

HUMAN DRUG CGMP NOTES

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A Memo for FDA Personnel on Current Good Manufacturing Practice for Human Pharmaceuticals

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Office of Compliance

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Subject Contact List -- **UPDATED**

GENERAL COMMENTS

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

This division recently hired several new compliance officers to handle CGMP casework and, of course, other duties as assigned. We welcome (in order of arrival):

Rosa Motta, from ORA's Division of Field Science

Anthony Charity, previously an investigator with Philadelphia District Office

Karen Hirshfield, previously an investigator with Denver District Office

As we increase our staff we hope to spend more time in guidance development and international cooperative activities.

Speaking of guidance, we are actively working in several important areas:

- Updating the 1987 industry guidance: *Sterile Drugs Produced by Aseptic Processing*
- Finalizing the industry guidance: *Investigating OOS Test Results for Pharmaceutical Production*
- Drafting for public comment the CGMPs and associated guidance on Positron Emission Tomography (PET) products

Also, our intrepid ICH drafter/negotiator of the API CGMP guidance to industry, Edwin Rivera, reports that the guidance is now final and can be found at

<http://www.fda.gov/cder/guidance/index.htm>

Look in the ICH guidance section under Quality, Q7A. Also, Edwin will be participating in the soon-to-be-launched nationwide training in Q7A sponsored jointly by FDA and industry. A future edition will cover this topic in more detail.

Remember that we are now publishing the *Human Drug CGMP Notes* EXCLUSIVELY for FDA personnel. ("Exclusively" means that we're not posting directly for public consumption,

but each edition is fully releasable under FOIA.) With last year's promulgation of the Good Guidance Practices, publishing at our INTERNET website would require each edition to be subject to extensive internal review and approval. Since the intended purpose of the *Notes* is to provide agency personnel with timely answers to their CGMP questions, we've decided to publish in-house only. Be assured, however, that every edition now published comes with the Division's seal of approval, as before.

In this edition we have included an **UPDATED** list of Division of Manufacturing and Product Quality subject contacts.

We are **no longer** appending to each edition of the *Notes* a fax feedback sheet. Let's use Email instead (hasselbalchb@cderr.fda.gov). You can still call (301-594-0098) or fax (sans form) your questions, requests, and opinions to 301-594-2202. Also, you can submit your CGMP questions directly from our INTRANet site where we're posting new editions:

<http://cdernet.cderr.fda.gov/dmpq/hdn>

Thank you. Brian

QUESTIONS AND ANSWERS:

Do the CGMPs require that the lots used in a process validation study also be placed on stability?

No. There is no CGMP requirement that the lots used in a process validation study also be placed on stability. A satisfactory process validation study may be completed without placing samples from the validation lots into the manufacturer's stability testing program. Although both satisfactory process validation and primary stability studies must be conducted before a new product is marketed, unless there is a different requirement in a drug application, the validation and stability testing may be conducted on different production lots and may be evaluated separately. However, the formula, equipment and method of manufacture of the production lots used for both the validation and stability studies must be the same.

References:

- 21 CFR 211.100(a): Written procedures; deviations
- 21 CFR 211.166: Stability testing

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Should equipment be as clean as the best possible method of residue detection or quantification? Must a firm quantify the amount of residue on equipment surfaces in support of validating the cleaning procedure? Should lab glassware be included in a firm's equipment cleaning validation

program?

No, no, and mostly no. The CGMPs require that equipment be cleaned to prevent contamination that "would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements" (see 211.67(a)). The preamble indicates that this phrase was added to account for the fact that absolute cleanliness is neither valuable nor feasible in many circumstances for multi-use equipment. The answer to the question "how clean is clean?" can not, therefore, be "it depends on the method of detection." If the method of detection determined levels of contamination, advances in the sensitivity of detection methods would necessitate correspondingly ever-lower limits and ever-increasing wash cycles. So, how clean should equipment be? It should be as clean as can reasonably be achieved, to a residue limit that is medically safe and that causes no product quality concerns (other than the fact of the contaminant's presence), and that leaves no visible residues. Reasonably avoidable and removable contamination is never acceptable.

