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
Center for Drug Evaluation and Research

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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 are still great and we 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. 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.

Important Notice: Budget cutbacks may force us to stop sending paper copies of the NOTES to Field District Offices. That means if you prefer paper you'd have to download an electronic edition from our web site, http://www.fda.gov/cder/dmpq/cgmpnotes.htm, and print out your own copy. Alternatively, you can subscribe to the ASCII edition by e-mail. Let us know your preference by completing the brief FDA survey in this issue of *FAX FEEDBACK*; your vote will determine the outcome.

As a reminder, although the document is fully releasable under the Freedom of Information Act, our intended readership is FDA field and headquarters personnel. 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 check-off line in *FAX FEEDBACK*. We're also on the Internet at http:/www.fda.gov/cder/dmpq.

Thanks!

Paul J. Motise

POLICY QUESTIONS:

Does FDA have a policy regarding use of the "Matrix" or "Family" approaches to process validation?

Reference: 21 CFR 211.100, Written procedures; deviations; 211.110, Sampling and testing of in-process materials and drug products; May 1987, Guideline on General Principles of Process Validation

No. The CGMP regulations, at section 211.110, require a manufacturer to "validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product." Although some guidance is presented in the May 1987 "Guideline on General Principles of Process Validation," CDER has not published any formal written policy on the "matrix" or "family" approaches to process validation.

Nonetheless, because the general principle is to validate a drug manufacturing "process," in theory it may be possible for a manufacturer that uses the same "process" for several related products to develop a scientifically sound validation plan for that process, rather than different plans for each product manufactured by that process.

We have reviewed several plans that use a "matrix approach," and have received inquiries regarding a "family approach" to process validation. Within these proposals, a "matrix approach" generally means a plan to conduct process validation on different strengths of the same product, whereas the term "family approach" has been used to describe a plan to

conduct process validation on different, but similar products. In the cases we're aware of, both approaches generally call for a plan to validate the process using a minimum number of production batches of each strength or product. Either approach may be in accord with CGMP if the study demonstrates that the process is consistent for all the strengths or products involved. It is important that any such validation plan be designed to evaluate all sources of variation in the products manufactured by the process.

Each plan should be evaluated on a case by case basis and it is up to the manufacturer to develop and justify the appropriate matrix according to the specific similarities and differences in the different strengths or different products. For example, if there are significant differences in the equipment or process, we would expect that each strength/product would need to be validated separately.

The agency has not yet established its current thinking about the principles of the matrix or family approach; thus, our limited experience cannot yet be broadly extrapolated to applied CGMP. Those principles are gradually emerging, though, and we anticipate addressing them thoroughly in future guidance documents.

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Has FDA established a required number of runs to be performed during Operational Qualification (OQ) testing? If a firm qualifies one type and model of equipment, can it be used in a different process without additional qualification?

Reference: 21 CFR 211.100, Written procedures; deviations; May 1987, Guideline on General Principles of Process Validation

Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ), along with other similar terms, are commonly used in the pharmaceutical industry to discuss the generally accepted concept that a firm should *qualify* equipment and systems as part of *validating* a manufacturing process. The FDA Guideline on General Principles of Process Validation does not use the term Operational Qualification. It defines Installation Qualification as establishing confidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerances. This includes IQ and OQ. The FDA Guideline also defines Process Performance Qualification as establishing confidence that the process is effective and reproducible.

The guideline states that "*it is important that equipment qualification simulate actual production conditions, including those which are 'worst case' situations,"* and that "*tests and challenges should be repeated a sufficient number of times to assure reliable and meaningful results."*

Regarding the first question, the often-cited "three consecutive batch" recommendation is intended for process validation rather than for equipment qualification. FDA has not recommended any specific number of "runs" for equipment qualification, but expects multiple tests to simulate actual operating ranges and to establish consistency.

As to the second question, FDA expects Installation Qualification on each piece of equipment to document that it is installed correctly and operates consistently according to established limits and tolerances. Operational Qualification should also be performed for each different use of the equipment or system to document the suitability for that use, but would not be required for additional pieces of the same type/model of equipment when used in the same process. Process Performance Qualification would also not be required for each piece of the same type/model of equipment used in the same process, provided installation qualification has been performed.

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Can a facility that produced penicillin dosage forms be decontaminated and renovated for production of non-penicillin solid dosage forms provided there is no further penicillin production in the renovated facility?

Reference: 21 CFR 211.42(d), Design and construction features; 211.46(d), Ventilation, air filtration, air heating and cooling; 211.176, Penicillin contamination; FDA By-Lines #3, Nov.77, Procedures for the Detection of Residual Penicillins in Drugs; 21 CFR 436.104 Penicillin Activity; and FDA Guide to Inspections of Validation of Cleaning Processes, July 1993.

