HUMAN DRUG CGMP NOTES

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(A Memo on Current Good Manufacturing Practice Issues on Human Use Pharmaceuticals)

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Office of Compliance
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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 excellent and we especially 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, as several of you have done. 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.

As a reminder, although the document is fully releasable under the Freedom of Information (FOI) Act, our intended readership is 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, 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 us by interoffice paper mail, using the above address, by phone at (301) 594-1089, or by electronic mail.

To receive this document by electronic mail, see the check-off line in *FAX FEEDBACK*. Note that our DOCNOTES e-mail account has been deactivated.

Thanks!

Paul J. Motise

POLICY QUESTIONS:

Must annual evaluations include failed batches? What if such batches are made for "research" purposes?

Reference: 21 CFR 211.180(e) General Requirements, Subpart J Records and Reports

Yes. 21 CFR 211.180(e) requires an annual evaluation of the quality standards of each drug product to determine the need for changes in specifications and/or manufacturing or control procedures.

Failed batches made for commercial distribution must be included in the inventory of batches from which a number of batches are selected for a 211.180(e) annual review of the product.

There is no category of manufacture which includes a batch which is intended for commercial distribution if it passes specifications upon testing and at the same time for "research", or "experimental", or any other similarly designated purpose, if it does not pass all specifications upon testing. The status of a

batch is to be designated unequivocally and in advance.

Equivocation in the status of a batch or changes in status from commercial distribution to research, etc. is unacceptable as good manufacturing practice, and may have data reliability implications.

Obviously, information derived from the failed manufacture of a commercial batch may be used for research or product development purposes, but this does not change the commercial nature of the batch.

Information on a failure of a batch of new drug product to meet a specification is required to be submitted to the A/NDA Annual Report under 21 CFR 314.81(b)(2)(i) and 314.81(b)(2)(iv) because it is "significant new information from the previous year that might effect the safety, efficacy, or labeling" and "new information that may affect FDA's previous conclusions about the safety or effectiveness of the drug product." FDA will accept as adequate to meet this requirement submission of a §314.81(b)(1) Field Alert Report on the incident, or inclusion in the A/NDA Annual Report.

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

Can field investigators review information in a firm's database on manufacturing errors, problems and complaints? Is such a database considered part of a quality assurance internal audit and therefore not subject to routine inspection?

References: See 21 CFR 211.180(c) General requirements (under Subpart J Records and Reports), 211.192 Production record review; 211.198 Complaint files

The database records are subject to inspection. A QA internal audit is a systems self-inspection -- to see if a firm follows its own procedures and has the kinds of controls and records required by the CGMP regulations. The kind of record we would not routinely seek to inspect is the type of report that says, for example, employees are not endorsing batch records properly, or required tests are not being performed.

Examination of production records to spot problems with a product, investigate discrepancies, or determine the need for changes in production and control measures is not a QA internal audit. As such, the database would be subject to inspection.

Furthermore, the FD&C Act, 704a(1)(B) authorizes us to inspect all things in a prescription drug facility that have a bearing on whether provisions of the law are being met.

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

What information should be contained in a component supplier's certificate of analysis?

Reference: 21 CFR 211.84(d), Testing and approval or rejection of components, drug product containers, and closures.

Except for at least one specific identity test which the drug product manufacturer must perform (in addition to periodic validation of the supplier's test results), the report of analysis (commonly called a certificate of analysis) would cover the remaining required component tests to ensure conformity with specifications for purity, strength, and quality.

Much of the information in the reports of analysis would parallel the same information that the drug product manufacturer's own laboratory (or contract laboratory) would determine and document. This information would include, at a minimum, the name and lot number of the component, the date of testing, the methods used, results of the tests expressed in quantitative terms whenever the test itself is quantitative (rather than pass/fail), the range of acceptable test results, the report date, and the signature of the responsible party that issues the report. If the component has an expiration date, that information should also be in the report.

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

Laboratory Issues

1) How often should dissolution test apparatuses be calibrated when they are used with both baskets and paddles?

References: 21 CFR 211.160(b)(4) General Requirements, Subpart I, Laboratory Controls; USP 23, Section 711, Dissolution

The CGMP regulations call for apparatus calibration at suitable intervals. Although specific time periods are not given, apparatuses should be calibrated every six months as part of a firm's routine SOP. This calibration requires testing with both baskets and paddles at both 50 and 100 rpm with both USP Calibrator Tablets, Prednisone Tablets and Salicylic Acid Tablets. The only exception is if a company uses either baskets or paddles exclusively. In those rare instances, the firm only needs to calibrate with both Calibrator Tablets at both speeds and the single stirring element that it uses.

In case of any event that might change operating characteristics of an apparatus, such as construction or moving it, it should be calibrated as described above prior to use.

2) How should USP dissolution calibrators be stored?

Reference: 21 CFR 211.160(b), General Controls, Laboratory; and "Calibration of Dissolution Apparatuses 1 and 2--What To Do When Your Equipment Fails," Pharmacopeial Forum 20(6), November-December 1994.

The only lots of USP Calibrator Tablets that have official status are Prednisone Tablets, Lot K, and Salicylic Acid Tablets, Lot M. All previous lots have expired. Both official lots are labeled to "Keep container tightly closed. Store in a desiccator or in a dry place at room temperature." It has been found that high humidity is the primary cause of instability of both calibrator tablets.

Contact for further info on above two items: Bob Rippere, HFD-354, phone (301)594-0104, e-mail: rippereb@cder.fda.gov

3) What is an appropriate temperature for incubating media-filled units in the validation of an aseptic process?

Reference: Guideline on Sterile Drug Products Produced by Aseptic Processing (June 1987)

The above guideline states:

"It is also important to incubate the media sample units for a sufficient time (a period of not less than 14 days is acceptable) at a sufficient temperature to detect organisms that may not grow in other incubation conditions because of the possible shock administered to them by sampling methods and environmental conditions."

