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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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 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, for now, we cannot extend our distribution list (for paper copies) 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, present 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 the Policy and Guidance Branch, HFD-323, 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, see the checkoff line in FAX FEEDBACK, or else send e-mail to MOTISE, or DOCNOTES@FDACD.BITNET.

Thanks!

Paul J. Motise

POLICY QUESTIONS:

Is the sale of expired OTC drugs by a retailer a violation of the Food, Drug and Cosmetic Act?

We have received calls from both FDAers and state agencies inquiring as to what violation can be charged against a retailer found to be selling expired OTC drugs. We have been told of instances where retailers were found to be selling expired OTC drugs at a discounted price. Some retailers apparently feel that as long as they openly disclose to customers that the drugs being offered for sale are expired, they can be sold legally. Some state and local agencies have indicated they lack authority under their laws to pursue legal action against purveyors of expired OTC drugs, and therefore seek support for a legal action under the FD&C Act.

We regard expired drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Food, Drug and Cosmetic Act, which states that drugs must be manufactured, processed, packed, and held in conformance with current good manufacturing practice. The holding of drug products past their

expiration dates supports the 501(a)(2)(B) charge. It should be noted that it would not be appropriate to cite a retailer for deviations from the CGMP regulations in 21 CFR Parts 210 and 211, because the CGMP regulations apply to drug product manufacturers. Additionally, openly disclosing that the drugs are expired is not any basis for an exemption from the Act. From a public health standpoint, there is no assurance that drug products held past their expiration dates are safe and effective, even if they are OTC drugs.

Contact for Further Info: Barry Rothman, HFD-325, 301-594-0098, e-mail: rothmanb@fdacd.bitnet.

Does FDA "prefer" polyvinylidene difluoride over stainless steel for construction of recirculating loops in water for injection (WFI) systems?

Reference: 21 CFR §211.65, Equipment construction, and §211.67, Equipment cleaning and maintenance.

There is no official agency preference for one material over another. Whatever material a firm selects for its water for injection system must be suitable for the intended use. This holds true for virtually any production equipment.

In the case of a WFI system, factors to consider in evaluating the suitability of the piping would include interior smoothness, the ability to withstand high temperatures and pressures, and the ability to hold up to sterilizing and sanitizing agents.

As a general matter, equipment surfaces that contact components, in-process materials, or drug products must not be reactive, additive, or absorptive so as to alter the drug product's safety, identity, strength, quality, or purity beyond its official or established requirements.

Contact for Further Info: John Levchuck, HFD-322, 301-594-0095, e-mail: levchukj@fdacd.bitnet.

What should manufacturers do if they have one of the "flawed" Pentium® chips in their computerized systems?

References: See 21 CFR §211.68, Automatic, mechanical, and electronic equipment.

As covered by numerous press reports, certain early versions of Pentium® processors, manufactured by Intel Corp. of Santa Clara, CA since May of 1993, contain a defect that will cause incorrect results if certain mathematical calculations are performed with computers containing the Pentium® processor. The error happens when floating point divide instructions use certain pairs of numbers. Intel has undertaken a program to replace, without charge, defective Pentium® processors with new Pentium® processors that do not contain the defect.

During your inspections, you may encounter computer systems which contain the Pentium® processor and which are being used to monitor or control manufacturing or laboratory functions, within the context of CGMP.

We expect firms to ensure that computer systems are suitable for their intended use and that, as part of production or lab processes such systems monitor or control, they have been covered by validation of those processes. The Pentium® processors may be in personal computers or in other automated systems. We expect firms to know what systems may contain the processors in question (if they don't know, then equipment vendors should be able to advise them).

Firms should replace defective processors as soon as possible, or, where such replacement is impractical, firms should determine if floating point divide instructions are used in the manufacturing or analytical application. No immediate remedial action need be taken if floating point divide instructions can't, under any circumstances, be performed in that application.

If floating point divide instructions can be performed in a CGMP application, firms should evaluate the application to determine if potential errors will be detrimental to the process control

or analytical functions; firms should be mindful of possible errors caused by compounding.

No immediate remedial action is necessary where firms determine that potential errors are not detrimental . On the other hand, if firms find that potential errors are detrimental and replacement of the defective Pentium® processor is impractical, software designed to prevent the errors should be installed. If appropriate remedial action cannot be taken, manufacturers should stop using the equipment containing defective Pentium® processors.

