HUMAN DRUG CGMP NOTES

(Volume 7, Number 3)

September, 1999

(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

Project Manager: Paul J. Motise, HFD-325

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.

IN THIS ISSUE

Updates

Botanicals Guidance Availability--Not Yet.

Attachments

Division of Manufacturing and Product Quality, Subject Contacts

FAX FEEDBACK (Your input requested)

MOTISE'S NOTEBOOK

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 are great and we appreciate your suggestions. You need not, however, limit the dialog to FAX FEEDBACK. Feel free to call, write, or e-mail your comments. 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!

Paul J. Motise

Policy Questions

Does FDA approve materials of construction for equipment? For example, are there any specific CGMP requirements regarding ferrite content and other properties of 316L stainless steel used in storage tanks for pharmaceutical water systems?

Reference: 21 CFR Sections 211.63, Equipment design, size, and location, 211.72, Filters, 211.65, Equipment construction, 211.67, Equipment cleaning and maintenance, and 211.48, Plumbing; Guide To Inspections Of High Purity Water Systems, July, 1993.

FDA does not approve or prohibit specific equipment or materials (with rare exceptions such as the requirements relating to asbestos filters found at 21 CFR 211.72). A storage tank or other piece of equipment is subject to the general CGMP requirements addressing equipment suitability. For example, section 211.65 requires surfaces that contact components, in-process materials, or drug products not be reactive, additive, or absorptive so as to adversely affect product quality. Section 211.63 requires that equipment be of appropriate design to facilitate operations for its intended use and for cleaning and maintenance. Section 211.67 requires firms to clean, maintain, and sanitize equipment at appropriate intervals to prevent malfunctions or contamination that would adversely affect product quality.

To illustrate, it's important that interior surfaces of a sanitary storage tank are capable of being cleaned, sanitized, and (if needed) sterilized. For such sanitary equipment, design provisions to prevent backsiphonage (see Section 211.48) and stagnation are among the attributes that prevent microbial contamination of a drug product. Likewise, smooth interior surfaces (e.g., welds) help prevent collection of microbial contamination and formation of a biofilm. (See the above inspection guide for more information on biofilms.)

So choosing materials or components for any equipment involves evaluating whether there is any potential for an adverse impact on drug product quality. In this respect, various compatibility considerations (e.g., leachables, interaction with formulations/sanitizers, ability of material to withstand sterilization) can often take on the most CGMP significance.

Ultimately, provided that such CGMP requirements are met, firms are afforded the flexibility to select the material and grade which best satisfies the needs of their particular application. Given this information, it should be no surprise that the CGMP regulations do not include specifics on what ferrite content is appropriate in stainless steel. However, a number of references may provide a useful starting point when researching issues such as sanitary design standards, surface grit/smoothness, pits, folds, crevices, and steel composition (including ferrite content). The milk industry has publications (e.g., "3-A Accepted Practices for Permanently Installed Sanitary Product Pipelines and Cleaning Systems") written jointly with the U.S. Public Health Service regarding sanitary design. ANSI (American National Standards Institute) also publishes documents addressing design of seamless and sanitary piping. Such literature should be available through a search on the American Iron and Steel Institute (1000 16th Street, N.W., Washington, D.C. 20036) website at www.steel.org. A search on words such as "seamless" and "weld" at www.nssn.org will yield further relevant references.

Contact for further information: Richard L. Friedman, HFD-322, 301-594-0095; e-mail: friedmanr@cder.fda.gov

Do CGMP requirements apply to manufacturers of clinical supplies? Can such firms be inspected for CGMP compliance?

Reference: Federal Register (43 FR 45013), September 29, 1978, preamble to the Current Good Manufacturing Practice regulations, comment 49 (at 43 FR 45029), and Guideline on the Preparation of Investigational New Drug Products, March, 1991.

The answer to both questions is yes. The Center for Drug Evaluation and Research may request that firms that make clinical supplies for Investigational New Drug (IND) trials be inspected for compliance with Current Good Manufacturing Practice (CGMP) regulations. Such inspections may be requested on a "for cause" basis, or with respect to "treatment INDs." The CGMP regulations do apply to investigational new drug products that are intended for administration to humans.

Investigational trials are typically divided into phases. Initially, at phase 1, trials usually involve small patient populations and are intended to evaluate the safety of the investigational product. At phase 3, trials usually consist of much larger patient populations and are used to evaluate both safety and efficacy.