Yes. However, the decontamination process is extremely difficult and we are unaware of any firm that has successfully decontaminated a penicillin facility and converted it to production of non-penicillin products.

Note that at section 211.176 the CGMP regulations require that if a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin product must be tested for the presence of penicillin and not marketed if detectable levels are found using the codified method. Such a reasonable possibility may be present where decontamination has not been conducted effectively. That would put the responsible firm in a position of having to test each and every lot of non-penicllin product for the presence of penicillin.

In sum, while the CGMP regulations would not prohibit decontamination and conversion, the difficulty of cleaning up penicillin residues makes the chore daunting.

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

Reference: 21 CFR 211.176, Penicillin contamination; 21 CFR 436.104 Penicillin Activity; FDA By-Lines No.3, Nov.77, A Review of Procedures for the Detection of Residual Penicillins in Drugs.

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.

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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Do the CGMP regulations require a contract laboratory to have a quality control unit for the operations it performs?

Reference: 21 CFR 210.2(b), Application of current good manufacturing practice regulations; 210.3, Definitions; 211.22, Responsibilities of quality control unit

Yes. By definition, testing and quality control of drug products are part of manufacturing. At section 210.2, the regulations explain that where persons engage in only some operations subject to provisions of parts 210 and 211 (of Title 21), persons need only comply with those regulations applicable to the operations they perform. Therefore, a contract laboratory is subject to those portions of the CGMP regulations that cover activities it performs.

We would expect that many of the laboratory's activities would fall under Subpart I, Laboratory Controls, of the CGMP regulations. (Other provisions, such as those pertaining to

personnel qualification, recordkeeping, facilities, and laboratory animals would also apply.)

The responsibilities of a quality control unit are pervasive in the CGMP regulations, and many lab functions require review and approval of a quality control unit. For example, per section 211.160, the quality control unit must review and approve test procedures and laboratory control mechanisms.

It should be clear, therefore, that section 211.22 applies to a contract laboratory and that the lab would have to have a quality control unit. However, that unit's responsibilities would only extend to the CGMP operations that the lab performs.

What's more, be aware that in smaller establishments, as might be the case in a contract laboratory, the responsibilities of a quality control unit may be assigned to as few as one or two individuals. In a larger organization, of course, an effective quality control unit may warrant a larger staff. This is consistent with the definition of quality control unit, at section 210.3(b).

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If a contract laboratory obtains an OOS result, what are the CGMP responsibilities of the dosage form manufacturer and the lab with respect to follow up investigations?

Reference: 21 CFR 211.22(a & b), Responsibilities of quality control unit, 21 CFR 211.160(b), General requirements [Subpart I—Laboratory Controls]; 21 CFR 165, Testing and release for distribution; Draft Guidance for Industry: Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production, 9/30/98; 21 CFR 211.194, Laboratory records

There are a number of possible scenarios under this question. Under CGMP, FDA would expect the contract laboratory to have a quality control unit. The lab's QC unit has the CGMP responsibility to ensure the analytical results obtained are accurate for the tested material. This means the contract laboratory needs to investigate any OOS result with the purpose of ascertaining such accuracy. This would be accomplished by ensuring that personnel performed the tests properly using: (1) The current validated analytical procedure; (2) correct reagents and reference standards; and, (3) equipment that has been properly maintained and calibrated.

There are basically two possible results of the lab's investigation.

1) If the lab determines the analyst made an error, or that instrument malfunction occurred, the test results may be invalidated. The analysis would be re-run according to the approved analytical method. The re-run test results would be considered the original results, and these results would be reported to the manufacturer. The lab does not have a CGMP obligation to report the initial (invalidated) results to the manufacturer; however, the lab must, per 211.194, retain the records pertaining to those initial results.

2) If the laboratory determines that there was no analyst error, and that no instrument malfunction occurred, then the results must be considered accurate and reported to the pharmaceutical manufacturer.

In the event of outcome number two, the pharmaceutical manufacturer would have analytical results indicating the material does not meet its specifications. Under CGMP, an investigation must take place. The manufacturer is responsible for investigating the production process to determine if any mistakes were made--things to consider could include charge-in of components, mixing times, and quality of components. Storage conditions of the analyzed material, and the sampling method used also need to be reviewed to ascertain whether the tested material might not have been representative of the batch.

If the manufacturer's investigation fails to find a cause, it might also consider whether the contract laboratory is suspect (i.e., if perhaps the lab made an unrecognized error.) The

CGMPs do not, however, explicitly require the manufacturer to extend its investigation to the lab's operations. However, it is considered CGMP for manufacturers to qualify their contract laboratories. At comment paragraph 94 of the September 29, 1978 CGMP revisions, 43 FR 45034, the agency said "[a] manufacturer does have a responsibility, however, to see that the outside laboratory used is qualified to do the work and that the work is performed satisfactorily."

