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
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Center for Drug Evaluation and Research

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IN THIS EDITION:

INTRODUCTION:

Dear Readers- I just wanted to make some comments as we change project managers for the Human Drug CGMP Notes. Paul Motise has departed the Division and we want to wish him well in his new endeavors. We also want to continue this valuable publication with Russ Rutledge taking on this important task. This publication is written for all of FDA. We welcome and encourage articles from folks in headquarters and the field alike who have a stake in CGMP issues and can contribute articles on CGMP issues.

Joe Famulare

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. As many of you are aware, our first and only project manager (Mr. Paul Motise) has departed the Division of Manufacturing and Product Quality for another exciting career opportunity. This left the division with a deep void and a choice- should we continue to publish CGMP Notes or accept the easier solution of letting it quietly go away? The feedback received over the past 7 years has been overwhelmingly positive, from the field and the regulated industry, so we concluded that this newsletter is serving a valuable function and should live on. I volunteered to step into this position, so here is my first attempt to continue what I consider a tough act to follow. Paul- I wish you well in your new position.

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. These may be addressed to any individual in DMPQ, especially the contributing authors. 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.

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 document is to enhance field/headquarters communications on CGMP issues in a timely manner. This 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 memo 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! *Russ*

POLICY QUESTIONS:

For a non-sterile compendial drug product, which includes an antimicrobial preservative in the original formulation, is it acceptable to release and market lots of this drug product that have initial release test results exhibiting out-of-specification total aerobic plate counts, when these lots test within specification two weeks later?

References:

21 CFR 211.113(a)

21 CFR 211.165(f)

USP 24 General Chapter <51>

No! 21 CFR 211.113(a) provides for appropriate written procedures to be followed during manufacturing to assure that objectionable microorganisms are not introduced into drug products not required to be sterile. This regulation mandates the establishment and adherence to written procedures to prevent the inclusion of objectionable organisms in drug products during manufacture.

Additionally, the second paragraph of USP 24 General Chapter <51> reads in part:

> "…Antimicrobial preservatives should not be used as a substitute for good manufacturing practices or solely to reduce the viable microbial population of a nonsterile product or control the presterilization bioburden of multidose formulations during manufacturing... "

This compendial section advises against the

use of antimicrobial preservatives as a sole means of reducing viable microbial populations in nonsterile products. We interpret this to mean that drug manufacturers should not rely upon antimicrobial preservatives to reduce initial out-of-specification plate counts to within specification levels and then market the product. This is particularly true when the initial out-of-specification results may have been due to organisms that were contributed to the product during the manufacturing process.

For example, in a recent case, a drug manufacturer had initial release test results for several lots of a non-sterile drug product that were each out-of-specification for total aerobic count. Testing a short time later on samples from the same lots gave results that were in specification. We did not regard it acceptable for the manufacturer to release and market these products, even though a reduction of microbial counts to levels near zero had been demonstrated to be attributable to the effectiveness of the preservative.

21 CFR 211.165(f) mandates that drug products failing to meet established standards or specifications shall be rejected. A company's reliance on an antimicrobial preservative to reduce out-of-specification levels of microbes to within specification levels does not disqualify the initial release test. We would still expect the manufacturer to reject the drug product based on the initial out-of-specification results found upon release testing.

It is also not acceptable for a company to allow an inappropriate amount of time to pass before testing the product to permit the preservative to reduce levels of microbes possibly added during manufacture. This is particularly true when testing data demonstrates that initial release testing conducted a short time after manufacture shows the drug product to be frequently out-of-specification for total aerobic plate count.

Finally, manufacturing procedures should be reviewed to determine procedures or equipment that might be contributing organisms to the process and product. In the case discussed above, standing water that had been allowed to remain in equipment after cleaning, was identified as a CGMP deficiency likely to have contributed to microbial growth in the product. Removal of the standing water has resulted in no detectable total aerobic counts to date. Adherence to CGMPs should prevent manufacturing conditions that contribute microbes to the finished product.

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Does the OGD Draft Guidance document on Blend Uniformity Analysis (BUA) represent CGMP requirements?

References:

Draft Guidance for Industry ANDAs: Blend Uniformity Analysis August 1999

21 CFR 211.110 Sampling and testing of in-process materials and drug products

No, this Office of Generic Drugs (OGD) guidance document presents recommendations for application filing based on 21 CFR 314, not on CGMP regulations. Also, this is a draft document subject to review and comment, and has not yet been implemented. OGD current policies are based on earlier policy documents rather than on this draft guidance. Additionally, the guidance document presents recommendations only, not requirements. Alternative approaches may also be used to submit data with an application.