In applying this principle, it is generally acceptable in regard to compliance with CGMP to incubate at 20-25 degrees C for a minimum of 14 days without having to collect data to support this incubation schedule. It is similarly acceptable for firms who prefer a two-temperature incubation schedule to incubate at 20-25 degrees C for a minimum of 7 days followed immediately by incubation at a higher temperature range not to exceed 35 degrees C for a total minimum incubation time of 14 days. Investigators should scrutinize other incubation schedules on the basis of supporting data. Further details on the latter, as well as associated topics, will appear in the next issue of HUMAN DRUG CGMP NOTES.

Contact for further info: John Levchuck Ph.D., Sr. Regulatory Compliance Officer, HFD-325, 301-594-0095, e-mail: levchukj@cder.fda.gov.

Gas What? (Policy Questions on Medical Gases):

1) Is the use of a stainless steel sampling cylinder, more commonly known as the hoke bomb, acceptable for the testing of a storage tank?

Reference: 21 CFR 211.84(d)(2) Testing and approval or rejection of components, drug product containers, and closures; and 211.165(d) Testing and release for distribution

Yes, provided the firm has validated the process. A hoke bomb is a stainless steel cylinder with a valve on each end which allows a gaseous product to flow through. The most significant step in the validation process is the time required to fully purge the cylinder which provides assurance that complete evacuation of the cylinder has been accomplished.

2) What are the CGMP requirements for equipment used for industrial grade products and then used for medical products?

Reference: 21 CFR 211.67(a, b, & c) Equipment cleaning and maintenance, 211.100(a) Written Procedures; and 211.25(a) Training

Equipment, i.e., hoses, temporary vessels, etc. used in the delivery of a medical drug product is considered an integral part of the drug delivery system and as such is a regulated under the drug CGMPs.

Any equipment used for medical use is required to be cleaned, maintained, and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official requirements in the delivery of a medical product.

Detailed written procedures should be established, and records maintained of the cleaning, sanitizing, and inspection. Another vital CGMP requirement is the assurance that all personnel involved with the equipment on the medical side are adequately trained to perform their designated function.

Problems arise from the contaminants that may be introduced while being used for industrial grade products. Equipment used for industrial products must be qualified prior to being used for medical product, i.e., should be tested for any contaminant that the equipment may have come in contact with, before a medical drug product is introduced.

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

On Stability (Policy Questions on Stability) .

1) Are expiration or retest dates required on bulk pharmaceutical chemicals (BPCs)?

Reference: FD&C Act, Section 501(a)(2)(B); "Guide to Inspections of Bulk Pharmaceutical Chemicals"

Where stability testing reveals a limited shelf-life or where ongoing long-term stability studies have been conducted through a limited time only (e.g., in either case less than approximately two years), the label on a bulk pharmaceutical chemical should bear a supportable expiration or retest date.

Where stability testing reveals that the BPC is stable for the intended period of use, or for approximately two years or longer, we do not consider the omission of an expiration or retest date to be a violation of current good manufacturing practice. An exception is antibiotic BPCs, where expiration dates are required by the antibiotic regulations.

2) What's the regulatory status of the ICH guideline, "Stability Testing of New Drug Substances and Products"? Is it appropriate to cite on an FDA-483 instances where this guideline is not being followed?

Reference: Federal Register, Volume 59,Number 183, September 22, 1994

While conformance to the ICH (International Conference on Harmonization) guideline is recommended in applicable situations, it is not presently a requirement. Therefore, presently, it is inappropriate to cite a firm on an FDA-483 for not conforming to this guideline, per se.

On the other hand, if a firm commits itself to following the ICH document, (by, for example, incorporating the document or parts of it in its standard operating procedures or in an approved new drug application) it would be appropriate to cite on an FDA-483, the failure of a firm to conform to those requirements.

3) For drug products formulated with preservatives to inhibit microbial growth, is it necessary to test for preservatives as part of batch release and stability testing?

Reference: 21 CFR 211.165, Testing and release for distribution; 211.166, Stability testing

Yes. Two types of tests are generally used. Initially firms perform antimicrobial preservative effectiveness testing to determine a minimally effective level of preservative. Once that level has been determined, firms may establish appropriate corresponding chemical test specifications. Firms may then apply the chemical tests for preservative content at batch release and throughout the shelf-life of lots on stability.

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

Toward The Electronic Government:

Road trip help on the Information Superhighway

FDAers who are on the road frequently may find some helpful information on an Internet Web Site called MAPQUEST. A subpage of the site, named TripQuest will calculate the mileage between two U.S. cities and give you simple text based directions on how to get there as well.

Point your web browsers to: http://www.mapquest.com

Select the TripQuest link and complete a simple on-line form that asks for the city, state and county of your starting and destination cities. Don't worry if you don't know the county of the destination city -- you may leave that field blank. Then click the "calculate" button.

The system will then return a report that states the mileage between cities and a suggested route. The directions are brief, but clear (e.g., Go Southeast on I-270 for 11.8 miles, Go West....). The report also tells you whether a given part of the route is a toll road. However, it won't tell you how much you'll have to pay.

You may also want to explore Mapquest's Interactive Atlas. This graphics based database will show you where to find a given business, street address or city. For instance, you could quickly locate that new establishment you've got to inspect but have never been to, or find your favorite hotels and restaurants in the destination city. You might even be able to pinpoint your destination by street address only. I say "might", because recently built roads or facilities may not yet be part of the Mapquest database. At any rate, it's worth a try and could be helpful on your next road trip.

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

P. Motise 5/1/96
DOC ID CNOTES66.w6

FAX FEEDBACK

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