HUMAN DRUG CGMP NOTES

(Volume 5, Number 1)

March, 1997

(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

Project Manager: Paul J. Motise, HFD-325

IN THIS ISSUE:

Attachments:
Division of Manufacturing and Product Quality, HFD-320, Subject Contacts

FAX FEEDBACK (Your input requested)

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 are still great and we appreciate your suggested topics for coverage. You need not, however, limit the dialog to FAX FEEDBACK. Feel free to call, write, or send us e-mail. We also welcome brief articles FDAers may wish to contribute. Subjects should be CGMP related and would be especially valuable if they address emerging new technologies.

Although the document is fully releasable under the Freedom of Information (FOI) Act, our intended readership is FDA field and headquarters personnel. Therefore, we can't extend our distribution list for the paper edition to people outside the agency. The primary purpose of this memo is to enhance field/headquarters communications on CGMP issues, in a timely manner. This document is a forum to hear and address your CGMP policy questions, update you on CGMP projects in the works, provide you with inspectional and compliance points to consider that we hope will be of value to your day to day activities, and clarify existing policy and enforcement documents. This publication supplements, not supplants, existing policy development/issuance mechanisms.

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 us by interoffice paper mail, using the above address, by phone at (301) 594-1089, or by 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).

Thanks!

Paul J. Motise

Policy Questions:

In formulating a batch to provide not less than 100 percent of the labeled or established amount of active ingredient must firms consider such ingredient attributes as assayed potency and water content?

References: See 21 CFR 211.101(a), Charge-in of components

Yes. Per section 211.101 of the CGMP regulations, the batch must be formulated to provide not less than 100% of the active ingredient, meaning firms should take into consideration loss on drying, moisture content or other factors which may affect the potency.

For example if an active pharmaceutical ingredient (API) has a known moisture content of 5.0%, this means that its potency is 95% and this should be factored into the amount added to the batch to ensure that the formulation is 100% of the product label claim; therefore each 100 gms of the API used "as is" would provide potency equivalent to 95 gms of the active ingredient and the weight would have to be adjusted upward to compensate for the moisture, in this hypothetical case 105.26 gms for each "100 gms" of active ingredient required.

This is the same rationale used with standards and is the reason why most USP reference standards are dried before use to ensure that what is weighed out and diluted to make a standard has a potency of "100%." For those standards which are known to have significant moisture content, the moisture content is determined and factored into the calculations to determine the potency of the standard solution in much the same manner described above.

Firms should justify overages because formulations are expected to set 100% as the target. Having less than 100% as the target (which would be the case if these different factors aren't considered) should be justified also.

Contact for further info: Monica E. Caphart, HFD-325, 301-594-0098; e-mail: caphartm@cder.fda.gov

Should a data audit protocol ensure coverage of analytical results from batches not submitted to an application?

References: CPG 7150.09; General Policy Fraud, Untrue Statement of Material Fact, Bribery and Illegal Gratuities; and, Points to Consider for Internal Reviews and Corrective Action Operating Plans, dated June 1991.

Yes. Audit protocols that do not provide for the identification of batches and associated records that an applicant (1) inadvertently failed to submit to the application, or (2) intentionally chose not to submit to an application, can result in the failure to identify significant non-submitted failing analytical results or other problem information to an application.

Therefore, data audit protocols should include consideration of analytical results and manufacturing information on batches made and tested during development (including the clinical/biobatch) but not submitted to the application. The objective of this consideration should be to review an applicant's decisions to not submit the failing data or other information that might be pertinent to the approval process.

The Application Integrity Policy states that credible internal reviews (i.e., audits) should be conducted by outside consultants. Audit protocols/plans should be prepared prior to the audit and agreed upon by both the applicant and the outside consultant/auditor.

Contact for further info: Randall Woods, HFD-324, 301-827-0062; e-mail: woodsr@cder.fda.gov

How soon must firms complete CGMP failure investigations?

Reference: 21 CFR 211.192, Production record review; Guide to Inspection of Pharmaceutical Quality Control Laboratories, July 1993

The CGMP regulations, at 21 CFR 211.192, establish the requirement for an investigation, but do not explicitly state a time interval for completing it, including the preparation of a report. Our expectation for "closure" of a failure investigation (including any other "unexplained discrepancy") is that the investigation be conducted and reported in a reasonable time. The Barr decision called this "timely" (see paragraph 23 of that decision).