As explained in the above guideline, the degree of CGMP control needed increases as the investigational trials near completion. An inspection of a phase 1 clinical supplies manufacturer would be expected to ensure that there are no added safety concerns based strictly on the failure to follow CGMP requirements, and that sufficient documentation is available so that the manufacturing process can be duplicated. For phase 3 trials, the degree of CGMP compliance would approach the control required for marketed products. For example, as explained in the guideline, at early clinical stages only limited process validation may be possible, and extensive in-process controls and intensive product testing may be used to demonstrate that a process run did, in fact, produce a finished product that meets all its specifications. As additional uniform batches are made under replicate conditions, we expect that more comprehensive validation will be conducted.

Investigational trials can begin 30 days after the submission of the IND to the agency unless a clinical hold is applied by the CDER review unit. Inspections of clinical supplies manufacturers which identify significant CGMP noncompliance may be a basis for a clinical hold; however, CGMP based holds are rare.

Contact for further information: Bruce W. Hartman, HFD-324, 301-827-0062; e-mail: hartmanb@cder.fda.gov

Do the CGMP regulations require firms to keep as "raw data" results from employee CGMP training tests?

Reference: 21 CFR Sections 211.25, Personnel qualifications, and 211.34, Consultants

No. Section 211.25 of the CGMP regulations requires that persons engaged in manufacture, processing, packing, or holding of a drug product have the education, training, and experience, or any combination thereof, to perform their jobs. The regulation also requires that employees receive training, on a continuing basis, in those aspects of CGMP that are pertinent to their duties. However, the regulation is silent on training records.

Note that section 211.34 requires firms to retain records of the qualifications of consultants, along with the type of service they perform.

In implementing section 211.25, it should be obvious that firms need some kind of documentation regarding their employees' qualifications. Accordingly, during your inspections it would be reasonable to ask firms to show you documentation of their employee qualification and CGMP training, for your case by case assessment.

Absence of training documentation combined with clear evidence that employees are not qualified to do their jobs would be appropriate observation on an FDA 483. However, absence of CGMP training test score records would not, by itself, warrant listing on the 483.

Contact for further information: Paul J. Motise, HFD-325, 301-594-0098; e-mail: motise@cder.fda.gov

Case Studies

Formulating a drug product using active ingredient overages; what can happen when there's too much of a good thing.

Reference: 21 CFR Sections 211.101, Charge-in of components, 211.165, Testing and release for distribution, and, 211.186 Master production and control records.

The CGMP regulations, at Section 211.101(a) require that a batch be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient. However, this section is silent on formulating to provide more than 100 percent (i.e., overages.) Nonetheless, as discussed below, other sections of the regulations do address overages. The following case study illustrates potential problems that can result from using formulation overages when firms do not follow other CGMP provisions intended to ensure that products meet established specifications**.**

A pharmaceutical manufacturer was routinely adding 10-16% overage (above the labeled amount) of active ingredients into a tablet formulation. The firm did this to ensure that the assay of this tablet met the label claim near the end of its expiry period. This overage did serve to extend the tablet's shelf life. However, it also caused the product to be superpotent upon release for distribution. Samples were collected and analyzed at an FDA laboratory. The laboratory results demonstrated that not only was the product superpotent, it also failed content uniformity. Moreover, CDER medical officers advised that the degree of superpotency posed a health hazard to consumers. Upon FDA's complaint, the court subsequently seized the lot that was in distribution. (The firm did not claim the goods and the court ordered the product destroyed.)

This problem was not limited to the lot seized. The firm formulated all lots of this product with these overages, resulting in similar potency problems with every batch. The firm's master formula record did not justify its use of overages. The batch records demonstrated that the use of overages was inconsistent from lot to lot. (The firm has since discontinued manufacturing this product for a variety of reasons.)

During your inspections, if you encounter a firm that is formulating a product at less than 100% of labeled active ingredient, the practice would

be a clear CGMP violation that you should consider listing as an objectionable condition in an FDA 483. You should not automatically so list the use of overages. When you find use of overages you need to investigate the practice further to determine if, among other things, the resulting product is superpotent, or otherwise outside of its established specifications, upon its release for distribution.

Section 211.165(f) of the CGMP regulations requires that drug products failing to meet established standards or specifications be rejected. It would therefore be objectionable for a firm to release for distribution a lot it had determined to be superpotent. Therefore, as part of your investigation, determine the firm's end product testing results.

