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
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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 continue to be 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 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 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 instructions in FAX FEEDBACK.

Thanks!

Paul J. Motise

POLICY QUESTIONS:

Do pharmaceutical manufacturers need to have written procedures for preventing growth of objectionable microorganisms in drug products not required to be sterile? What does "objectionable" mean, anyway?

Reference: 21 CFR sections 211.113(a) Control of Microbiological Contamination, and 211.111 Time limitations on production [subpart F-Production and Process Controls]

Yes, the CGMP regulations do require these written procedures. 21 CFR 211.113(a) specifies that appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, be established and followed. This means that even though a drug product is not sterile, a firm must follow written procedures that proactively prevent contamination and proliferation of microorganisms that are objectionable.

The meaning of "objectionable" has several facets that need to be evaluated on a case by case basis by each drug manufacturer. The primary meaning relates to microbial contaminants that, based on microbial species, numbers of organisms, dosage form, intended use, patient population, and route of administration, would adversely affect product safety. Of course, most objectionable would be organisms that pose a threat of patient infection or mortality.

Microorganisms may be "objectionable" by virtue of other problems. For example, microbial content that adversely affects product stability, would be objectionable. Likewise, microorganisms that react with, or potentially damage the integrity of, the container closure system (fermentation creating gaseous pressures that explode a container would be an extreme, though legitimate, example), would be objectionable. Similarly, microbial content that interferes with analytical methods, or active ingredient bioavailability, would be objectionable.

For new drugs, the above considerations will likely have been addressed during the new drug review process and may result in microbial specifications for the end product.

Establishing production time limits is an example of a control to prevent objectionable microorganisms. Per 21 CFR 211.111, when appropriate, time limits for the completion of each phase of production must be established and followed. Where a firm finds it necessary to hold a bulk topical or liquid product for several months until it is filled, the firm might establish a holding time limit to prevent microbial build up that would be objectionable. Validation and control over microbial content of purified water systems used in certain topical products are also examples of such procedures.

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What constitutes a "representative number of batches" that must be reviewed periodically for quality standards under the CGMP regulations?

Reference: 21 CFR 211.180(e), General requirements [Subpart J - Records and Reports], 21 CFR 314.81(b)(1), Other post marketing reports [Subpart B - Applications]

The annual review established by 211.180(e) is for the purpose of "evaluating the quality drug standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures". The selection of records to be reviewed needs to consider "records required by this part" which have "data therein" and include the records specified in 211.180 (e)(1) and 211.180(e)(2).

The number of batches whose associated records will be reviewed must achieve the purpose of the review. Any reasonable approach to achieve the purpose can be acceptable; the word "representative" was inserted into this regulation in January 1995 to simply confirm that every batch does not necessarily have to be included.

Reviewing batches which exhibit varying manufacturing experiences is a critical element in ensuring that a "representative" selection is made. Batches showing different categories of experiences would include those that: (1) Have been approved, rejected, and recalled; (2) have unexplained discrepancies; (3) were the subject of FARs (field alert reports); and, (4) have any other kind of outcome that may indicate changes are needed.

Where any of these categories include multiple problems, the number of batches selected for review should fully represent the different kinds of problems in each category.

Every drug product must have at least one batch included in the annual review. Different products may not be grouped by "similar processes" or any other similar approach, because the necessary differences in the process and/or specifications which make each product unique may result in different manufacturing outcomes.

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Is the employment of HIV infected workers in drug manufacturing facilities in conformance with CGMPs?

Reference: October 17, 1986, Letter from Frank E. Young, M.D., Ph.D., Commissioner of Food and Drugs to 3M company request for FDA's opinion; 21 CFR 211.28(d), Personnel responsibilities.

FDA's position was delineated in the Commissioner's letter which states in part:

> "...a person infected with the AIDS virus should not be restricted a priori from working in a pharmaceutical... manufacturing facility... We are not aware of any epidemiological data that suggest any increased product safety risks associated with the employment of persons with AIDS under the conditions which would exist in... drug... manufacturing... based on the fact that all...evidence...indicates that

> bloodborne and sexually transmitted infections like AIDS would not be transmitted under normal conditions in the workplace."