The CGMP regulations, 21 CFR 211.110, do not require Blend Uniformity Analysis (BUA). It requires some type of test or examination on each batch, but that test or examination does not have to be BUA as described in the guidance document. Failure to perform BUA type testing on routine production batches should not be cited as a CGMP deficiency. BUA type testing is recommended for low dose powder blend products *(e.g., less than 50% or 50 mg)* but other approaches may

also be used to satisfy this CGMP requirement.

The draft guidance also permits the submission of a supplement to delete BUA testing. This is also an application filing issue and does not exempt a manufacturer from the CGMP requirement for some type of test or examination on each batch. If BUA type testing is discontinued, an alternate approach to comply with 21 CFR 211.110 should be implemented.

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PENICILLIN ISSUES:

1. **What do the CGMPs mean by separate facilities? Must the buildings be totally separated, or are the CGMPs satisfied when the floors are physically separated with separate air filtration units installed?**

References:

21 CFR 211.42(d) Design, and construction features

21 CFR 211.46(d) Ventilation, air filtration, air heating and cooling

21 CFR 211.176 Penicillin contamination

Federal Register, 9/29/78 (Vol.43, No.190, Book 2) Preamble to the CGMPs at comment 142

CGMP regulations [21 CFR 211.42(d) and 211.46(d)] require separation of penicillins from non-penicillins during processing. The discussion of the comments in the preamble to the regulations note that "…isolation of penicillin production operations…can be achieved by sealing off…the two operations." "…does not necessarily mean…separate buildings." Thus, there can be a "building within a building"- i.e. two buildings are not required. However, there must be total separation of operations, meaning every aspect of the operations must be separate. Adequate separation should include physical barriers and separate air handling systems. Personnel and equipment from the penicillin facility should not enter the non-penicillin facility. These should operate with well established written procedures and controls. The separation should be audited, procedures validated, and where necessary monitored.

Even with separation, if any possibility of contamination exists, the non-penicillin products must be tested (21 CFR 211.176). An example of possible contamination could be inadequate controls over movement of equipment or personnel. Section 211.176 requires non-penicillin products to be tested for traces of penicillin where the possibility of exposure exists, and not marketed if detectable levels of penicillin are found.

While this section prohibits marketing of products found to be contaminated with penicillin, it does not sanction marketing of non-penicillin products based only on test results that show no detectable levels of such contamination. Other CGMP requirements must still be met. For a discussion on this issue, please review the article "Is it acceptable under section 211.176 to release products to market as long as the products are tested and no penicillin is found?" published in "Human Drug CGMP Notes" (Volume 6, Issue 2, June 1998).

Cross contamination issues have been a concern for a number of years, and continue to be problematic. In one penicillin cross-contamination case reviewed it was demonstrated how a non-penicillin facility was contaminated by a separate penicillin facility located in the same manufacturing campus. This occurred due to lack of controls regarding movements of personnel, equipment and materials. In another case, CDER concurred with a district recommendation to withhold approval on a sensitizing beta-lactam manufacturing facility that was adjacent to another drug processing building, due to the lack of containment controls which ensured against cross contamination of the other drugs.

2. **Is it acceptable to manufacture penicillin and non-penicillin products**

in the same facility on a campaign (i.e., the conversion of production facilities to a different product line on a routine basis) basis, with adequate cleaning validation procedures in place?

References:

21 CFR 211.42(d) Design, and construction features

21 CFR 211.46(d) Ventilation, air filtration, air heating and cooling

21 CFR 211.176 Penicillin contamination

Federal Register, 9/29/78 (Vol.43, No.190, Book 2) Preamble to the CGMPs at comment 148

No, it is not acceptable. The discussion of the comments in the preamble to the regulations state that "…it is important to make clear in these regulations that completely separate air-handling facilities for penicillin and non-penicillin production are required.". And "…because it is possible for air-handling systems between penicillin and non-penicillin production areas to be interconnected, ...the Commissioner finds it necessary to state that any such interconnection would be unacceptable."

