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RUTLEDGE'S NOTEBOOK

FDA Viewpoint

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KNOW YOUR CURRENT GMP

The primary purpose of Rutledge's Notebook - "A Memo on Current Good Manufacturing Practice Issues on Human Use Pharmaceuticals" - is to enhance FDA field / headquarters communications on cGMP issues in a timely manner. This is a forum to address FDA cGMP questions, get updated on cGMP projects, and clarify and help FDA'ers apply existing policy to their day-to-day inspection and compliance activities. These memos do not supplant agency policy, development or issuance mechanisms.

POLICY QUESTIONS:

Q. - For a *non-sterile* compendial drug product (i.e. liquid/suspension), 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>

A. - **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..."

Preservatives are
for Consumer
Inoculation
NOT
Substituted GMP

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.

Reduce bioburden via low bioburden excipients, materials & procedures

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 anti-microbial 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.

Antimicrobials & Preservatives do not substitute for adequate cGMP

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.

Eradicate high BIOBURDEN contaminating Excipients, Equipment & Procedures

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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Q. - 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

A. - NO the Office of Generic Drugs (OGD) guidance document currently present 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 (as of May 2000).

**FDA's
Blend Uniformity Analysis
is still a draft
It is not cGMP or
CFR 21**

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.

**Three Times the
Tablet/Capsule weight
is an excellent
Statistical approach!**

[One is not a statistical number
- three is!]

Remember:-
"A one unit dose sampling is simply a
snap-shot and when it comes to BUA,
it's a poor shot indeed!" - Editor]

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.

**Most times
Tapped & Bulk Density
& particle size
are the best granule
conformity controls**

Failure to perform BUA type testing on online 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.

**For Low Dose Units
Tapped & Bulk Density
& U of C
using 3 times weight
is the way to go!**

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:

Q. - 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.

A. - 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;

CFR Quote;

“...isolation of penicillin production operations... ..can be achieved by sealing off... ..the two operations.”
“...does not necessarily mean.....separate buildings.”

Sealed Buildings
not
Separate Buildings
is the key

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.

Separation must be complete (i.e. PEG) People, Environment and Goods

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.

Sealed Buildings
should have
no link to
other Buildings

['Sealed' means completely sealed']

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). - See end of the article for discussion.

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 (goods).

Prevent any
PEG
movement between
facilities

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.



Q. - Is it acceptable to manufacture penicillin and non-penicillin products in the same facility on a campus (i.e., the conversion of production facilities to a different product line on a routine 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

A. - NO, it is not acceptable. The discussion of the comments in the preamble to the regulations state that: CFR Quotes:-
 "...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."

**Separate & unlinked
with no joint access of
People, Environment
(+air handling)
and Materials
is the basic rule.**

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.

**Cleaning Validation
normally excludes the
Air Handling System**

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.

Decontamination of air systems is technically difficult

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.

The 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.²¹ CFR 211.176 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.



Q. - 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

A. - 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.

What applies to penicillins Applies to Cephalosporins

[It's as simple as that!]

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.

Cross Sensitivities are a medical, NOT a CFR 21 Fact.

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 cepheids, 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.

In the final analysis

SEPARATE

Beta-lactams as well

[Not just Penicillins alone]

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.

Beta-lactams
or
Non beta-lactams
That is the
question!

We don't know of a satisfactory shared facility as of today. Furthermore, if necessary, other sections of the cGMP regulations could be applied to control contamination between beta-lactam and non-beta-lactam drug products [i.e., 211.28; 211.42(b) & (c); 211.46(c); 211.67; and 211.80(b)].

In summary the Agency considers the **separation** of production facilities for sensitizing beta-lactam based products to be current good manufacturing practice.

In the World of GMP
Cross Contamination
Prevention between
Beta-lactams and
Penicillin
is a Prerequisite!

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PENICILLIN LIMITS

(Excerpt from FDA'er Paul Motise Volume 6, Issue 2, June 1998 Ref. IJGD Vol.02 1998).

Q. - Is there an acceptable level of penicillin residue in non-penicillin drug products?

A. - Any detectable levels of penicillin residue are considered violative because 21 CFR 211.176 indicates that a non-penicillin drug product must not be marketed if detectable levels of penicillin are found when tested according to procedures specified in *The Procedures for Detecting and Measuring Penicillin Contamination in Drugs*.

003% is the current
Detection Limit
for Penicillin G
and Ampicillin
006% is the limit

The current analytical standard for demonstrating adequate decontamination of facilities, separation within the same building, or measurement of cross-contamination is codified at 21 CFR 211.176 and 436.104 and has a limit of detectability of 0.006 ppm (as Penicillin G using *S. Lutea*) and a violative detection amount of 0.03 ppm.

Note that the latter amount reflects the method's limits with respect to confidence and reproducibility and does not represent a tolerance level. This analytical methodology is limited to the detection of Penicillin G and ampicillin in a limited number of products listed in the referenced method, not including other beta-lactam antibiotics.

In situations where this methodology is not workable, it is the firm's responsibility to develop, validate, and use other methodology with similar sensitivity.

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