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
Center for Drug Evaluation and Research

Project Manager: Paul J. Motise, HFD-325

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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 really 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 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 issues in a timely manner. This document is a forum to hear and address your CGMP questions, update you on CGMP projects, and help you apply real life situations to existing policy and enforcement documents. This publication does not supplant 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) 594-0098, or by electronic mail.

If you would like to receive an electronic version of this document via electronic mail, see the check-off line in FAX FEEDBACK. We're also on the Internet at http:/www.fda.gov/cder/dmpq.

Thanks!

Paul J. Motise

POLICY QUESTIONS:

Is a dosage form manufacturer required to conduct full monograph testing on a USP ingredient used in a drug product?

Reference: 21 CFR 211.84, Testing and approval or rejection of components, drug product containers, and closures; 211.160(b), General Requirements [Subpart I - Laboratory Controls]

This question has several facets, namely, what tests need be done and who performs them. The tests that need to be performed are those to ensure that established specifications for the component have been met. The CGMP regulations, at section 211.160(b) require the dosage form manufacturer to establish appropriate component specifications. If the manufacturer adopts all of the component monograph specifications then all of those specifications would have to be met as demonstrated by laboratory testing. A firm may commit itself to those specifications, for example, in an approved new drug application.

A firm would also adopt full monograph specifications for a USP component if the material is an active ingredient in a USP drug product where the dosage form monograph requires use of an active ingredient that meets the active ingredient monograph. The firm could exempt itself from this USP requirement if it labels the USP end product with a specific disclaimer as to how the dosage form does not meet USP specifications.

The next facet relates to who performs the component tests. Before the dosage form manufacturer incorporates the ingredients, the testing must have been completed. Section 211.84(a) specifies that **each lot of components,** drug product containers, and closures shall be withheld from use until sampled, tested, or examined, as appropriate, and released for use by the quality control unit. Component means ingredient and therefore both actives and excipients require testing. The CGMPs give firms considerable latitude when it comes to who does the testing. The dosage form manufacturer may elect to: (1) Perform the tests itself; (2) have the tests done by a contract laboratory; (3) have tests done by the component supplier; or (4) perform a combination of these options.

Where a firm elects to have the component supplier perform testing, section 211.84(d)(2) states that "a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analysis through

appropriate validation of the supplier's test results at appropriate intervals."

We have found that establishing reliability of the supplier's analysis generally involves comparing results of independent tests against the supplier's corresponding certificates of analysis (COAs), usually accomplished by initially conducting full testing on a number of lots. In addition, audits of the supplier's laboratory operations, while not explicitly required by CGMPs, can be enlightening. That's because some chemical suppliers are merely distributors or brokers who might be photocopying the makers' results on their own letterhead, thereby representing that they conducted the analysis themselves. This might only be revealed through a supplier audit. Moreover, this audit may be the only way to establish that the laboratory controls, specifications, standards, sampling plans, and test procedures are scientifically sound.

The CGMPs require that the reliability of the supplier's results be conducted at appropriate intervals. Some FDA investigators have included on an FDA-483 that the manufacturer has not conducted this "Vendor Validation" at least once per year. This is an inappropriate citation because the regulations don't specify the frequency, as per 211.84. There is no requirement to conduct this validation annually. Manufacturers have the discretion to determine the interval, and, on a case by case basis, we assess whether or not that interval is appropriate. For instance, if a firm discovers problems with ingredients that contradict COAs, then that may indicate that the frequency of the test comparisons is insufficient.

Contact for further info: Brian G. Nadel, HFD-325 (301) 594-0098, e-mail nadelb@cder.fda.gov

What records do the CGMPs require a firm to examine under the 211.180(e) periodic review? Must such records be stamped with a review or expiration date?

Reference: 21 CFR 211.180(e), General requirements, Subpart J - Records and Reports; Federal Register 1/20/95 (60 FR 4087) Final Rule, Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; Amendment of Certain Requirements for Finished Pharmaceuticals

Section 211.180(e) states that, "Written records required ***by this part*** shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in ***drug product specifications or manufacturing or control procedures.***" (Emphasis added)

This section is intended to require firms to perform a systematic review of data relating to product specifications and manufacturing and control procedures to determine if changes are warranted. Data that indicate a need for such changes can be contained within a broad range of records. That's why the regulation is explicit in referring to records required "by this part"; part means 21 CFR part 211. The data must be in a retrievable form so firms can use the information as needed when conducting the evaluation. This does not mean that every record a firm creates to meet a part 211 requirement must be reviewed. Rather, records specified by 211.180(e)(1) and (2) must always be part of that review whereas other records would be reviewed as indications for needed change arise.