Note that a firm may be able to justify its decision to use overages, and the practice may not always result in product that is superpotent. It is therefore important that you review the firm's documentation, especially the master production and control record. The CGMP regulations, at section 211.186, require that the master record contain the weight or measure of each component, along with justifications for reasonable variations in the amount of components necessary for the dosage form's preparation. This section also requires that the master record contain "[A] statement concerning any calculated excess of component." Thus, the regulations allow for the justified use of overages in some instances. In general, firms will have determined justifiable amounts of excess components during the product's development and process validation.

Contact for further information: Brian G. Nadel, HFD-325; phone 301 594-0098; e-mail: nadelb@cder.fda.gov

Validation and equipment qualification; when "identical" really isn't.

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

As explained in the 1987 validation guideline, the general requirement for process validation is contained in section 211.100 of the CGMP regulations which states that "[T]here shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess."

The validation guideline addresses several general principles of equipment suitability. For example, installation qualification is described as establishing confidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerances. Installation qualification includes examination of equipment design, determination of calibration, maintenance, and adjustment requirements, and identifying critical equipment features that could affect the process and product. Another principle is that equipment is evaluated and tested to verify that it is capable of operating satisfactorily within the required process operating limits and that actual production conditions, including "worst case" situations, are simulated. The guideline cautions that "[I]n assessing the suitability of a given piece of equipment, it is usually insufficient to rely solely upon the representations of the equipment supplier…"

The guideline further states that each specific process should be appropriately qualified and validated, noting the inherent danger in relying on perceived similarities between products, processes, and equipment.

The following case illustrates the importance of performing adequate equipment qualification on each piece of processing equipment, and the problems that may result when firms fail to verify equipment supplier representations.

A pharmaceutical firm used two blenders to produce a tablet. Both blenders were from the same equipment manufacturer, had the same model number and same design. Although one blender was older than the other, the supplier told the drug manufacturer that the units were "identical." The drug manufacturer took the claim at face value and did not include the older blender as part of its process validation.

The drug company marketed about 100 lots of tablets made using the old blender. In testing

retain samples, the company found that some lots failed the content uniformity specification.

The firm's investigation traced the out of specification lots to one of the two "identical" blenders, namely the old one. The pharmaceutical firm's own investigation found the older blender to have a slightly smaller capacity and different RPM (revolutions per minute) operational characteristics when run at the same settings as the newer blender.

Subsequently, the firm recalled its total production of the product it made using the older blender. This extensive recall involved multiple strengths of product totaling approximately one half million bottles from U.S. and foreign consignees. The firm plans to qualify the old blender using production size lots.

In light of this case study, during your audits of a firm's process validation, it would be appropriate to determine if the firm's validation protocol includes equipment qualification for all units of significant equipment, even where multiple units are supposedly "identical." Moreover, as explained in the validation guideline, the validation should reflect production size lots.

Contact for further information: Michael J.Verdi, HFD-301, 301-594-2456; e-mail: verdim@cder.fda.gov

On Stability

1) How should the start of the expiration dating period be calculated for new lots of drug products?

Reference: 21 CFR Sections 211.137, Expiration dating, and 211.166, Stability Testing; Guideline For Submitting Documentation For the Stability of Human Drugs and Biologics, February, 1987

As explained in the stability guideline, the expiration date assigned to a new lot of finished drug should be calculated from not later than the date of release of the lot provided that the date of release does not exceed approximately 30 days from the start of manufacturing (i.e., from the initial date an active, preservative, or anti-oxidant ingredient is added to the lot). If more than 30 days have elapsed between the date of manufacture and date of release of the lot, the expiration date should be calculated from within 30 days of the date of manufacture of the lot, and not the date of release.

2) When the labeled expiration date states only the month and year does that mean that the drug expires at the end of the specified month?

References: Same as above

When the expiration date on a label states only the month and year it means that the product will have the identity, strength, quality and purity it purports or represents to posses through the last day of the specified month. For products that are labeled with the month and year of expiry, when a lot is released at the beginning of the month, the entire first month should be included in the calculation of the expiration date. For example, a lot that has a supportable 2 year expiry period that is released on February 10 1998 should be assigned an expiry date of no later than January, 2000.

Contact for further information: Barry Rothman, HFD-325, 301-594-0098; e-mail: rothmanb@cder.fda.gov

Gas What? (Questions on Medical Gases)

Do the CGMP labeling control requirements apply to medical gases packaged in cryogenic vessels?