We see both the 30 day time period in the court decision and the 20 day time period in the referenced inspectional guide as being reasonable or timely; both are guidance and not requirements. The times differ because the Court addressed an investigation by a manufacturing site having a laboratory, whereas the guide addresses investigation in the laboratory only. We see the investigation in the manufacturing site that has a laboratory including other manufacturing aspects along with laboratory aspects.

In discussing this topic, it may be helpful to point out what would not be reasonable, like performing an investigation but not progressing to a decision point as recorded in a final report/decision document, delaying a decision on investigation findings beyond the expiration date of the lot(s) in question, or delaying/excluding the investigation from CGMP or application related records which require their inclusion.

Contact for further information: Nicholas Buhay, HFD-325, 301-594-0098; e-mail: buhay@cder.fda.gov

What should firms use as microbial limits for purified water?

Reference: 21 CFR 211.113, Control of microbiological contamination; 211.84(c)(6), Testing and approval or rejection of components, drug product containers, and closures.

In the CGMP context firms should set and justify their own microbial limits for purified water (PW) based on at least two factors in production. First is the microbial specification of the finished product or the equipment surfaces which contact the water. The microbial limit for the water as a component should be more stringent than the limit set for the end product. For example,

where a finished product has a microbial limit of not more than 100 cfu/ml, the corresponding limit for water as an ingredient in that product should be less than 100 cfu/ml.

The second factor is the validated water system's operational data. Properly controlled and well designed PW systems should be capable of producing validated water quality in the range of 30-50 cfu/ml. Such operational data would not justify establishing a less stringent specification of "not more than 100 cfu/ml."

Contact for further information: Michael J. Verdi, HFD-322, 301-594-0095; e-mail: verdim@cder.fda.gov

Must firms certify the qualifications of personnel?

Reference: 21 CFR 211.25, Personnel qualifications

No. Per the CGMP regulations, personnel engaged in pharmaceutical production must have the education, training and experience (or any combination) to enable them to perform their assigned tasks. Although we expect firms to have some type of documentation covering employee qualifications, that documentation need not be in the form of a formal certification.

Contact for further information: Paul J. Motise, HFD-325, 301-594-1089; e-mail: motise@cder.fda.gov

On Stability

1) When the labeled expiration date states only the month and year does that mean that the drug expires at the end of the specified month?

Reference: 21 CFR 211.137, Expiration dating

Yes. We expect that the product will meet approved specifications through the last day of the specified month. Manufacturers should take this into consideration when assigning the expiry to a new lot of drug product. Many firms assign the expiry period for a new lot starting with the date of QC release. Generally, this is acceptable if the date of release is not longer than approximately 30 days from the start of manufacturing. The start of manufacturing is the date that the first active ingredient, preservative or antioxidant is initially introduced into the lot. For products that are labeled with the month and year of expiry, when a lot is released at the beginning of the month, that entire first month should be included in the expiry period. For example, a lot which has a supportable 2 year expiry period that is released on February 10, 1997, should be assigned an expiry date of no later than January 1999.

2) Is it acceptable to run accelerated stability testing for less than three months, when predicting a tentative expiration date?

References: 21 CFR 211.137, Expiration dating; 211.166, Stability testing; February, 1987 "Guideline For Submitting Documentation For The Stability of Human Drugs and Biologics"

The referenced 1987 document provides guidance for submitting in ANDAs, 3 months of accelerated stability data, for the purpose of determining a tentative expiration dating period of up to 24 months. On several occasions we have received inquiries from manufacturers of grandfathered (not new) drugs asking if it would be acceptable to conduct accelerated testing for a time shorter than 3 months. Mostly, the firms have proposed that they shorten the tentative expiration dating period proportionately. However, other firms have indicated that they would compensate for the shortened period of accelerated testing by using elevated storage temperatures for samples on stability.

Firms are not required to use the approach specified in FDA's guideline. However, if a different approach is taken, firms should be able to demonstrate that the approach is scientifically valid. It should not be assumed that a firm can take the parameters specified in FDA's guideline and, without scientific justification, proportionately modify the period of accelerated testing and tentative expiration dating, or test at a very high temperature for a short time and use

a very long expiration dating period. For example, performing accelerated testing at very high temperatures for a short time to extrapolate a long expiration dating period may not be acceptable because the mechanism of degradation at high temperatures may be different from that at room temperature. We recommend that firms discuss alternative approaches with FDA to avoid expenditure on an effort which may not be acceptable.

