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

Project Manager: Paul J. Motise, HFD-325

IN THIS ISSUE:

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 great and we appreciate your suggestions and questions. In addition to FAX FEEDBACK, feel free to call, write, or send us e-mail, as several of you have done. 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.

As a reminder, 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 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:

Are there CGMP regulations or guidances specific to Botanicals? What other references are available?

Reference: FDA Guidance "Guideline For Submitting Supporting Documentation in Drug Applications For The Manufacture of Drug Substances", 2/87; FDA draft guidance, "Guidance For Industry, Botanical Drug Products," 8/98

There are no regulations specific to Botanicals, per se, but there are some applicable guidance documents. Botanicals are generally either starting materials for the production of active pharmaceutical ingredients or drug substances for use as ingredients in dosage forms. In either case there are no applicable CGMP regulations for preparation of Botanicals as components. Note that the CGMP regulations (21 CFR Parts 210 and 211) do, however, apply to production of dosage forms that incorporate botanical drug substances.

The agency has addressed factors that affect quality attributes of Botanicals in the Guideline for Submitting Supporting Documentation In Drug Applications. The document notes the following points:

> The description of the collection and preparation should include the botanical species and part of the plant. That is, what part of the plant contains the desired chemical. Is it the leaves, the roots, the fruits and berries, or the whole plant? Other factors which influence the quality or composition of the final product should be described. These should include: geographical location where the plant is grown, storage and transportation issues, drying conditions, and grinding conditions. Also, seasonal variations in active constituents may be an important factor in determining the best time for harvest.
>
> The description of the collection and preparation procedure should include the test method(s) for identity and assay for the drug substance in the original and crude material. Attention should be devoted to identification of impurities and minor components.

Be aware that an August 1998 draft guidance called "Guidance For Industry, Botanical Drug Products" was published for comment. However, this document addresses use of

Botanicals in drug products for clinical investigation.

As a point of information, USP monographs for active ingredients used in drug products generally focus on single synthetic compounds. By contrast, Botanicals generally consist of complex mixtures of active ingredients that work in synergy. Traditionally, before Botanicals are used in drug manufacturing it is important that the active ingredients that provide the pharmacological properties be identified.

The USP has several monographs for Botanicals. These include Belladonna Leaf, Opium, Senna, and Witch Hazel. Where such articles are not dosage forms the CGMP regulations would not apply. Nonetheless, the general CGMP provisions of Section 501(a)(2)(B) of the Act apply to the manufacture of dosage form components regardless of whether or not those substances are Botanicals. Keep in mind, though, that FDA has not published regulations or guidance documents that address CGMPs for dosage form components that are Botanicals.

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

How often must manufacturers examine finished product reserve samples? Can FDA investigators visually examine a manufacturer's reserve samples?

Reference: 21 CFR 211.170(b), Reserve Samples; 211.192, Production record review; 211.160, General requirements [Subpart I, Laboratory Controls]

The CGMP regulations, at section 211.170, require that at least annually manufacturers visually examine reserve samples from representative lots of each drug product manufactured, unless such examination would affect the integrity of the samples. This section also requires firms to use acceptable statistical procedures in selecting the samples. (Note that the regulation exempts medical gases, radioactive drug products, and radioactive drug kits from the reserve sample retention requirement; therefore, the examination provision would, of course, not apply to those products.)

Per section 211.160, firms must have written procedures for those reserve sample examinations.

Although section 211.170 specifies at least annual visual examination, firms may themselves determine that for certain products, and under some circumstances, a more frequent interval may be warranted. The regulation gives manufacturers considerable leeway in this regard. For example, as part of complaint or failure investigations performed in accordance with section 211.192 (that requires a thorough investigation of any unexplained discrepancy or failure of a batch to meet specifications), a firm may, in addition to conducting an immediate examination of the reserves, conclude that reserve samples for one or more products, or particular lots of one or more products, merit more frequent visual examination for a given period of time.

During inspections, investigators should not on a surveillance basis routinely examine a manufacturer's reserve samples. However, on a for cause basis, such as when investigating product contamination or mix-ups, it may be appropriate for investigators to open and examine a manufacturer's reserve samples. In those situations, if the manufacturer produces evidence that such examination would affect the integrity of its remaining reserve samples, an attempt should be made to examine samples of the suspect products taken from other sources, such as commercial inventories.

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

Is there a requirement specifying the level of light intensity when performing visual inspection of parenteral drug products for the presence of particulates?

Reference: 21 CFR 211.160 (b), Laboratory Controls, General Requirements

No. However, 21 CFR 211.160 (b) requires that laboratory controls include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity. Accordingly, a test method for the visual detection of particulates would be expected to account for the intensity of the light as well as backgrounds that may be needed for the adequate visual detection of particulates in the finished drug product. We would assess, on a case by case basis, the adequacy of a firm's determination of what levels of light would be sufficient.