As part of its investigation, the manufacturer might take the opportunity to requalify the contract laboratory, or may consider changing contract laboratories. Retesting could also be part of this process.

It must be stressed that in this situation the manufacturer has information that the batch does not meet its quality standards, and unless that information can be invalidated, it must be used to reach a batch disposition decision, namely, whether to destroy the batch, or reprocess it to bring it into compliance.

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What is the purpose of an environmental monitoring program in aseptic processing? What are some major factors that ensure the environment does not contaminate product throughout a batch's manufacture?

Reference: 21 CFR 211.42, Design and construction features [Subpart C-Buildings and Facilities]; 211.113, Control of microbiological contamination; 211.22, Responsibilities of quality control unit; 211.46, Ventilation, air filtration, air heating and cooling; 1987 Guideline on Sterile Drug Products Produced by Aseptic Processing; July 1994 Guide to Inspections of Sterile Drug Substance Manufacturers

The environmental monitoring program is a vital part of a quality control unit's CGMP responsibility to monitor and ensure ongoing control of an aseptic process. The CGMP regulations, at section 211.113 require firms to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile. This section is particularly applicable to sterile drug products made by aseptic processing, and the aseptic guideline addressed at length various aspects of environmental monitoring.

An environmental monitoring program is vital for aseptic processing operations because it: 1) Provides crucial information on the quality of the aseptic processing environment during manufacturing; 2) prevents release of a potentially contaminated batch if appropriate quality standards (defined by a firm's written procedures) are not fulfilled; and, 3) prevents future contamination by detecting adverse trends.

In addressing the environmental monitoring program, the aseptic guideline discussed regular sampling and testing of the manufacturing environment, including air, floors, walls, and equipment surfaces. Evaluating the quality of air and surfaces in cleanrooms should start with a well-defined and specific written program, including validated test methods.

As explained in the guideline, among issues normally addressed by an environmental monitoring program are: sample location, appropriate sampling frequency, timing of sample collection, duration of sampling, size of sample, specific sampling equipment and techniques, limits, identification of microorganisms, trending systems, and procedures to promptly address out of limit results or adverse trends.

A number of major variables influence environmental control, all of which need to be addressed by appropriate written SOPs, in accordance with section 211.113.
It is important that a personnel qualification and monitoring program address operator practices, critical in maintaining environmental control of the aseptic processing area. In addition, the CGMPs at section 211.46 require equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature when appropriate for the manufacture, processing, packing, or holding of a drug product. In this context, the Heating, Ventilation, and Air Conditioning (HVAC) system

design and controls play a key role in providing an adequate environment (e.g., particulate cleanliness, air pressure, and airflow) for aseptic processing.

Adequate cleaning and sanitizing procedures, facility design, equipment design, personnel flow, and material flow are among other key variables which significantly impact on the suitability of the environment in which aseptic processing operations are conducted.

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On Stability

Should investigators cite firms for not conducting accelerated stability testing during ongoing stability studies? If firms use more stressful conditions than their protocols require should they be cited?

Reference: 21 CFR 211.137, Expiration dating, 211.166, Stability testing, and 314.70(b)(1), Supplements and other changes to an approved application; February, 1987 "Guideline For Submitting Documentation For The Stability Of Human Drugs and Biologics"

No and no! The CGMP regulations allow for the use of accelerated stability studies to project a tentative expiration dating period provided that full shelf-life stability studies are conducted to verify the tentative expiration dating period. After the expiration dating period has been verified there should be no reason to conduct stability testing under accelerated conditions during ongoing stability studies. Ongoing stability studies generally involve adding a new lot from the current year's production on stability annually for testing under shelf-life (long-term) conditions.

It would be a CGMP violation, and may be a new drug violation as well, if a firm deviates from its approved stability protocol. However, it's not enough for investigators to just report that there was a protocol deviation. For example, if the protocol deviation was well documented by the firm in both its stability test records and NDA submissions and it is very clear that the alternative condition was more stressful than what is required in the approved protocol, the deviation would not be significant and should not be cited on an FDA 483. If the investigator has any doubt as to whether the alternative condition exceeds protocol requirements (i.e., higher temperatures or humidity are not always more stressful; it depends on such factors as the dosage form and labeled storage condition), CDER Office of Compliance should be contacted for guidance and coordination with CDER reviewers. One note of caution, however, it would not be acceptable if, after using the alternative condition, a firm ignores the data generated. Also, it would not be acceptable if stability chambers are not properly controlled, and there are haphazard excursions from required storage conditions. If the latter is found, it should be cited on an FDA 483. In any event, investigators should fully describe in their inspection reports any changes from approved protocols, even if it appears that the alternative conditions used were acceptable.

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CGMP Sorites

Sorites are a series of logically connected propositions made popular by Lewis Caroll. In this series we use sorites to help you understand and apply the CGMP regulations.