The referenced section of the CGMP regulations that covers the suitability of personnel associated with the manufacture of drugs reads in part:

> "Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products..."

It is the manufacturer's responsibility to ensure that employees will not contaminate drug products with infectious agents.

Joyce E. Bloomfield, HFD-322, 301-594-0095; e-mail: bloomfieldj@cder.fda.gov

Is it acceptable for repackagers to assign a single lot number to two or more co-mingled lots of bulk finished product repacked during the same run?

References: See 21 CFR 210.3(b)(10) and(11), Definitions, and 211.130(c), Packaging and labeling operations

No. Co-mingling of bulk lots during repackaging, even if repackaging records clearly identify the co-mingled lots, would cause the finished, repackaged product to be in violation of the CGMP regulations which define a "lot" as "a batch or a specific identified portion of a batch," (but not more than a single batch). Further, the CGMP regulations specify that the lot identification on finished product allow for, "the complete history of the manufacture, processing, packing, holding and distribution of a batch," and such would not be the case when product lots are co-mingled. Moreover, identifying problem lots or batches in the event of a complaint or finding of defective product, the use of appropriate expiration dating assignments, and the collection of representative samples, are additional concerns when product from different lots or batches are co-mingled.

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On Stability (Questions on drug product stability)

Should a manufacturer be cited on an FDA-483 for CGMP violations on the part of a contract testing lab it uses for stability testing?

Reference: CFR 211.22, Responsibilities of quality control unit ; 211.180(c), General requirements [Subpart J- Records and Reports]; FD&C Act 501(a)(2)(B)

No. CGMP deviations that relate to the practices of a contractor should be documented at the contractor facility. And if the deviations appear to be significant, the contractor should be cited on an FDA-483 for the deviations. It would not be appropriate to cite the manufacturer for CGMP deviations relating to any aspect of manufacturing, packaging or testing of drugs performed at the contractor's facility. If the deviations are serious, regulatory action could be taken against the adulterated drugs, even though the adulteration occurred at the contractor facility.

Moreover, if it can be shown that the manufacturing firm's QC unit releases product for distribution, even though it is aware of CGMP deviations, (e.g., it is aware that the test methods used by the contractor have not been validated), it then would be appropriate to cite the manufacturer for the CGMP deviation of releasing the inadequately tested drug.

In both cases, the contracting firm also could be held responsible for shipping adulterated drugs in interstate commerce.

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Do the CGMP regulations prohibit a firm from outsourcing (contracting out) the functions of the quality control unit?

Reference: 21 CFR 210(3)(a),(b)(15), Definitions and 211.22 Responsibilities of quality control unit

No. The CGMP regulations do not prohibit a firm from contracting out the functions of the quality control unit, or any other function the regulations identify. It would therefore be inappropriate to list such QC unit outsourcing, per se, as an FDA 483 item.

The CGMP regulations define a quality control unit as “any person or organizational element designated by the firm to be responsible for the duties relating to quality control”. The regulations incorporate by reference the definitions in the Federal Food Drug, and Cosmetic Act. The Act’s definition of “person” includes an individual, partnership, corporation and association. Therefore, a quality control unit could be a corporation external to the drug product manufacturer.

More important than who takes on the QC role is the matter of how well the quality control unit performs its responsibilities as required in section 211.22 and elsewhere in the CGMP regulations. That should be the primary focus of inspectional attention when it comes to auditing the work of the QC unit. For example, the unit must have available to it adequate laboratory facilities for testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products. Those facilities may be at the manufacturing location or elsewhere, but the regulations mandate their availability to the QC unit.

Nonetheless, investigators who encounter firms that contract out the Q.C. unit should be aware of any aspect of the outsourcing that might impair the unit’s ability to perform its many CGMP responsibilities. For example, if the contracted QC unit is remote from the manufacturing operations it is charged with monitoring, it might not be able to perform that oversight effectively and in a timely manner. Again, any FDA 483 item should speak directly to QC unit performance and not to outsourcing arrangements themselves.