Where firms install a replacement processor or remedial software, equipment should be qualified using appropriate validation methods. Of course, we expect firms to thoroughly document their evaluations, remedial actions and re-validation efforts.

Contact for Further Info: Paul J. Motise, HFD-323, 301-594-1089, e-mail: motise@fdacd.bitnet.

Policy Questions on Cleaning Validation:

Reference: 21 CFR §211.67, Equipment cleaning and maintenance; and, Guide to Inspections of Validation of Cleaning Processes, July 1993 (reformatted May 1994)

1) What is the level of detergent residue that would be acceptable to FDA? What is the basis for arriving at this level, if any?

FDA has repeatedly stated that it is the firm's responsibility to establish acceptance limits and be prepared to provide the basis for those limits to FDA. Thus, there is no fixed standard for levels of detergent residue. Any residues must not adversely alter drug product safety, efficacy, quality, or stability.

2) If the ability of a procedure to clean a piece of equipment made of a particular material, such as 316 stainless steel, is shown to be acceptable and validated, can that "material" specific cleaning procedure be used without "extensive" validation for other pieces of equipment and compounds?

No. The design of the equipment is a major component of its cleanability. Therefore, firms should have data that relate to a given piece of equipment.

Contact for Further Info: Anthony Lord, HFD-322, 301-594-0095, e-mail: lord@fdacd.bitnet.

Bulk Beat (Policy Questions on Bulk Drugs):

Reference: Guide to Inspection of Bulk Pharmaceutical Chemicals, September, 1991.

1) What is the current regulatory status of bulk pharmaceutical chemicals in the United States?

At present, the United States does not have a good manufacturing practice regulation for bulk pharmaceutical chemicals. The CGMP regulations promulgated under the Food, Drug, and Cosmetic Act and codified in Title 21 of the Code of Federal Regulations, Parts 210 and 211, apply only to finished pharmaceuticals. Although the drug CGMP regulations have been used as a general guide where applicable to BPC processing, they were not intended to be applied to the production of BPCs. The preamble to the September 1978 revision of the CGMP regulations states:

"These CGMP regulations apply to finished dosage form drugs (under §§210.3(b)(4) and 211.1) and are not binding requirements for chemical manufacturing. The Commissioner maintains that these regulations can serve as useful guidelines in the manufacture of chemicals."

Nonetheless, the definition of "drug" in the Food, Drug, and Cosmetic Act encompasses bulk pharmaceutical chemicals and Section 501(a)(2)(B) of the Act also requires that all drugs be manufactured, processed, packed, and held in accordance with CGMPs. No distinction is made between BPCs and finished pharmaceuticals in the Act, and failure of either to comply with CGMP constitutes a violation of

the Act.

2) What is the FDA doing to address the lack of GMP regulations for BPC's?

FDA recently formed a task group to develop a good manufacturing practice regulation specific to bulk pharmaceutical chemicals and to define acceptable approaches or "points-to-consider" when validating BPC processes. This task group consists of representatives from the Office of Regional Operations, the Office of General Counsel, CDER, CBER, and CVM. We will provide additional details on this effort in future editions of Human Drug CGMP Notes.

Contact for Further Info: Edwin Rivera, HFD-322, 301-594-0095, e-mail: rivera@fdacd.bitnet.

Gas What? (Policy Questions on Medical Gases):

1) What is pressure swing adsorption (PSA) and what are the requirements for the nitrogen produced by PSA, if the product is used during the manufacture of a drug product, such as tablets, capsules, etc.?

Reference: 21 CFR §211.110(a & c), Sampling and testing of in-process materials and drug products.

We have received numerous inquiries regarding the use of PSA in the manufacture of pharmaceutical drug products, where the nitrogen will be used as a blanketing agent, etc.

The principle of PSA is where a stream of air is compressed, filtered, and then passed through a molecular sieve which selectively adsorbs oxygen, leaving the remaining process gas stream nitrogen rich. Some units are capable of producing flow rates up to 100,000+ scfh and purity levels as high as 99.9995% with purification.

If a firm is using PSA, then it should establish control procedures to monitor the output and to validate the performance of those manufacturing processes that may cause variability in the characteristics of in-process material and the drug product. This would also pertain to nitrogen received in large cryogenic vessels, i.e., tube trailers, storage tanks, etc.