This issue's CGMP sorites is shorter than those in previous editions. It has only two propositions/CGMP regulations. However, you will need to employ the concept of logical equivalence in solving it. This means that one of the following propositions (i.e., CGMP regulations) is phrased in a logically equivalent form. In order to solve the following sorites, you must rephrase that proposition in the form stated in the CGMPs. This process of rephrasing a proposition in a logically equivalent form is often necessary in solving a Lewis Carroll sorites. This is a valuable exercise and a characteristic of CGMP that enables flexible application of CGMP intent/content as the manufacturer applies the rule to a variety of manufacturing situations. For example, a

company's SOP may be written in a variety of ways, all of which can comply with the CGMP requirements. Now try the following CGMP sorites.

For each batch of drug product (i.e., for all drug products), there shall be appropriate laboratory determination of satisfactory conformance to final specifications (e.g., identity and strength for each active ingredient) prior to release of the drug product. 21 CFR 211.165(a)

Appropriate laboratory determination prior to release of drug products shall be used by the quality control unit to ensure that no drug products failing final specifications shall be not rejected (i.e., passed).

The answer appears at the end of the last article in this edition of the NOTES.

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Toward the Electronic Government

1) With respect to 21 CFR 11.50, can the display of a user identification code (such as "Big Apple") be used to satisfy the requirement that the signer's printed name be displayed?

Reference: 21 CFR 11.50, Signature manifestations; paragraph 102 of the 3/20/97 final rule Federal Register Notice; Electronic Records; Electronic Signatures (62 FR 13453)

No. A code used in this case is not the same as the signer's printed name. The printed name does not, however, have to be hard coded in the recordkeeping software in order to generate the display of the printed name. For example, a system could maintain a "look-up" table to identify and link the user name to a corresponding user identification code and password. Of course, if the system uses the individual's full name as the user identification in the first place, then it would meet the 11.50 requirement because the printed name and user id would be one and the same.

2) Clearance of CGMP warning letters having part 11 issues

Part 11 has been in effect since August 20, 1997 and several districts have begun to issue warning letters with respect to part 11 deviations as applied to CGMP records in electronic form. In order to ensure uniform application of the rule, we've asked field districts to clear with HFD-320 proposed warning letters that relate to part 11 issues in the CGMP arena.

This clearance at headquarters is a temporary measure until districts gain additional experience in applying part 11 and until additional enforcement guidance has been issued.

Where a CGMP warning letter contains a mixture of issues, some of which relate to part 11 and some which do not, CDER clearance will extend only to those portions of the case covering part 11 issues.

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Conclusion to CGMP Sorites

For each batch of drug product (i.e., for all drug products), it shall be ensured by the quality control unit that all those failing specifications shall be rejected. Note that this does not preclude investigations into out of specification results and appropriate follow-up actions.

Solving this sorites, requires that the second proposition (an obverse of the regulation) be reconstructed into the logical equivalent form of the CGMP (a universal affirmative – all drug products failing to meet established standards or specifications and any other relevant quality control criteria, shall be rejected 21 CFR 211.165(f).)

P. Motise 03/01/99
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(All numbers in area code 301)

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Aseptic Processing	Rick Friedman Tracy Roberts Edwin Melendez	594-0095 594-0098 594-0095
Barrier Isolators	Rick Friedman Edwin Melendez	594-0095 594-0095
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CGMP Guidance Documents	Paul Motise	594-0098
Cleaning Validation	Russ Rutledge Pat Alcock	594-2455 594-0095
Clinical Supplies/IND CGMP	Paul Motise Bruce Hartman	594-0098 827-0062
Computer Validation	Paul Motise	594-0098
Content Uniformity	Monica Caphart Russ Rutledge	594-2458 594-2455
Electronic Records/Signatures	Paul Motise	594-0098
Facility Reviews	Russ Rutledge	594-2455
Foreign Inspections	John Dietrick	594-0095
Impurities	Rick Friedman	594-0095
Inspections/ Investigations (For Cause)	Randall Woods	827-0065
Labeling Controls (CGMP)	Paul Motise	594-0098
Laboratory Issues	Monica Caphart Russ Rutledge	594-2458 594-2455
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Packaging	Barry Rothman	594-0098
Penicillin Cross Contamination	Edwin Melendez	594-2454
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Salvaging	Paul Motise	594-0098
Stability/Expiration Dates	Barry Rothman	594-0098
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Water Quality	Rick Friedman Edwin Melendez Tracy Roberts	594-0095 594-2454 594-0098

FAX FEEDBACK

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I found this issue of HUMAN DRUG CGMP NOTES to be [check as appropriate]:

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__not very; __somewhat; __ very; __ extremely useful to my inspectional/compliance activities.

Here's my question regarding _____
_____
_____

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