Division contact for stability matters: Barry Rothman, HFD-325, 301-594-0098, e-mail: rothmanb@cder.fda.gov

Gas What? (Policy Questions on Medical Gases):

1) What is SPORTS OXYGEN? Is it possible to import SPORTS OXYGEN into the US?

Reference: Import Alert 66-37

SPORTS OXYGEN is a small pocket-sized, personal use oxygen system, which has been imported from Japan. The product promises athletic enhancement and makes other drug claims. Because these products are incapable of supplying an oxygen flow rate of at least six (6) liters of Oxygen USP per minute for at least 15 minutes, they are regarded as new drugs Without approved NDAs they are not legal for importation into the U.S..

2) Is the February, 1989, Compressed Medical Gases guideline FDA's current guidance for the medical gases industry?

Yes. However, the February guideline is out of print and in need of updating. We are in the process of revising and re-issuing that guidance document.

For an idea of how the guidance document will be revised, see the December 4 version of "Fresh Air `96," presented during a Cincinnati District Office medical gases workshop. For a copy of "Fresh Air `96" contact this office either by phone or e-mail.

Division contact for further info: Duane Sylvia, HFD-325, 301-594-0095; e-mail: sylviad@cder.fda.gov

Purely Speaking (Information on Impurities)

What is an impurity profile?

Reference: 21 CFR 211.84(d)(2), Testing and approval or rejection of components, drug product containers, and closures; 211.160(b) General requirements (Subpart I - Laboratory Controls); U.S. Pharmacopoeia 23, <1086> Impurities in Official Articles

The USP defines an impurity profile as "a description of the impurities present in a typical lot of drug substance produced by a given manufacturing process." Each commercial lot should be comparable in purity to this standard release profile which is developed early on and maintained for each pharmaceutical chemical. We can also call this profile a "Reference Profile" because the quality control unit refers to it (1) when assessing the purity of each batch of active pharmaceutical ingredient (API), and (2) when evaluating the viability of proposed process changes.

To illustrate, one of the more critical process changes in the life of a pharmaceutical chemical (both API and key intermediate) is justification of scale-up from smaller development size lots to full-scale production batches. In the absence of a full impurity profile, there would be little support for claims of equivalency of the two process scales.

When reviewing an API impurity profile, the following basic information should be available for impurities present at or above the 0.1% level (or lower based on toxicity of the compound):

- Identity or some identifier (e.g., HPLC retention time)

- Ranges normally (historically) found. Note that some impurities may only be detected sporadically. However, for an impurity

profile to be considered complete, it's important to include these as well.

- Limits

- Description or type of impurity (e.g., organic solvent, in-process decomposition product, unreacted intermediate, etc.)

Many companies use at least two test methods (e.g., HPLC, GC) for routine purity testing of their pharmaceutical chemicals. It is vital that these methods are of appropriate sensitivity and capable of detecting and quantifying actual and potential impurities. We expect manufacturers to have fully characterized the purity of their pharmaceutical chemicals and consider the failure to perform sufficient impurity profile studies inconsistent with current good manufacturing practice for APIs.

In the future we'll cover more about impurities.

Contact for further information: Richard L. Friedman, HFD-322, 301-594-0095; e-mail: friedmanr@cder.fda.gov

Toward The Electronic Government:

1) CFR now on-line

Titles 1-50 (absent graphics) of the Code of Federal Regulations (CFR) are now on the Internet at the following address:

http://www.access.gpo.gov/nara/cfr

At that page, follow the link that says "Search your choice of CFR books, available on line." Click on item 21 in the page section that says "Jump Down to Title".

To go directly to the page for searching 21 CFR, add the following extension to the above address: /cfr-table-search.html#Title21.

The Internet site is the product of the National Archives and Records Administration/ Government Printing Office which prints the familiar paperback edition.

The on-line CFR corresponds to the printed edition, and so is current as of April 1996. Yearly updates are planned to coincide with each annual paper revision. That means its up to you to keep current on ongoing changes to the regulations that have yet to show up in the annual reprint. One way to keep up with changes to the CGMP regulations is to monitor the division's Internet World Wide Web site at http://www.fda.gov/cder/cgmp.htm where we'll post not only the current revised CGMP regulations, but also Federal Register notices of ongoing changes.)

