

‘HUMAN DRUG CGMP NOTES’

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(A Memo for FDA Personnel on Current Good Manufacturing Practice For 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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This level 2 guidance document represents the agency's current thinking on Current Good Manufacturing Practice for human use pharmaceuticals. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

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Fax-Feedback (Your input requested)

RUSS'S RAMBLINGS

Welcome to another edition of Human Drug CGMP Notes, our periodic guidance memo for FDA personnel on CGMP for human use pharmaceuticals.

Your FAX FEEDBACK responses have proven valuable, and we appreciate your suggestions. This is one way which we identify and attempt to address items of current interest. Additionally, you may use other means to communicate with us. Feel free to call, write, or e-mail your comments. Specific questions on an article would best be answered by the contributing authors. We also welcome brief articles which other FDAers may wish to contribute. Subjects should be CGMP related and would be especially valuable if they address emerging new technologies.

Since DMPQ decided to publish Human Drug CGMP Notes exclusively in electronic format, the requests for inclusion on the electronic subscription list have tapered off. I still receive several requests per week and continue to answer each of these with an explanatory letter. Hopefully these requests will cease with this edition

The articles in this edition are a reflection of the many questions we have received on various CGMP issues, with Penicillin contamination continuing to be a topic of intense interest. I think you will find these articles a valuable resource.

Brian Nadel was kind enough to submit an article addressing the issue of reprocessing of bulk pharmaceuticals prior to his departing the agency. I wish him well in his new career.

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.

Once again, we're now available exclusively on the Internet at:

<http://www.fda.gov/cder/dmpq>

Thanks!

Russ

POLICY QUESTIONS:

1) How can one obtain a copy of the procedures for detecting and measuring penicillin contamination in drugs?

References:

21 CFR 211.176, Penicillin Contamination;

FDA By-Lines No.3, Nov. 77, A Review of Procedures for the Detection of Residual Penicillin in Drugs.

The bioassay referenced in 21 CFR 211.176 can be used whenever there exists a reasonable possibility that a non-penicillin drug product has been exposed to cross-contamination with penicillin. The non-penicillin drug product should be tested for the presence of penicillin and not marketed if detectable levels are found when tested according to procedures specified in "Procedures for Detecting and Measuring Penicillin Contamination in Drugs", which is incorporated by reference. Copies are available from the Division of Pharmaceutical Analysis, (HFD-923), Center for Drug Evaluation and Research, Food and Drug Administration, 8301 Muirkirk Road, Laurel, MD, 20703. To request copies of the procedure contact:

Valarie A. Flournoy, Tel 301-827-8236,
FAX 301-827-8073, E-Mail
FLOURNOY@CDER.FDA.GOV.

For further information contact: Edwin
Melendez, 301-594-0098,
melendeze@cder.fda.gov

2) Can section 21 CFR 436.104 (Penicillin Activity) continue to assist in determining residues of penicillin contamination in non-penicillin drugs?

Reference: 21 CFR 211.176, Penicillin Contamination; FDA By-Lines No.3, Nov.77, A Review of Procedures for the Detection of Residual Penicillin in Drugs.

No, it can not. Section 436.104 was in part 21 CFR 436. Parts 429 through 460 existed for the purpose of enforcing Section 507 of the FD&C Act "Certification of Antibiotics". This section of the Act was repealed by FDAMA (FDA Modernization Act). Therefore, section 436.104 was deleted from the CFR and does not exist any longer.

Section 436.104 (methodology for penicillin activity) is derived from the original tests for penicillin contamination in foods and drugs published in FDA By-Lines No.3 (Nov.1977). The FDA codified method continues to exist because it still is required in 211.176 – "...such drug product shall not be marketed if detectable levels are found when tested according to procedures specified in 'Procedures for Detecting and Measuring Penicillin Contamination in Drugs,...". The elimination of 436.104 does not change anything for the following reason: In the By-lines, the

test sensitivity is stated to be 0.01 units/ml as penicillin G, using *S. lutea*, equivalent to 0.006 PPM. The 'standard response line' cited at 436.104 covers a range of concentrations equivalent to 0.003 to 0.120 PPM, as penicillin G. However, the test method as cited in 211.176 has always indicated a limit of sensitivity of 0.006 PPM. We always indicate that the sensitivity should be at 0.006 PPM and not necessarily 0.003 PPM. So nothing has changed because the By-lines also covers a range of concentrations which can be used as 'standard response lines' similar to 436.104.

For further information contact: Edwin
Melendez, 301-594-0098,
melendeze@cder.fda.gov

3) If a chemical company manufactures an active pharmaceutical ingredient and sells it to another company, who then formulates the finished dosage form, are the manufacturing activities of the chemical company covered under CGMPs?