In validating the original cleaning procedure, a firm need not quantify the level of chemical contamination remaining after manufacturing a product and before cleaning during validation exercises. The firm must, however, ensure that they validate the proposed cleaning procedure as for routine use, and not pre-clean or otherwise attempt to make it easier for the procedure being validated to meet its cleaning objectives. For example, batches significantly smaller than full-scale would not offer sufficient assurance that the cleaning procedure could reliably remove residues to below acceptable levels after full-scale production. A validated cleaning procedure may be relied upon as long as the material being cleaned was manufactured at similar scale and manner as during validation. Also, equipment stored unclean for a longer time than during validation should be sampled to demonstrate that the cleaning procedure was effective. Once cleaned by a validated procedure, a firm generally should not be expected to analytically examine equipment surfaces to demonstrate cleanliness (see the Dec. 1998 *Notes* article). Hand cleaning methods may be an exception to this general rule because of inherent variability in operator compliance and abilities. Usually, visual inspection of equipment surfaces, including hard to clean nooks and crannies, along with rinse water testing would suffice.

Do not expect lab glassware to be included in the processing equipment cleaning validation program. Glassware must, of course, be clean and the CGMPs consider lab equipment to be included in the scope of 211.67. The assurance of cleanliness is best assessed by inspecting laboratory procedures for the use of non-dedicated glassware and other equipment, method validation (ruggedness, e.g.), and the absence of extraneous or interfering data in the results of sample analyses. Lab cleaning procedures may include repetitive rinses with the solvent used to prepare the analyte and oven drying. The equipment need not be swabbed or otherwise tested to ensure removal of potentially contaminating residues. A firm may elect to sample its glassware for residual contamination to exclude or explore the possibility of interference in the case of particularly sensitive analyses or highly difficult to clean compounds. The possibility of carryover contamination affecting a method's performance or integrity of the results is generally considered to have a low risk to product or consumers. Contaminated lab equipment, however, should not be a frequent excuse for rejecting or discarding aberrant results. We expect that firms maintain lab equipment in a clean and sanitary manner so as to provide confidence in the results of analysis.

References:

- Preamble to the Good Manufacturing Practices for Human and Veterinary Drugs, Federal Register, September 29, 1978, pages 45040-1, paragraphs 167-175

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

- 21 CFR 211.67
- *Guide to Inspections of Cleaning Validation*, 1993
- *Human Drug CGMP Notes* editions Dec. 1998, Sep. 1998, Sep. 1997, Jun. 1995

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Do the CGMPs (i.e., 21 CFR 211) apply to drug product warehouse and/or distributors that do not manufacture?

No. The CGMP regulations at 21 CFR 211 do not apply to companies solely warehousing and/or distributing finished pharmaceutical products. The regulations at 21 CFR 211 covering warehousing and distribution operations apply only to companies manufacturing drug products. However, all drug products--R and OTC--being held by warehouse and/or distributors are still subject to the adulteration provisions of the Federal Food Drug and Cosmetic Act, including section 501(a)(2)(B).

Therefore, when performing inspections of companies engaged only in the warehousing and/or distribution of drug products, investigators should evaluate such operations to assure that controls like 21 CFR 211.142 (warehousing procedures) and 211.150 (distribution procedures) are in place. In addition, inspections of companies engaged only in the warehousing and/or distribution of prescription drug products should determine compliance with 21 CFR 205, which provides minimum requirements for the storage and handling of prescription drugs. Deficiencies of 21 CFR 205 can be cited on a FDA 483 and in warning letters.

A common problem area in warehousing and distribution operations is storing and handling drugs consistent with the labeled storage conditions.

Districts are to forward proposed warning letters citing of 21 CFR 205 to HFD-330 for concurrence (HFD-330 consults with HFD-320 on the appropriateness of the adulteration citation).

District offices must not cite 21 CFR 211 CGMP deficiencies in warning letters issued to drug product warehouses and/or distributors engaged only in warehousing and distribution of OTC products. Rather, district offices must cite storage and distribution deficiencies at such sites as violations of Section 501(a)(2)(B) of the FD&C Act. Center concurrence for the proposed warning letter should be sought.

