriate and send it back intact, formatting codes included.

With a little imagination, we can send more "exotic" files, such as graphic images derived from scanned documents (a firm's labeling or records -- color included-- or native digital photographs (taken with modestly priced digital cameras). Take things a step further and transfer slide presentations, and even video clips. When timeliness is crucial and (to paraphrase an old express mail ad) it positively, absolutely, has to get there BEFORE overnight, e-mail is the method of choice.

I understand that the field has been using Banyan based e-mail to transfer binary files for some time. The new twist is that our agency e-mail system can be used in the same manner. Here's the trick: the binary file should be an attachment to the basic e-mail you send to CDER, and (on the CDER side) file extensions must be unrecognizable to CDER's VAX computer. Don't use file names like "letter.**wpg**", or "info.**txt**". Files having numeric extensions (like "letter.**323**") are safest. This is important because CDER staff can maintain the integrity of the binary file only if the ALLINONE mail system treats it as a foreign type.

One other consideration for CDER recipients, the ALLINONE e-mail message attachment will not be readable from within ALLINONE. The binary attachment will display a message saying the document is foreign. CDER staff can detach the file, and transfer it to their VAX directories, from where it can be transferred further to local PCs via the local area network.

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

NEW TECHNOLOGY EMERGING:

Substitute for DOP in HEPA filter Integrity Testing

Reference (on HEPA filter integrity testing): Guideline on Sterile Drugs Produced By Aseptic Processing

Dioctylphthalate (DOP) aerosols have long been used to test the integrity of high efficiency particulate air (HEPA) filters. However, concerns about the potential health risks attendant to exposure to DOP has precipitated a search for acceptable alternatives. The agency has recently accepted one of the alternatives, Emery 3004.

Various groups in FDA have reviewed data generated by a pharmaceutical company and the U.S. Army on the use of a compound called Emery 3004, as a substitute for DOP. Emery 3004 is a poly-alpha olefin, manufactured by Henkel Corporation, that has physical properties similar to DOP. We have concluded from the data that Emery 3004 performs at least as well as DOP in hot-smoke filter pentrometer machines, and many other machines. The material is inexpensive, readily specifiable (unlike natural petroleum products), non-corrosive, clean to work with, free of natural impurities, thermally and chemically stable, and (most important) not mutagenic. Emery 3004 can replace DOP directly in existing penetrometer and other machines without machine modification, simply by adjusting existing machine controls. This means that there is no need to change the methods and procedures currently used to integrity test HEPA filters.

Division Contact for Further Info: Terry Munson, HFD-322, (301-594-0095).

PUBLISHED IN FINAL:

The following CGMP related document has been published in final form:

Guide to Inspections of Oral Solid Dosage Forms Pre/Post Approval Issues for Development and Validation (Contact: William C. Crabbs, HFD-323, 301-594-1089)

P. Motise 2/24/94
DOC ID CNOTESC.394

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
	Tony Lord	"
	Edwin Rivera	"
Biotechnology	Walter Brown	594-1089
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
	Bruce Hartman	594-0098
Computer Validation	Paul Motise	594-1089
Content Uniformity	Charles Ahn	594-0098
Criminal Litigation Support	Nick Buhay	410-962-8054
Data (Application) Integrity	Bruce Hartman	594-0098
	LuAnn Summy	"
Dissolution	John Dietrick	594-0098
Electronic Records/Signatures	Paul Motise	594-1089

Establishment Evaluation Requests	J. Dave Doleski	594-0098
	Mark A. Lynch	"
Foreign Drug EIs (Compliance)	Jerry Kirk	594-1089
General Microbiological Issues	Terry Munson	594-0095
Labeling Controls (CGMPs)	Tony Lord	594-0098
Laboratory Issues	Monica Caphart	594-0098

DIVISION OF MANUFACTURING AND PRODUCT QUALITY, HFD-320
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LAL/Pyrogens	Terry Munson	594-0095
Medical Gases	Duane S. Sylvia	594-0095
NDA/ANDA Pre-Approval Inspections	Bruce Hartman	594-0098
	Brenda Holmes	594-1029
	Randy Woods	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
Pharmacy CGMPs Issues	John Levchuk	594-0095
Process Validation (General)	Paul Motise	594-1089
(Non-Sterile Dosage Forms)	John Dietrick	594-0098
(Sterile Dosage Forms)	John W. Levchuk	594-0095
	Edwin Rivera	"
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
Supplements for Sterilization Validation	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).

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:

Application Integrity Program ___	Pre-Approval Validation ___
Labeling Controls ___	Binary Files by E-mail ___
Computerized Batch Records ___	Emery 3004 ___
Clean Room Isolation Chambers ___	Other _____

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

_____
_____
_____