2) What's the current policy regarding the filling of a vacationing patient's vessel, either high pressure cylinder or cryogenic home vessel?

Reference: 21 CFR §211.84, Testing and approval or rejection of containers and closures; 21 CFR §211.94(c), Drug product containers and closures; 21 CFR §211.165(a), Testing and release for distribution.

This type of scenario, which is similar to the filling of a cryogenic vessel at a patient's home, is considered an emergency need for the drug product. If a patient is on vacation and/or traveling away from his/her residence, and encounters a need for oxygen, then a firm would be allowed to fill the patient's vessel without performing all the required testing or all the required prefill inspections, provided 1) the firm receives a prescription, 2) the patient remains at the firm, i.e., cannot leave the premises, 3) the employee who receives the vessel performs the filling and returns it promptly to the patient, 4) the incoming drug product has been tested and meets all specifications, and 5) the minimum visual inspections are performed, i.e., valve and external examination, labeling, coloring, correct valve, etc. Finally, the firm should obtain the patient's final destination including an address and a telephone number, in case of a recall.

Contact for Further Info: Duane Sylvia, HFD-322, 301-594-0095, e-mail: sylviad@fdacd.bitnet.

Final Rule on Cut Labeling Controls: Effective Date Partially Extended

Reference: 60 FR 20897, No. 82, April 28, 1995

In the above FR notice, FDA announced that the date for compliance with §211.122(g) for items of labeling other than immediate container labels is being extended to August 2, 1996. The date of

compliance for all other provisions of the final rule, as published in the Federal Register of August 2, 1994 (at 59 FR 39255), remains the same.

The agency is taking this action in order to adequately assess comments received on the scope of that rule.

Be aware that §211.125 makes a waiver of labeling reconciliation conditional on a 100 percent examination for correct labeling performed in accordance with §211.122(g)(2), meaning the labeling reconciliation must still be performed until §211.122(g) is in effect for labeling other than immediate container labels.

Division Contact for Further Info: Paul J. Motise, HFD-323, 301-594-1089, e-mail: motise@fdacd.bitnet.

Toward The Electronic Government:

What is the status of the proposed rule on electronic signatures and electronic records?

Reference: Federal Register, 59 FR 45160, No. 168, August 31, 1994.

The comment period for proposed Part 11 has closed and the agency has begun its deliberations toward a final rule. A total of 49 respondents submitted about 544 discrete comments. The agency-wide effort garnered comments from virtually all FDA regulated industries, although the pharmaceutical industry provided most of the comments.

The rulemaking project has been put on a fast track, as part of the administration's reinventing government project.

While it is impossible to predict a final outcome, our best guess at this point is that a final rule would not be published prior to the last quarter of this calendar year.

CDER Launches Internet Gopher Server.

CDER recently inaugurated an Internet gopher (file retrieval facility) server to help distribute electronic documents (including this newsmemo). Internet savvy readers can point their gopher clients to **gopher.cder.fda.gov**to see a simple menu structure of available files, their formats and sizes. A typical menu entry for a file looks like this (filename, date and time, size and file type):

hdcgmpw5.395 [13-Feb 12:52, 547KB] <PC Bin>

Downloading files from gopher is much easier than from FTP servers. Typically, client applications call for you to position your cursor on the line corresponding to the target file and then type the letter "s" for save; programs generally let you rename the file for your local system, and then the transfer begins.

CDER's strategic information technology plans call for the establishment of a CDER World Wide Web server/home page, but that's still sometime off.

All in all, the center is committed to distributing documents electronically and using information technology to enhance communication with field units, industry and the public.

Contact for Further Info: Paul J. Motise, HFD-323, 301-594-1089, e-mail: motise@fdacd.bitnet.

P. Motise 5/9/95
DOC ID CNOTESW6.695

FAX FEEDBACK

TO: Paul Motise, HUMAN DRUG CGMP NOTES, HFD-323
FAX: 301-594-2202 (Phone 301-594-1089)

HUMAN DRUG CGMP NOTES **June, 1995**

FROM: _____

AT: _____ MAIL CODE: _____

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To receive the electronic version of HUMAN DRUG CGMP NOTES via E-mail, check here _____, or send e-mail request to docnotes@fdacd.bitnet.

This FAX consists of this page plus _____ page(s).

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 for: _____ on the subject of:

_____
_____
_____

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

_____
_____
_____