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:

Welcome to the first edition of our fourth year of Human Drug CGMP Notes, our periodic memo on CGMP for human use pharmaceuticals. As always we welcome your FAX FEEDBACK responses and appreciate your suggested topics for coverage. In addition, feel free to call, write, or send us e-mail, as several of you have done. We also welcome brief articles FDAers may wish to contribute. Subjects should be CGMP related. Your input would be especially valuable if it addresses emerging new technologies.

Although the document is fully releasable under the Freedom of Information (FOI) Act, our intended readers are FDA field and headquarters personnel. Therefore, we cannot 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 policy issues and to do so in a timely manner. This document is a forum to hear and address your CGMP policy questions, update you on projects in the works, provide you with inspectional and compliance points to consider that will hopefully be of value to your day to day activities, and clarify existing policy and enforcement documents.

We intend to supplement, not supplant, existing policy development/issuance mechanisms, and 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 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 the 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:

Laboratory Issues

1) Does FDA have a CGMP policy on use of recycled solvents for HPLC columns?

References: See 21 CFR 211.67, Equipment Cleaning and Maintenance, and 211.160(b), General Requirements

The agency has no specific policy on recycled HPLC solvents above and beyond the CGMP requirements regarding suitability of laboratory equipment and analytical methods. Therefore, it would be acceptable to use recycled solvents which do not interfere with analytical results or equipment operation.

A potential problem to avoid with using recycled solvents is the possible retention of drug residues that could interfere with analytical findings. To minimize the chances of such interference some firms prudently restrict reuse of solvents to testing only one drug product. It's also a good idea to segregate recycled from virgin solvents.

2) Is dissolution testing past the Stage 1 level significant enough to be cited on FDA-483s?

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

The Center has received several inquiries from industry regarding the interpretation of dissolution specifications as outlined in the USP general chapter on Dissolution <711> [and the chapter on Drug Release <724>]. The inquiries stemmed from FDA-483 observations issued by field investigators citing dissolution testing past the Stage 1 (S1) level as indications of product failure and/or lack of process control. This has prompted several pharmaceutical companies to ask the Agency to set "wider" dissolution specifications which will allow all batches manufactured to pass at the S1 level. The CDER/OGD Office of Clinical Pharmacology and

Biopharmaceutics works with firms to set dissolution specifications based on the in vitro results of the batch(es) used in clinical and/or bioavailability studies. This is done to ensure the same level of bioavailability for future batches. If "wider" dissolution specifications are set, this assurance is lost.

Similar situations have come to this division's attention by way of regulatory case review, where, as part of the GMP violations cited, 483 observations such as "Lack of failure investigation(s) for lot(s) ... which failed dissolution testing at the S1 level." or "Lack of process control for ...product due to dissolution failure at the S1 level." are made.

Having to test a drug product through the three stages [S1, S2 and S3] for dissolution does not, by itself, indicate that there is a problem with the product, nor does it indicate that there are problems with control of the manufacturing process. The USP clearly states in the "Interpretation" section of the chapter on dissolution <711> [and the chapter on drug release <724>], "Unless otherwise stated in the individual monograph... Continue testing through the three stages unless the results conform at either S1 or S2....".

Depending on the context of the occurrence of dissolution testing past the S1 level, other 483 observations would be more appropriate. For example, if a large percentage of all batches manufactured, within a specific period, have to be tested past the S1 level, a more appropriate 483 observation would be "Failure to determine why batches manufactured during this specific period had to be tested through to S2 or S3." Another example is if a large percentage of batches manufactured suddenly have to be tested through S2 or S3, after only rarely having to be tested past S1; a more appropriate observation would be "Failure to determine why a majority of recently manufactured batches now have to be tested through to S2 or S3." Such observations could be made assuming that:

1> Initial dissolution testing for the product in question only rarely proceeded past S1 and is now always proceeding to S2 or S3; and,

2> The firm failed to recognize the possibility of a process or testing problem by this change in the dissolution profile of its product.

[This issue was also addressed in the March 1995 issue of Human Drugs CGMP Notes]

Division Contact (for above questions): Monica Caphart, HFD-325, 301-594-0098, e-mail CAPHARTM@cder.fda.gov

3) Is routine product pH testing required for Endotoxin (LAL) Assays?

References: See 21 CFR 211.167, Special testing requirements

No, not unless a firm has committed to such testing in a new drug application. Measurements of pH on routine endotoxin samples each time a specimen is tested are not required for a validated method. The positive product control on routine testing, which must be included during each test, will fail if the specimen pH is out of control.

We do recommend you review the firm's endotoxin validation and compare this with the finished product release pH range to make sure the validation lots covered the upper and lower limits used to release product. If the validation lots covered only a narrow range this would be an appropriate issue for a CGMP citation, rather than the lack of pH testing of each test specimen.

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

On Stability (Policy Questions on Stability Issues):

1) Is it acceptable for a firm to export expired drugs for charity?