Contact for further information: Tracy Roberts, HFD-325, 301-594-0098, e-mail: robertst@cder.fda.gov

When should a firm perform a sterility re-test? How should a microbiology laboratory handle deviations during sterility testing?

Reference: 1987 Guideline on Sterile Drug Product Produced by Aseptic Processing; USP 23, Section <71>, Sterility Tests; 21 CFR 211.22, Responsibilities of quality control unit; 211.192, Production record review; 211.160 General Requirements [Subpart I, Laboratory Controls]

The USP Sterility Test is limited in its ability to detect whether a batch contains contaminated units. Finding any unit that exhibits growth is a serious matter, and the subsequent investigation is generally quite involved and covers both the laboratory and production areas. The drug product lot fails the USP test requirement if any microbial growth is found and the test is not invalidated. The USP (Supplement 8) states that a firm should not perform a sterility re-test without evidence that the sterility test positive can be attributed to contamination introduced by the laboratory. Further, the 1987 Aseptic Guideline explains that a batch should not be released without clear documented evidence that the contamination occurred during testing.

It is difficult to justify invalidation of an initial sterility positive result. For example, the presence of any specific microorganism in both the test sample and the sterility testing environment would not alone rule out the aseptic manufacturing operation as the origin of the contamination. A comprehensive evaluation of manufacturing and testing operations, as well as multiple trending reports (e.g., long term trends at specific environmental monitoring locations) which can be revealing, would be consistent with section 211.192 of the CGMP regulations. Because of the low sensitivity of sterility testing, a finding of no growth during retesting should be afforded minimal weight relative to other parts of the investigation.

In summary, a high threshold of justification is needed for a decision to invalidate a sterility test positive result and perform re-testing. When investigations into the origin of the product's contamination are inconclusive, the decision to release or reject the batch should err on the side of patient safety.

Per section 211.160 of the CGMP regulations, when deviations occur during sterility testing, they should be documented concurrent with the test, investigated, and remedied. As explained in the 1987 guideline, such deviations should be trended, with corrective measures taken in a timely manner. If any of these deviations may have compromised the integrity of the sterility test, it would be consistent with CGMP not to proceed with the test. For example, if asepsis is compromised during sample manipulation, then samples should not be incubated. Finally, it is important to note that an unreliable laboratory is an objectionable condition that underscores the need to err on the side of safety when investigating a sterility positive rather than risk overlooking a genuine production problem.

Contacts for further information: Richard L. Friedman, HFD-322, 301-594-0095; e-mail: friedmanr@cder.fda.gov; Tracy Roberts, HFD-325, 301-594-0098, e-mail: robertst@cder.fda.gov

Gas What! (Policy questions on medical gases)

1) NEW Compliance Aid On The Medical Gas Home Page

[http://www.fda.gov/cder/dmpq/gases.htm] under Medical Gas Regulatory Actions

The Division of Manufacturing and Product Quality and the Division of Compliance Management Operations has compiled, and posted to the Internet at the above address, a listing of all medical gas warning letters issued for Fiscal Years 1993 to the present.

This list was developed to assist the field in determining if a facility or multiple site corporation received prior notice and whether more severe regulatory enforcement may be warranted (i.e., seizure, injunction, etc.) on a corporate wide basis.

It would be inappropriate to issue consecutive warning letters (i.e., back to back) to the same location or to multiple sites of the same corporation. Such issuances would be contrary to the Regulatory Procedures Manual (RPM), Chapter 4, Warning Letters, under Follow-up Enforcement Action (page 82, August 1997 Revision). Note that the RPM states that post warning letter regulatory actions should include seizure, injunction, etc., but not another warning letter.

Firms having multiple sites that have received warning letters may also use this information to signal that they may need to make corporate wide CGMP corrections.

2) Must firms validate use of non-USP testing methods for USP medical gases?

Reference: 21 CFR 211.160, General requirements [Subpart I, Laboratory Controls]; 211.165(e), Testing and release for distribution; 211.194, Laboratory records

Yes. The CGMP regulations, at sections 211.165(e) and 211.194(a)(2), require a firm or individual utilizing a non-U.S.P. testing methodology to perform a validation study establishing and documenting the accuracy, sensitivity, specificity, and reproducibility of the test method employed.

This would include paramagnetic analyzers, handheld analyzers, pressure differential methods, etc.; all would be required to undergo validation. In addition, any firm using one of these non-U.S.P. testing methods must have complete documentation, per 211.194, for the entire validation study, not just the data.

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

On Stability

Are manufacturers of excipient (inactive) components required to label the drugs with expiration or retest dates?

Reference: Guide To Inspection of Bulk Pharmaceutical Chemicals, 9/91; Inspection Technical Guide #41, Expiration Dating and Stability Testing for Human Drug Products, 10/18/85; FD&C Act, Section 501(a)(2)(B)

Expiration or retest dates are not a CGMP requirement for all excipients, and generally their absence from excipients is not objectionable.