References:

- Federal Food, Drug, and Cosmetic Act - Section 501(a)(2)(B)
- Preamble to the Good Manufacturing Practices for Human and Veterinary Drugs, Federal Register, September 29, 1978, page 45027, Section VI, paragraph 42(g)

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

- 21 CFR Part 211.142: Warehousing procedures
- 21 CFR Part 211.150: Distribution procedures
- 21 CFR Part 205.50: Minimum requirements for the storage and handling of prescription drug products...

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What is an aseptic processing isolator? What is the difference between an isolator and a barrier?

An aseptic processing isolator ("isolator") can be fundamentally defined as a unit that provides full separation of two environments: an enclosed environment in which a product is processed or manipulated; and that which surrounds the isolator. A barrier, on the other hand, is a physical partition that affords aseptic manufacturing zone protection by partially separating it from the surrounding area (which is, with few exceptions, of lower air cleanliness) and activities occurring near the processing line.

Some have used the tandem term "barrier-isolator," but this term does not connote a single technology, and instead very broadly refers to both. Knowledge of the definitions of the separate terms is becoming increasingly important as these two technologies evolve and gain in popularity.

Isolators and barriers are used by aseptic processors in order to help satisfy 21 CFR 211.113, which requires that procedures be designed to prevent microbiological contamination of drug products purporting to be sterile. Aseptic processing operations utilizing isolators designed and operated in accord with CGMPs (e.g., 21 CFR 211.42, 211.63, and 211.65) can be quite effective in diminishing such microbiological contamination risks to the product. Barriers are also frequently helpful in fulfilling this CGMP requirement.

There are some further key differences in operation and design of aseptic processing lines contained in an isolator versus one that utilizes barriers. One major distinction lies in the need for an isolator to employ an air pressure differential that provides uncompromised, continuous isolation of its interior from the external environment (e.g., surrounding room air and personnel). In addition, the interior of isolators, which is supplied with HEPA or ULPA-filtered air, is also regularly biodecontaminated (i.e., surface-sterilized) with a sporicidal agent.

In contrast with isolators, which are full enclosures, barriers provide a partial barricade. They are normally found as carefully placed flexible plastic curtains or rigid shields (e.g., Plexiglas). In some cases, firms have essentially enclosed parts of the processing line with the latter rigid walls, but the resulting box-like structure is not designed to employ a separative pressure differential and operators routinely access the line by opening panel doors found throughout the line to monitor and control the aseptic filling process. This design represents an extensive barrier, but does not provide for isolation

of the aseptic line from the surrounding environment.

What is the difference between an open and closed isolator system? What is a positive pressure isolator?

It is helpful to become acquainted with some of the terms used to characterize the different types of isolators. For example, isolators have been categorized as either "open" or "closed":

A "closed" isolator is a unit that does not include any portals (or "mouseholes," as they are commonly called) that directly communicate air with the surrounding environment.

Closed isolators are most commonly used in sterility testing laboratories and for smaller batch applications, such as clinical-scale aseptic filling operations. Their use is limited by the quantity of filled units that can be stored in or transferred out of the isolator during operation.

An "open" isolator, popular for high speed/output lines, includes an exit portal for product egress.

Thus, while both open and closed isolators normally interface with the surrounding environment through aseptic transfer ports and air filters (e.g., HEPA, ULPA, or microbial-retentive filters), the open isolator also includes an exit portal in its design. Both are also known as positive-pressure isolators because they operate under air pressures greater than the external environment.

An important part of qualifying an open isolator is demonstrating that its design and the positive pressure differential used achieve full physical separation from the external environment at the product exit portal. An appropriately qualified minimum positive air pressure differential specification should be established and followed to ensure the continuous isolation of environments. For example, it is important to demonstrate that the air overpressure remains acceptable during use of gloves and half-suits, and is unaffected by activities in the external environment, such as opening and closing cleanroom doors.