Reference: 21 CFR 210.3, 21 CFR 211 Subpart G, Packaging and Labeling Control, Sections 211.122 to 211.137; 21 CFR Part 201, Labeling; Compressed Medical Gases Guideline, February 1989

Yes. Although we addressed this issue in the September 1995 edition of the NOTES, this matter continues to be an area of confusion and one of the most frequently asked questions we receive. Therefore, it is worth revisiting. Medical gases are not exempt from the general labeling requirements of 21 CFR Part 201. The filling of medical gases is considered a

manufacturing operation and, as defined in 210.3, applying labeling to containers is also a manufacturing operation. Therefore, cryogenic vessels are subject to the labeling controls of Subpart G - Packaging and Labeling Control, Sections 211.122 - 137. This would include all high pressure cylinders, large dewars or cryogenic vessels, and home or patient vessels.

Accordingly, any individual or firm filling cryogenic vessels, including patient or home vessels, is required to apply a drug label containing all of the required information and to follow CGMP labeling control measures.

See the medical gases guideline for additional information regarding labeling controls.

Contact for further information: Duane Sylvia, HFD-325, 301-594-0095, e-mail: sylviad@cder.fda.gov

Toward The Electronic Government

1) Part 11 Enforcement CPG Publishes

Compliance Policy Guide (CPG) 7153.17 (Section 160.850); Enforcement Policy: 21 CFR Part 11; Electronic Records; Electronic Signatures, issued on May 13, 1999. The agency published a notice of availability, and full text, of the CPG in the July 21, 1999 Federal Register (64 FR 39146.) The CPG gives a brief background on part 11, and makes the following points:

(1) Legacy systems (those in place before August 20, 1997, part 11's effective date). Older electronic records systems may not have reached full compliance by 8/20/97 and their modification may take more time. However, legacy systems are not grandfathered and FDA expects firms that use legacy systems will begin taking steps to achieve full compliance.
(2) Regulatory action determinations. For all systems (legacy, too) decisions on whether or not non-compliance merits pursuit of regulatory action will be based on a case by case evalution. The evaluation may include consideration of the:

a. Nature and extent of part 11 deviations. Deviations would be more signficant if they are numerous, make it difficult for FDA to audit or interpret data, or undermine data integrity;

b. Effect on product quality and data integrity. Lack of an audit trail, for example, would be highly significant when there are data discrepancies and individuals deny record entry responsibility. Likewise, lack of operational system checks that result in adulterated or misbranded product would be significant;

c. Adequacy and timeliness of planned corrective measures. Firms should have a reasonable timetable for coming into compliance, and demonstrate progress toward that goal. While technical controls may take longer to install on some older systems, FDA expects that procedural controls will already be in place; and,

d. Compliance history of the establishment, especially with respect to data integrity. A history of part 11 violations or inadequate or unreliable recordkeeping would make part 11 deviations more significant. Until firms reach full compliance, FDA investigators will be more vigilant to detect such problems as inconsistencies, unauthorized changes, and poor attribution.

(3) Headquarters consultation. Program monitors and center compliance offices should be consulted before recommending regulatory actions.

(4) Regulatory citations. Regulatory citations should reference the applicable predicate regulations in addition to part 11.

2) Internet Resource: On-line Search Engine, "Ask Jeeves!"

"Ask Jeeves!" is a relatively new search engine you may find useful in your work. The site has two addresses (http://www.aj.com and http:/www.ask.com). Jeeves allows you to enter

a search in the form of a question in plain English. It then parses that question, checks your spelling, and quickly returns a page of results (hits) from several search engines and newsgroups. Compared to keyword searches, parsing your prose is intended to be more efficient and precise, meaning you're supposed to get far fewer meaningless or irrelevant hits.

I asked Jeeves, "What are pyrogens?" and was impressed with the answers. The results page displayed multiple lines of information. Each line showed: (1) The hyperlinked name of the Internet search engine (including Jeeve's own) that came up with one or more hit documents; (2) the number of hit documents found; (3) the first few words (header) of the first hit document; and, (4) an icon labeled "Ask" that links directly to the hit document itself. When a given search engine returns multiple documents the resulting list of headers takes the form of a drop down menu. I found this feature to be more convenient than what other search engines generally produce, namely a long list of documents that can span several screens.

When you click on the Ask icon to get to a specific hit document, Jeeves inserts an advertising banner in a frame at the top of the display. The Internet address for the document appears in your web browser as a combination of the Jeeves site and the destination site. These attributes bother me, especially when I want to identify the specific Internet address that corresponds precisely to the final document (e.g., for use as a reference or to store as an Internet bookmark). Click on the words "delete frames" at the bottom edge of the banner to make it disappear and make your browser display the document's direct address (without the Jeeves part.) Another work-around is to click on the name of the search engine itself, and then link to the document from that site instead of clicking on the Jeeves Ask icon.