The regulations give firms a great deal of latitude in exactly how they conduct periodic evaluations. However, the CGMPs establish key principles. First, the purpose of the review itself is to determine if changes in specifications or manufacturing or control procedures are needed. Second, the review both corrects and prevents product quality problems; that's why the regulations specify that reviewed batches represent those that have been both approved and rejected. [Note that although 211.180 states that ***"batches"*** and applicable associated records are to be reviewed, the preamble to the 1995 final rule that last modified this section clearly indicates that ***"batches"*** means ***"batch records."***] In other words, indications of the need for change can be contained in records relating to conforming and non-conforming products. For example, production records for conforming lots may nonetheless indicate that a

process is drifting out of control. Third, the review must be conducted at least annually.

A broad CGMP principle that runs throughout the regulations is the concept of redundant checks and balances to ultimately ensure product quality. The 211.180 periodic review provides that balance with respect to change control because, in addition to having an effective change control system, reviews of records that establish product specifications or manufacturing or control procedures can help firms maintain the currency and accuracy of such things as: (1) Cross references to other documents and standards; (2) materials' specifications (e.g., ensuring they match what's in a firm's most recent NDA submission or USP monograph); (3) equipment references (e.g., too generalized a manufacturing instruction to use a "suitable mixer" where different types and sizes are at hand would need to be made specific); (4) process step sequencing; (5) process step parameters; and, (6) acceptance criteria. Especially where a firm makes significant or frequent changes, this complex matrix of interrelated instructions and specifications can make change control difficult and may result in operators using outdated or otherwise incorrect procedures or standards to make medicine. We have encountered situations where an effective periodic review could have prevented such problems.

The regulations mandate that certain core records most likely to indicate a need for changes be reviewed. Included are records: (1) For each drug product covering complaints, recalls, returned or salvaged products and discrepancy/failure investigations conducted under section 211.192; and, (2) applicable to, and associated with, a representative number of batches produced over the review period. Master production records would be part of the second (batch related) grouping. Also included in that grouping would be other records that establish product specifications or manufacturing or control procedures. These records are intrinsically relevant to the review because: (1) Per CGMP, batches must be made according to those procedures and specifications; and, (2) those very procedures and specifications are what may need to be modified. Because those records may in and of themselves hold indications that changes are needed (e.g., outdated/superseded instructions), a meaningful assessment of the need for change would thus be impossible without at least a minimal review of those records. Be aware that some firms may call some records in this latter category standard operating procedures (SOPs) (e.g., how to collect an in-process sample).

Although we expect that the primary indicators of the need for change reside in those records explicitly identified in 211.180(e)(1) and (2), other records may also hold indications of the need for change. Although the CGMPs don't specify those records, any included in the review need to be identified in a firm's review procedures. During your inspections, be aware of evidence indicating that a firm's review procedures may be inadequate by virtue of failing to consider relevant records that hold change indicators, especially where product defects can be attributable to a failure to make needed changes.

Examples of records we would not normally expect to hold indicators of the need to change product specifications or manufacturing or control procedures include written procedures for component purchasing methods and product distribution recordkeeping.

CGMPs don't require that records be affixed with review dates, nor expiration dates. Records that establish product specifications or manufacturing or control procedures (including such records that firms call SOPs) can therefore continue in effect until superseded or discontinued.

Contact for further info: Paul J. Motise, HFD-325 (301) 594-0098, e-mail motise@cder.fda.gov

Is testing rinse solution alone enough to support residue determinations for cleaning validation?

Reference: FDA Guide to Inspections of Validation of Cleaning Processes, July 1993

While it is understood that rinse samples are

capable of sampling larger surface areas, particularly ones which are difficult to access, for the purposes of cleaning validation, rinse samples alone would not be acceptable unless a direct measurement of the residue or contaminant has been made. One disadvantage of rinse samples is that the residue or contaminant may not be soluble or may adhere to the equipment. Some firms use both swab samples, where feasible, and rinse samples during the course of their cleaning validation.

For routine equipment cleaning after validation, some firms may be able to justify use of rinse samples to demonstrate the process continues to consistently clean the equipment.

FDA has compared rinse samples to that of a "dirty pot analogy." When evaluating the cleaning of a dirty pot, the rinse water is not what is looked at to see if the pot is clean.

The purpose of cleaning validation is to demonstrate that a particular cleaning process will consistently clean the equipment to a predetermined limit; the sampling and analytical test methods should be scientifically sound and provide adequate scientific rationale to support the validation.

Contact for further info: Patricia L. Alcock, HFD-322, (301)594-0095; e-mail: alcockp@cder.fda.gov

What is the significance of the Total Organic Carbon (TOC) test for compendial processing waters (Purified Water, Water for Injection)?

Reference: 21 CFR 211.80 General requirements [Subpart E-Control of Components and Drug Product Containers and Closures]; 211.84, Testing and approval or rejection of components, drug product containers, and closures

Implicit in the term "Purified Water" is that it has some reasonable, objective level of purity. TOC testing allows for evaluating impurities in water besides those which are inorganic anions and cations. Carbon-based (organic) compounds are often more complex than inorganic impurities. TOC allows for a quick, broad test for organic impurities. Numerous compounds can be detected under the umbrella of TOC, but it is important to be aware that this method is not capable of differentiating between specific organic compounds.