Despite any division of CGMP activities, both the manufacturer and the outsourced Q.C. unit can be held responsible for introducing, or causing the introduction of, violative products into interstate commerce, each firm with respect to its actions. In addition, the violative products themselves would be subject to seizure.

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Gas What? (Policy Questions on Medical Gases):

1) Has there been any change regarding the calibration requirements for vacuum gauges used to evacuate high pressure cylinders, as described in the September 1995, edition of the Human Drug CGMP Notes?

Reference: 21 CFR 211.68 (Automatic, mechanical, and electronic equipment).

Yes. Vacuum gauges are used during the essential evacuation of residual from high pressure cylinders, and therefore, need adequate calibration.

Vacuum gauges should undergo two calibrations. The first calibration is performed on a daily basis. The vacuum gauge should be checked with no vacuum present to ensure that the needle on the gauge returns to the "zero." This check could be recorded on the batch production record or on a separate vacuum gauge log.

The second and more significant calibration requires the vacuum gauge to be calibrated to standards established by the National Institute of Standards and Technology. The frequency of calibration could be what the gauge

manufacturer recommends, or a firm could establish its own.

2) Has there been any change regarding which oxygen analyzers are acceptable to perform United States Pharmacopeia testing, as identified in the June, 1994, and the December, 1995, Human Drug CGMP Notes.

Reference: 21 CFR 211.165(a) and (e), Testing and release for distribution; and 211.194(a)(2), Laboratory Records

No. The following oxygen analyzers have been found to be acceptable for use to qualify Oxygen U.S.P.: Servomex Models 570A® and the 244A® analog model only; MADA Medical OAP640® and the Western Medica TR104® which are actually Servomex 570A®. For these oxygen analyzers only, a firm can rely on the manufacturer's instruction manual to satisfy Section 211.165(e). All other analyzers used for the analysis of medical gases need to undergo a validation study demonstrating the accuracy, sensitivity, specificity, and reproducibility of the analyzer showing U.S.P. equivalency. Further, the actual validation study should be maintained on file.

This is a change, because in the past, we have allowed a letter, provided by the analyzer manufacturer, attesting to U.S.P. equivalency, to suffice in lieu of having the actual study on file at each location. However, this is no longer acceptable since several manufacturers we contacted no longer had the validation study available.

In addition, in accordance with 211.194(a)(2) the suitability of all testing methods used shall be verified under actual conditions of use.

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Toward The Electronic Government:

More on collecting electronic copies of electronic records

Reference: 21 CFR 11.10(b); November 1997 Investigations Operations Manual (IOM)

In our last edition we addressed some potential methods of ensuring the integrity of electronic records that investigators collect. Be advised that the November 1997 revision to the IOM, at section 527.3 “Filmed or Electronic Records”, now gives explicit instructions on this matter. Investigators are expected to strictly follow the revised procedures and not use alternative methods, such as use of digital signatures we identified in December. Until future revisions to the IOM sanction such alternates, especially for evidence collection, they should not be used.

We are working with ORO to develop various training materials to help you implement Part 11. You can expect that, as is customary with field training documents, ORO will be the issuing unit.

Contacts for further info: ORO contact for IOM: James L. Dunnie, Jr., HFC-132, 301-827-5652, e-mail: JDUNNIE@ORA.FDA.GOV; CDER contact: Paul J. Motise, HFD-325, 301-594-0098; e-mail: motise@cder.fda.gov

P. Motise 3/1/98
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Botanicals Manufacturing	Brian Hasselbalch	594-0098
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Cleaning Validation	Russ Rutledge	594-2455
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Clinical Supplies/IND CGMP	Paul Motise	594-0098
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Electronic Records/Signatures	Paul Motise	594-0098
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Foreign Inspections	John Dietrick	594-0095
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Salvaging	Paul Motise	594-0098
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Here's my question regarding _____
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Future editions of HUMAN DRUG CGMP NOTES should address the following CGMP questions/issues:
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