Reference: 21 CFR 211.137(a) and (d), Expiration Dating

No. While we recognize the dire need for drugs in distressed parts of the world, once the expiration date has passed there is no assurance that the drugs have the safety, identity, strength, quality and purity characteristics they purport or represent to possess. As such, expired drugs are adulterated within the meaning of section 501 (a)(2)(B) of the FD&C Act, and section 301 of the Act prohibits the introduction or delivery for introduction into interstate commerce any drug that is adulterated.

Firms may wish to extend the labeled expiration date, thus making them suitable for export, provided that any extension of the expiration dating is supported by appropriate stability studies. Any extension of the expiration dating should be of sufficient duration to ensure that the drugs do not again reach their expiry before their anticipated use.

2) How should the start of the expiration dating period be calculated for repackaged drugs?

Reference: 21 CFR 211.137, 211.111, and 211.166; CPG 7132b.10, 7132b.11, 7132.13; CPGM 7356.002b

The CGMP regulations require that drug repackagers use an expiration date on repackaged drugs that is based on scientific evaluation and/or testing of the drug in the container-closure in which the drug is to be marketed. However, in a limited number of situations a repackager may extrapolate from the expiration date on the original manufacturer's container, an expiration date that is suitable for the repackaged drug, without conducting additional stability studies. Such situations are described in the guidance referenced above.

Where an expiration dating period is derived from stability studies conducted on the repackaged drug, the repackager should develop controls to ensure that an appropriate expiration dating period is assigned at the time of repackaging. For example, it may be appropriate to assign a two-year expiration date to a drug that is one-month old at the time of repackaging, whereas it may not be appropriate to assign a two-year expiry when the same drug is repackaged after it has been held in the original manufacturer's container for substantially longer than one-month, and after the container has been opened numerous times.

Contact for Further Info: Barry Rothman, HFD-325, 301-594-0098, e-mail: rothmanb@cder.fda.gov.

Gas What? (Policy Questions on Medical Gases):

1) May a firm use industrial grade nitrogen as a blanketing agent during the manufacturing of a drug product?

Reference: 21 CFR 211.110(a) and(c), Sampling and testing of in-process materials and drug products; 211.165(a), Testing and release for distribution

Unless the industrial grade product is analyzed for all possible impurities and contaminants, it would be unacceptable to use industrial grade products in the manufacturing of pharmaceutical drugs.

The filling of medical and industrial grade nitrogen whether it be gaseous or liquid is quite unique. The problems we have seen are usually not with the product itself, but rather with the container closure system, i.e., the high pressure cylinder and hazardous substances to which they have been exposed.

Industrial cylinders are widely distributed throughout all types of industry, and are routinely exposed to hazardous substances, some of which are extremely toxic, i.e., hydrocarbons, arsenic compounds, chlorine, etc. Therefore, it would be nearly impossible to determine what a specific cylinder had been exposed to and to analyze for that specific contaminant.

On the other hand, medical gas cylinders are

prepared under carefully controlled conditions to ensure that the drug product meets the requirements of both FDA and the USP, and are not exposed to contamination from industrial sources. Each high pressure cylinder undergoes rigorous pre-qualifying inspections and examinations with one of the most significant being the vacuum evacuation step, prior to filling a product.

According to USP23, the General Notices, Tests and Assays, Foreign Substances and Impurities, it is impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present. Tests suitable for detecting such occurrences should be employed in addition to the tests provided in the individual monograph.

Refer to the June 1995 HUMAN DRUG CGMP NOTES for nitrogen produced via pressure swing adsorption and cryogenic nitrogen.

2) Is it acceptable for the owner of a vessel to apply a small sticker to denote its ownership, even though the vessel is filled by a different firm that is identified in the vessel's labeling?

Reference: 21 CFR 211.130, Packaging and labeling operations, 201.1, Drugs; name and place of business of manufacturer, packer, or distributor.

Yes, a firm may place a small sticker, commonly referred to as a possession/ownership sticker, on a vessel as long as the sticker does not obstruct required labeling. In addition, the sticker must not be misleading. For example, it should be qualified by a statement such as, "This empty vessel or this vessel when empty is the property of, or belongs to, `Firm X, address, and telephone number.'"

Contact for Further Info: Duane Sylvia, HFD-325, 301-594-0095 e-mail: sylviad@cder.fda.gov.

What are the respective roles of ORA (field) and CDER staff in performing reviews of chemistry data in new drug applications?

Reference: Letter of October 14, 1994, issued jointly by the Director of CDER and the Associate Commissioner for Regulatory Affairs, to all NDA, ANDA and AADA Applicants

CDER and ORA personnel review the same chemistry data, but from different perspectives. CDER reviews chemistry data for scientific/technical adequacy and appropriateness, and evaluates submitted test methods and finished product specifications. ORA personnel audit the same chemistry data to verify authenticity and data accuracy at the applicant's location.