References:
Federal Food, Drug, and Cosmetic Act,
Sec. 501(a)(2)(B)
21 CFR 211

Yes. Section 501(a)(2)(B) of The Food, Drug and Cosmetic Act requires that all drugs (including active pharmaceutical ingredients), be manufactured in accordance with CGMPs. Therefore, the manufacturer of an active pharmaceutical ingredient is required by law to manufacture in accordance with CGMPs. While the CGMP regulations in 21CFR Parts 210 and 211 apply only to

finished products, the statute requires that CGMPs be followed for all drugs, including active pharmaceutical ingredients. You may wish to note FDA's draft guidance, "Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients" which is available on FDA's web site:
<http://www.fda.gov/cder/guidance/index.htm>

Further information is available in the draft ICH guidance "Q7A Good Manufacturing Practice for Active Pharmaceutical Ingredients"
<http://www.fda.gov/cder/guidance/index.htm>

Since these are draft documents, the guidance contained within them may be subject to change. There might be additional guidance to consider when they are finalized.

For further information, contact Russ Rutledge, 301-594-0098,
rutledgec@cderr.fda.gov

4) For a USP drug, is meeting the specifications in an official monograph sufficient to show compliance with CGMPs?

References:
Federal Food, Drug, and Cosmetic Act, Sec. 501 (a)(2)(B), Sec. 501(b)
21 CFR 211
USP 24, *General Notices*, "Test Results, Statistics, and Standards" p.10

No. The tolerances in the USP are based upon the consideration that the drug is manufactured in compliance with good manufacturing practices. Testing alone is not sufficient to demonstrate CGMP compliance, even when the results indicate that the drug meets criteria in an official monograph. Drugs

that are not manufactured in compliance with CGMPs, or do not comply with their official monograph, are considered adulterated in the FD&C Act.

For further information, contact Barry Rothman, 301-594-0095,
rothmanb@cderr.fda.gov

5) Should reprocessing of a bulk batch of finished product always be listed as a CGMP deviation on an FDA-483?

References:
Subpart F - Production and Process Controls
21 CFR 211.111 Time limitations on production,
211.113 Control of microbiological contamination.
211.115 Reprocessing.
Subpart J - Records and Reports
21 CFR 211.192 Production Record Review

No, reprocessing may be acceptable if it is performed according to CGMP. It must first be determined whether or not the firm has written and previously established procedures for reprocessing, according to 211.115. The next question that needs to be answered is did the quality control unit review and approve this reprocessing, according to 211.115(b).

Consideration should be given to the amount of time that transpired before the bulk batch was reprocessed. According to 211.111, time limits for completion of each phase of production shall be established to assure the quality of the drug product.

Another factor that should be considered is the possibility of microbiological contamination during the time that the bulk batch is held for reprocessing. According to 211.113, the firm must follow written procedures designed to prevent contamination by objectionable microorganisms. These written procedures must be followed whether or not the product is sterile.

The stability of reprocessed batches of finished drug products should be considered. Reprocessing may affect the stability, therefore the firm should determine if these batches should be placed into their stability program. Unless the firm has data from prior batches produced under the same circumstances, the fact that a reprocessed batch was not entered into the stability program may be included on the FDA-483.

The fact that a batch of drug product was reprocessed is not per se a CGMP violation. However, if this reprocessing was not approved by the QCU, then this should be listed on the FDA-483, according to 211.115(b). You should also consider listing on the FDA-483 that a manufacturing process is not adequately validated when there is evidence of repeated reprocessing on multiple batches.

Another item that may be listed on an FDA-483, if applicable, is the failure to conduct an investigation when a batch does not meet any of its specifications, according to 211.192, Production Record Review. Any time reprocessing occurs, there should be a written record of the investigation that includes conclusions and follow-up.

Article written by Brian G. Nadel

For further information contact: Edwin Rivera (301) 594-0098, rivera@cder.fda.gov

6) Are the use of ditto marks and arrows for redundant information acceptable practices under CGMP for documentation?

Reference:
21 CFR Part 211, Subpart J, Records and Reports

No. While there is no specific FDA documentation or guidance that discusses the practice of using ditto marks and arrows in place of required information, the use of these instead of specific information, initials, or signatures is not fully informative. Ditto marks and arrows are not sufficiently descriptive where actual values are needed, and more importantly, cannot be directly related to the recorder.

For further information, contact Rosa Motta, 301-594-0098, mottar@cder.fda.gov

FAX FEEDBACK

TO: C. Russ Rutledge, HUMAN DRUG CGMP NOTES, HFD-325
FAX: 301-594-2202 (Phone 301-594-0098)

FROM: _____

AT: _____ MAIL CODE: _____

PHONE: _____ FAX: _____

E-MAIL ADDRESS: _____

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/comment regarding:

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