The CFR is presented in a full text searchable database. You may narrow your search to specific CFR volumes (sets of parts). Search results are presented in Adobe® PDF, full text, or summary text formats.

2) Government job openings on-line

The U.S. Office of Personnel Management has established an Internet World Wide Web site, USA Jobs, at which federal, state and local government job vacancies are posted.

The site, at http:/www/usajobs.opm.gov, includes current vacancies, updated five days a week, general government information and an on-line application. Your browser must be enabled for tables and other HTML 2 browser specific extensions, meaning you must use such applications as Netscape Navigator® 2.0 or higher, or Microsoft Internet Explorer® 2.0 or higher.

Division contact for further info: Paul J. Motise, HFD-325, phone: 301-594-1089; e-mail: motise@cder.fda.gov.

P. Motise 2/28/97
DOC ID CNOTES37.w6

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

		(All numbers in area code 301)
Applications Integrity Policy		
Implementation/Removal	LuAnn Pallas	594-0098
Data Integrity Cases	Bruce Hartman	827-0062
Aseptic Processing	Michael Verdi	594-0095
Botanicals Manufacturing	Brian Hasselbalch	594-0098
Bulk Drugs	Edwin Rivera	594-0095
	Rick Friedman	"
Case Management	Joseph Famulare	594-0098
CGMP Guidelines	Paul Motise	594-1089
Civil Litigation Guidance	Nick Buhay	594-0098
Clinical Supplies/IND CGMP	Paul Motise	594-1089
	Bruce Hartman	827-0062
Computer Validation	Paul Motise	594-1089
Content Uniformity	Monica Caphart	594-0098
	Russ Rutledge	594-1089
Criminal Litigation Support	Nick Buhay	594-0098
Electronic Records/Signatures	Paul Motise	594-1089
Facility Reviews	Russ Rutledge	594-1089
Foreign Inspections	John Dietrick	594-0095
Impurities	Rick Friedman	594-0095
Inspections/ Investigations	Randall Woods	827-0065
(For Cause)	John Singer	827-0071
Labeling Controls (CGMP)	Paul Motise	594-1089
Laboratory Issues	Monica Caphart	594-0098
	Russ Rutledge	594-1089

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

		(All numbers in area code 301)
Medical Gases	Duane S. Sylvia Michael Verdi	594-0095 "
NDA/ANDA Pre-Approval Inspections	John Singer Randall Woods Mark Lynch	827-0062 " "
Packaging	Edwin Melendez	594-0098
Penicillin Cross Contamination	Duane S. Sylvia	594-0095
Pharmacies, CGMP	LuAnn Pallas	594-0098
Pre-Approval Program	Dave Doleski Melissa Egas	827-0072 594-0095
Process Validation, General	John Dietrick Paul Motise	594-0098 594-1089
Recycling Plastic Containers	Paul Motise	594-1089
Repackaging	Barry Rothman	594-0098
Salvaging	Paul Motise	594-1089
Stability/Expiration Dates	Barry Rothman	594-0098
Sterile Facility Construction (Clean Rooms)	Michael Verdi	594-0095
Topical Drugs	Randall Woods	827-0062
Transdermals	Brian Hasselbalch	594-0098
Videoconferencing	Russ Rutledge Paul Motise	594-1089 "
Water Quality	Michael Verdi Rick Friedman	594-0095 "

FAX FEEDBACK

TO: Paul Motise, HUMAN DRUG CGMP NOTES, HFD-325
FAX: 301-594-2202 (Phone 301-594-1089)

FROM: _____

AT: _____ MAIL CODE: _____

PHONE: _____ FAX: _____

E-MAIL ADDRESS: _____
This FAX consists of this page plus _____ page(s).

To receive the electronic version of HUMAN DRUG CGMP NOTES via E-mail, send a message to motise@cder.fda.gov. In the message subject field type SUBSCRIPTION REQUEST and in the body of the message type SUBSCRIBE Human-Drug-CGMP-Notes. To stop receiving the electronic edition send the same message, but use the word UNSUBSCRIBE instead of SUBSCRIBE.

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 regarding _____
_____
_____

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