Campaign production of penicillin and any non-penicillin product in the same facility and with the same equipment violates the CGMP regulations [211.42(d) and .46(d)]. A concern is that the cleaning validation process does not include the air handling system throughout the facility. This is important because campaign production has the potential for recontamination of the air handling systems and facilities, and can lead to cross contamination of non-penicillin products with penicillin. The concept of decontamination is broader than a typical cleaning procedure validation, in that sampling is extended to include the environment, as well as surfaces of the facility and equipment that are to be decontaminated.

A facility contaminated with penicillin could not begin non-penicillin production until extensive decontamination and clean-up of the facility is accomplished in accordance with the established procedures, and representative environmental samples demonstrate that the facility conforms with its decontamination protocol/specifications.

Current technology makes decontamination of air handling systems difficult. This is because the decontamination/cleaning procedures would necessitate sampling and residual testing of other parts of the air handling system, to include the ductwork. This would be difficult because the air handling system throughout its length has uneven areas and crevices that create the possibility of penicillin residue build-up, with slough-off at undetermined periods during the non-penicillin production period. Thus penicillin contamination would not be uniformly distributed in the air handling system, and "representative" samples (retain, surface and/or air) may not be an accurate portrayal of the level of contamination.

21 CFR 211.176 indicates that where the possibility of exposure exists, non-penicillin products must be tested for traces of penicillin and not marketed if detectable levels are found. This means that representative samples from all batches of non-penicillin products produced in each campaign must be tested with an acceptable method and found non-detectable for the penicillin product produced prior to the start-up of the non-penicillin campaign.

One case we reviewed demonstrated a positive environmental surface sample from the fan blade of an exhaust hood in the repack room for beta-lactam residue, even though the most recent beta-lactam repackaging operation had been performed more than six months prior to sampling.

3. Is it acceptable to manufacture penicillin products in the same facility as cephalosporin?

References:

21 CFR 211.28 Personnel responsibilities

21 CFR 211.42(b),(c)&(d) Design, and construction features

21 CFR 211.46(c)&(d) Ventilation, air filtration, air heating and cooling

21 CFR 211.67 Equipment cleaning and maintenance

21 CFR 211.80(b) Control of components and drug product containers and closures

21 CFR 211.176 Penicillin contamination

Beta-lactams are products with a chemical substructure that contains the beta-lactam ring. They have the potential to sensitize and cause allergic response in humans. Hypersensitivity, due to intolerance of beta lactam ingredients, can trigger reactions which range from a rash to life-threatening anaphylaxis**.** There is evidence that cross-sensitivity exists between penicillins and cephalosporins. Thus, patients who are intolerant of penicillin may also be intolerant of cephalosporins, and further, cephalosporins may induce anaphylaxis in patients with a history of penicillin anaphylaxis.

The immune system is exquisitely sensitive and can distinguish between very subtle changes in chemical composition. Patients may be tolerant of a given drug but intolerant of another drug with closely related chemical structures. There is evidence that patients tolerant of penicillin may be intolerant of cephalosporins. CDER recognizes the considerable potential for cross-sensitivity and the possible life-threatening consequences of unintended exposure. Therefore, although not a specific requirement of sections 211.42 (d), 211.46(d) and 211.176, it is recommended that manufacturing operations for cephalosporins, penems and cephems, be separated from non-beta-lactam products and other beta-lactam drug products. For example cephalosporin type products would be separated from penicillin type products or non-beta-lactam products.

Production of cephalosporin type products can be approached from two different regulatory/compliance perspectives:

1) If cephalosporins are considered to be non-penicillin drugs, they could not be manufactured in a facility lacking adequate separation from penicillin products. 2) For cephalosporin production with other non-beta-lactam drug products, similar health concerns exist for patients sensitive to cephalosporins who should not be exposed to it in a non-beta-lactam product.

For fundamental CGMP reasons and because of the difficulties in demonstrating and validating appropriate sampling and testing methodology for measuring cross-contamination, penicillin production should be performed in facilities separated from non-beta-lactam drug products and other beta-lactam drug products unless adequate separation is demonstrated. We don't know of a satisfactory shared facility as of today.

Furthermore, if necessary, other sections of the CGMP regulations [i.e., 211.28; 211.42(b) & (c); 211.46(c); 211.67; and 211.80(b)] could be applied to control contamination between beta-lactam and non-beta-lactam drug products. In summary the Agency considers the separation of production facilities for sensitizing beta-lactam based products to be current good manufacturing practice.

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FAX FEEDBACK

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