While we have described the use of positive pressure isolators as protection to the exposed sterile product and container-closures throughout operations, negative pressure isolators also exist. However, the objective of a negative pressure isolator is to protect workers by providing containment of a potent or toxic drug. These isolators have been used for various non-sterile applications and, in some cases, sterile operations. When used for aseptic operations, it is necessary for firms to include special design provisions to assure protection of the exposed sterile product. Since negative pressure isolators have significant potential to exchange air with the surrounding environment, common industry practice is to place these units in a Class 10,000, or when needed, a cleanroom environment of higher air cleanliness, when used for aseptic processing applications. Furthermore, personnel gowning would reflect that used in a traditional aseptic processing operation.

References:

- 21 CFR 211.42: Design and construction features
- 21 CFR 211.46: Ventilation, air filtration, air heating and cooling
- 21 CFR 211.63: Equipment design, size, and location
- 21 CFR 211.65: Equipment construction
- 21 CFR 211.113: Control of microbiological contamination
- *Guideline on Sterile Drug Products Produced by Aseptic Processing*, 1987

- PDA Technical Report No. 34, *Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products*, Supplement, PDA J. Pharm. Sci. Technol., 55, No. 5 (2001)

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Consider the following:

The product assay specification approved in the NDA is that the average of ten individual units falls between 90-110% label claim.

A firm records the following low and high assay values for a particular batch: 87.3% and 101.6%. The average of the ten units is 94.8%. In accord with their procedure, the firm tests 20 additional units because of the low average assay value of the first ten, and records the following low and high results: 88.8% and 112.1%. The average of the 30 units is 95.3%. No further investigation (i.e., beyond the second set of sampling) is conducted, and no change is made to the labeled expiration date.

Does the batch fail its assay specification? Should I be concerned?

No and yes. Individual assay values that are outside of the assay specification range (e.g., 90-110%) do not constitute failures of that test. This is simply because the spec is on the average, not individual values. After all, the test may even be performed on a portion from a composite of units. The test does not limit the range of values that can be included in the average value compared to the specification. In this case, the firm's investigation into this problem was limited to additional sampling and testing, which reaffirmed the original average.

Even though the example provided passes the test for assay, you should be concerned for a number of reasons. An assay well below the target value or label claim should be investigated to determine whether there was intent to provide for less than 100% label claim. If so, this would be a CGMP violation (21.101(a)). Also, the presumably unusually low assay result should have triggered an investigation to determine the cause. Areas to look into would include examining batch records, checking in-process test results, interviewing operators, reconciling inventory, sampling/testing the variability from beginning to end of the lot, confirming adequacy of method, and evaluating any effect on the expiration date. The firm should have a written procedure for dealing with aberrant but within-specification results, and include provisions for what to do after the additional testing of units confirms the average.

Another important issue is to determine if the assay sample of 10 individual units is a representative sample of the batch. The CGMP regulations require that all samples taken must be representative of the lot or batch (see 21 CFR 211.160(b)(1) and 21 CFR 211.165(d)). In this particular case, we suggest that you request all available documentation to show that the firm used valid, statistically

based sampling plans to demonstrate that a sample of 10 individual units is representative of the batch. The firm should be asked to prove to you that they make their batch release decision based on scientifically sound and appropriate sampling plans and testing procedures. It will be useful to take a look at the batch history for that particular product to determine if this is a recurring practice or a new development in the history of the use of this formula/process. If the trend is that the assay sample averages are usually borderline this may indicate a process in control but improperly targeted or centered. Process redesign and/or stricter in-process controls may be necessary.

References:

- 21 CFR 211.101(a): Charge-in of components
- 21 CFR 211.160(b)(1): General requirements (Lab Controls)
- 21 CFR 211.165(d): Testing and release for distribution
- Draft Guidance for Industry, *Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production*, September 1998

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DIVISION OF MANUFACTURING AND PRODUCT QUALITY, HFD-320

SUBJECT CONTACTS (Area code 301)

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Ingredients	Mike Gavini	594-0095
Application Integrity Policy	LuAnn Pallas	827-0062
Implementation/Removal Data Integrity Cases	Bruce Hartman	827-0062
Aseptic Processing	Richard Friedman	594-0098
	Edwin Melendez	594-2454
	Brenda Uratani	594-0098
Biotechnology Products	Brenda Uratani	594-0098
	Albinus D'Sa	594-0098