It is consistent with the referenced letter for field personnel to place comments on FDA 483's regarding authenticity and accuracy of data, even when that data has already been reviewed by CDER. However, be sure to discuss with CDER reviewers any test methods, specifications and chemistry data you find questionable. Such discussions should ideally occur before a 483 is prepared. ORA staff should contact CDER reviewers when an applicant:

(1) may have inadvertently omitted chemistry information from an application; or

(2) has already responded to a deficiency letter on the same matter and the response is questionable.

It is vital that when field personnel find inadvertently unsubmitted chemistry information, they promptly alert CDER reviewers who will evaluate the significance of the omission.

When ORA and CDER agree about the significance of the findings, CDER review chemists will decide as to whether the matter should be noted in a deficiency letter and/or an ORA prepared 483. Note that field personnel must never cite deficiency letter items as FDA 483 observations unless specifically directed by a CDER review chemist.

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

TOWARD THE ELECTRONIC GOVERNMENT:

1) What is the status of the Electronic Signature Rule (Proposed Part 11)?

Reference: Electronic Records; Electronic Signatures, 21 CFR Part 11, Proposed Rule, Federal Register of August 31, 1994, 59 FR 45160

We have begun preliminary clearance of a final rule Federal Register notice. We cannot at this point predict the exact outcome and publication date. However, the rulemaking remains a high priority in CDER and the agency.

A total of 49 respondents, representing all FDA regulated industries as well as other interested parties, submitted 544 discrete comments that addressed almost every part of the proposed regulations. The 49 included 11 trade associations that also reflected the same industry spectrum. However, most respondents represented the pharmaceutical industry.

2) Federal Register on the Internet

The Federal Register (F/R) is now available on the Internet's World Wide Web. In addition to 1996 notices, the U.S. Government Printing Office (GPO) has posted the 1995 and 1994 editions in a searchable database. (Also included are the Congressional Record, Congressional Bills, and information in 1400 Federal Depository Libraries.)

The Internet address for the free service is: HTTP://WWW.ACCESS.GPO.GOV/SU_DOCS/.

You can read and download the current daily F/R as ASCII (American Standard Code for Information Interchange) or PDF (Adobe's® Portable Document Format) files. To view PDF files you'll need Adobe's Acrobat® Reader software, a widely distributed freebie. Notices in PDF format look exactly like pages in the paper Federal Register.

Full text database searches are fast and flexible, allowing for boolean operators (e.g., AND, OR), wildcard word roots, hunts of multiple databases back to 1994, and results of up to 200 hits (records that contain your search term.)

Search results reports are comprehensive. They show the selected database(s), the number of hits, a time stamp (year, month, day, hour, minute and second), and a warning that the report is a temporary file that self-destructs (at GPO) after about one hour. A brief description of each hit states the F/R cite (e.g., FR31AU94), title, file size, and hyperlinks for TEXT (to download the full text in ASCII), SUMMARY (to download the ASCII file of only the notice's Summary section), and PDF (to download full notices back to 1995 in a PDF file.)

Be aware of a few limitations. The 1994 database lacks page numbers. Page numbers (ranges), volume and issue numbers are given for 1995 onward. The TEXT link search results files display your search terms in bold characters, but SUMMARY and PDF formats don't (Acrobat® Reader can highlight a search term offline, however). Graphics in 1994 notices are in TIFF format and must be downloaded separately. Graphics in newer notices are embedded in PDF files.

You should find this service a valuable tool that helps you stay current, and obtain F/R notices in convenient formats for your own files and for answering industry and public requests.

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Biotechnology	Walter Brown	594-1089
Bulk Drugs	Edwin Rivera Rick Friedman	594-0095 "
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 Bruce Hartman	594-1089 827-0062
Computer Validation	Paul Motise Charles Ahn	594-1089 594-0098
Content Uniformity	Monica Caphart Russ Rutledge	594-0098 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
Inspections/ Investigations (For Cause)	Randall Woods John Singer	827-0065 827-0071
Labeling Controls (CGMP)	Paul Motise	594-1089
Laboratory Issues	John Levchuk Monica Caphart Russ Rutledge	594-0095 594-0098 594-1089
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Pharmacies, CGMP	John Levchuk LuAnn Pallas	594-0095 594-0098
Pre-Approval Program	Dave Doleski Melissa Egas	827-0072 594-0095
Process Validation, General (Sterile Dosage Forms)	John Dietrick Paul Motise John Levchuk	594-0098 594-1089 594-0095
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)	John W. Levchuk Michael Verdi	594-0095 594-0095
Sterilization Validation	John W. Levchuk	594-0095
Topical Drugs	Randall Woods	827-0062
Transdermals	Brian Hasselbalch	594-0098
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Water Quality	Michael Verdi Rick Friedman	594-0095 "

FAX FEEDBACK

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Here's my question for: _____ on the subject of:

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

_____
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