There is a long history of testing water for the presence of organic compounds. TOC's predecessor, oxidizable substances, is widely considered a less accurate, outdated test. As of May, 1998, TOC is the official organic impurities test for USP pharmaceutical processing waters.

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

CGMP Sorites:

Here's another in our series on CGMP sorites. For an explanation of what sorites are, and how they can be used to train people on CGMP requirements, see our previous articles (June and September editions of this year's NOTES).

One of the challenges of a Lewis Carroll sorites is his out-of-order placement of the propositions. The reasoner must impose order on the propositions to join a subject and predicate that form a conclusion. The propositions of the sorites in the previous edition of CGMP notes were already in the correct order to form the conclusion. Now in the spirit of Lewis Carroll try the following out-of-order CGMP sorites.

Written procedures shall be established and followed for cleaning, maintenance and sanitizing of equipment and utensils used in the manufacture, processing, packing or holding of a drug product. 21 CFR 211.67(b)

Cleaning, maintenance and sanitizing shall include (but not necessarily be limited to) the following procedures:

Maintenance and cleaning schedules;

A description of the methods, equipment

and materials used in the cleaning and maintenance operations;

Protection of clean equipment from contamination and inspection of clean equipment prior to use;

Assigned responsibility;

Removal/obliteration of previous batch identification (21 CFR 211.67(b)(1-6)).

The answer appears at the end of the last article in this edition.

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

Toward The Electronic Government:

1) Does FDA have a complete list of all possible electronic signature meanings? Must the meaning of an electronic signature be displayed each time in every place it appears? Can the meaning be assumed to be present by reference to a separate user manual or SOP?

Reference: 21 CFR 11.50(a)(3), Signature Manifestations; paragraph 105 of the 3/20/97 final rule Federal Register Notice; Electronic Records; Electronic Signatures (62 FR 13453)

Part 11 requires that the meaning of a signature be displayed in human readable forms of a signed electronic record. FDA does not have a list of all possible signature meanings. Meanings of signatures are contextually determined and they are programmed in when the recordkeeping system is developed. When a signed electronic record is displayed in human readable form, what each signature means must be displayed either explicitly or contextually. In the drug CGMP arena, there are relatively few meanings to a signature (e.g., review, authorship, approval, and performance of an action such as a production step, sample collection or analysis.)

It is possible that a record contains a single statement of meaning that applies to multiple signatures in the record.

A cross reference to a manual or SOP would not meet this requirement if the signature meaning itself is not displayed in the record. The cross reference could be problematic, if, after a record is signed, the SOP is changed to indicate a new meaning that did not, in fact, apply at the time the record was signed.

2) Year 2000 Update

In the December 1996 edition of the NOTES we briefly addressed the nature of the year 2000 (y2k) problem and how it may show up in the CGMP area.

Be aware that on October 19, 1998 CDER Director, Dr. Janet Woodcock issued a reminder letter on y2k to the pharmaceutical trade groups. The correspondence reviews the nature of the problem, as well as FDA's expectations, and asks the groups to relay the information to their members. The letter is on the Internet at: http://www.fda.gov/cder/y2k/y2k_letter.htm.

Here are some other y2k Internet resources:

1. The Electronic Data Systems Corp. has posted a publicly searchable database of hardware and software y2k compliant products. We can't vouch for how accurate or complete the list is, but reportedly the information is supplied by product manufacturers. The site is at http://www.eds.com/vendor2000.

2. The President's Council on Year 2000 Conversion is at http://www.y2k.gov.

3. The U.S. Small Business Administration's y2k site is at: http://www.sba.gov/y2k.

4. The Washington Post has a searchable database of 474 company filings made to the Securities and Exchange Commission (SEC) regarding the impact of y2k. You can see what a given firm told the SEC regarding the impact of y2k costs and the status of its y2k efforts. There are also links to y2k background reports. The site is at:

http://www.washingtonpost.com/wp-srv/washtech/longterm/y2k/database.htm

3) Setting the Clock

The National Institute of Standards and Technology (NIST) offers two computer clock setting tools. The first, a program called NISTIME32, downloadable from http://www.bldrdoc.gov/timefreq/service/nts.htm, lets you synchronize your computer's clock to NIST's . The second is NIST's Java-based clock (at http://www.bldrdoc.gov/timefreq/java-clck.htm) that you can use when you set the time manually.

Contact for further info: Paul J. Motise, HFD-325, 301-594-0098, e-mail: motise@cder.fda.gov

Answer to CGMP Sorites:

Procedures used to clean, maintain and sanitize equipment and utensils that are used in the manufacturing, processing, packaging or holding of drug products shall be done at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity of the drug products. (21 CFR 211.67(a))

P. Motise 12/1/98
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FAX FEEDBACK

TO: Paul Motise, HUMAN DRUG CGMP NOTES, HFD-325
FAX: 301-594-2202 (Phone 301-594-0098)

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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:
_____
_____