All in all, I was pleased with the results of my search. Among the hit documents were the CGMP regulations, the Merck Manual, FDA's Guide to Inspections of Dosage Form Drug Manufacturers, and a paper on bacterial anatomy. Oh yes, there was also the following definition of pyrogens from a web site at the University of Kansas Medical Center:

> "Pyrogens are substances that cause fever. The most important endogenous pyrogens, meaning that they are pyrogens that are produced in the body, are the cytokines interleukin-1 and TNF-alpha."

[Consider this definition as informational, and not FDA's formal definition.]

If you try "Ask Jeeves!" I think you'll find it a useful research and reference tool in your day to day inspectional and compliance activities.

Contact for further information: Paul J. Motise, HFD-325; 301-594-0098; e-mail: motise@cder.fda.gov

Updates

Botanicals Guidance Availability --Not Yet.

In the prior issue of HUMAN DRUG CGMP NOTES we referenced a draft "Guidance for Industry, Botanical Drug Products." Response to the botanicals article reflects considerable interest in this topic. However, because FDA hasn't yet published the document for public comment, its general availability will have to await that issuance. The agency will announce its availability in the Federal Register.

As a reminder, during your inspectional and compliance work, you should not implement draft guidances, but rather treat them as informational until they've been finalized.

Contact for further information: Brian Nadel, HFD-325, (301) 594-0098: e-mail: nadelb@cder.fda.gov

P. Motise 09/01/99
DOC ID CNOTES99.doc

DIVISION OF MANUFACTURING AND PRODUCT QUALITY, HFD-320
SUBJECT CONTACTS

(All numbers in area code 301)

Active Pharmaceutical Ingredients	Edwin Rivera Pat Alcock	594-0095 "
Application Integrity Policy Implementation/Removal Data Integrity Cases	LuAnn Pallas Bruce Hartman	594-0098 827-0062
Aseptic Processing	Rick Friedman Tracy Roberts Edwin Melendez	594-0095 594-0098 594-2454
Barriers/Isolators	Rick Friedman Edwin Melendez	594-0095 594-2454
Biotechnology	Brian Nadel	594-0098
Botanicals Manufacturing	Brian Hasselbalch	594-0098
Case Management	Fred Blumenschein	594-0098
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

DIVISION OF MANUFACTURING AND PRODUCT QUALITY, HFD-320
SUBJECT CONTACTS (Continued)

(All numbers in area code 301)

Litigation Guidance and Support	Nick Buhay	594-0098
Medical Gases	Duane S. Sylvia	594-0095
NDA/ANDA Pre-Approval Inspections	Randall Woods	827-0062
Packaging	Edwin Melendez	594-2454
Penicillin Cross Contamination	Edwin Melendez	594-2454
Pharmacies, CGMP	LuAnn Pallas	594-0098
Pre-Approval Program	Melissa Egas Bruce Hartman	594-0095 927-0062
Process Validation, General	John Dietrick Paul Motise	594-0098 “
Recycling Plastic Containers	Paul Motise	594-0098
Repackaging	Barry Rothman	594-0098
Salvaging	Paul Motise	594-0098
Stability/Expiration Dates	Barry Rothman	594-0098
Sterility Issues, General	Rick Friedman Tracy Roberts Edwin Melendez	594-0095 594-0098 594-2454
Topical Drugs	Randall Woods	827-0062
Transdermals	Brian Hasselbalch	594-0098
Videoconferencing	Russ Rutledge Paul Motise	594-2455 594-0098
Water Quality	Rick Friedman Edwin Melendez Tracy Roberts	594-0095 594-2454 594-0098

FAX FEEDBACK

TO: Paul Motise, HUMAN DRUG CGMP NOTES, HFD-325
FAX: 301-594-2202 (Phone 301-594-0098)

FROM: _____

AT: _____ MAIL CODE: _____

PHONE: _____ FAX: _____

E-MAIL ADDRESS: _____

To receive the electronic version of HUMAN DRUG CGMP NOTES via E-mail, send a message to motise@cder.fda.gov. In the message subject field type SUBSCRIPTION REQUEST and in the body of the message type SUBSCRIBE HUMAN-DRUG-CGMP-NOTES. To stop receiving the electronic edition send the same message, but use the word UNSUBSCRIBE instead of SUBSCRIBE.

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:
_____
_____