Assigning an expiration date or a retest date to bulk pharmaceutical chemicals is not required by the CGMP regulations because the regulations are applicable to the manufacturing of finished pharmaceuticals (i.e., dosage forms.)

In the broader context of section 501(a)(2)(B) of the FD&C Act, the excipient manufacturer would have to implement controls to ensure that the drug has the identity and strength, and meets the quality and purity characteristics that it purports or is represented to possess. The chemical stability of the excipient would be relevant in this context.

In determining the need for an expiration or retest date it would be important for the manufacturer to begin with some baseline information about the relative stability of the drug. That information may be found in scientific literature. For example, although most excipients are known to be chemically inert, others, such as certain preservatives and antioxidants, can be expected to have a limited shelf-life.

Where stability information about the drug is absent, or indicates that one may expect a relatively limited shelf life, it would be feasible and valuable for the firm to perform stability studies. It would be consistent with CGMP for those studies to support a labeled expiration or retest date.

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

CGMP Sorites

Reference: 21 CFR 211.186, Master production and control records

Sorites are, in fact, extended syllogisms (i.e., series of syllogisms.) The most basic syllogism is a categorical syllogism. This is a valid logical argument relating three categories (i.e., sets or classes) in three propositions. These three categories are two premises and a conclusion.

In the following simple syllogism, the concept of set inclusion will be demonstrated. An example of set inclusion is when all members of one set/class are included in another set, whose members are then included in a third set. By virtue of the form of this argument, it follows necessarily that any member of the first set is a member of (or included in) the third set. This is known as a valid argument.

Notice as you solve this syllogism, how you need to identify the subject and predicate of each proposition, in essence identifying the sets. Furthermore, take note that each subject and predicate are each a set.

Now try the following CGMP syllogism.

- Proposition – As required by 21 CFR 211.186, all batch to batch uniformity (bbu) shall be assured by the preparation of master production (pmp) and control records (i.e., the preparation, dating and signing by one person and the independent checking, dating and signing by a second person.)

- Proposition – As required by 21 CFR 211.186, the preparation of master production and control records shall be described (i.e., assured) in a written procedure (wp) and followed.

The conclusion appears after the last article in this edition of the notes.
Contact for further information: Randall Woods, HFD-324, 301-827-0062; e-mail: woodsr@cder.fda.gov

Toward the Electronic Government

1) Under part 11, when a firm uses a contracted T1 line to a remote facility, is the system considered closed? Contrast this with communicating over the public Internet as being an open system.

Reference: 21 CFR 11.3(b)(4) and (9), Definitions; paragraphs 41 and 44 of the 3/20/97 final rule Federal Register Notice, Electronic Records, Electronic Signatures (62 FR 13430 at 13440 and 14331)

In classifying a system as open or closed, a firm needs to determine if it controls access to the system that holds records for which it is responsible. Lacking such control, its records could be vulnerable to unauthorized disclosure or modification; trade secret and confidential information may be at risk. Therefore, firms may wish to put into place added record protections such as encryption. Part 11 does not mandate those added controls in all cases, but rather permits firms to make that decision for themselves based on the circumstances. How well a firm safeguards its records may reflect the degree to which it regards the information as trade secret.

Let's assume that the firm is responsible for the content of the records in question and that the remote facility holds the firm's records. First, we need to consider if the communications line to the facility uses store and forward technology, meaning the records are stored on one or more servers before arriving at the remote facility. If the firm controls who can access those intermediate holding systems as well as the remote facility itself, the records would be in a closed system from the firm's perspective. On the other hand, if the firm does not control access to either those intermediate holding

systems or the final remote facility, the system would be open. Faced with an open system, the firm would need to evaluate the circumstances (such as the contents of the records themselves) and decide if added controls were warranted.

On the Internet, store and forward technology is customary, and the firm would not control access to servers that held its records (i.e., the system would be open.)

2) CPG on Y2K published

Reference: Compliance Policy Guide (CPG), Sub Chapter 160 – Regulatory, Section 160-800 Year 2000 (Y2K) Computer Compliance; 21 CFR Part 7, Enforcement Policy

On April 26, 1999 the subject CPG was issued. It represents current agency thinking on FDA regulated products that may not perform properly before or during the transition to the year 2000. The CPG notes that most FDA regulated products are vulnerable to Y2K computer problems. (In the drug CGMP arena, examples include inaccurate computations of expiration dates, erroneous scheduling of equipment maintenance, and certain process control problems.)

The CPG makes the follow key regulatory points.

1. Because lack of Y2K compliance is not in and of itself a violation of FDA regulation, it would be inappropriate to list such a condition as an FDA 483 observation. However, it is proper to list observations regarding specific processes or product deficiencies related to Y2K.

2. When an FDA regulated product held for sale or in commercial distribution is relabeled, returned, reprocessed, repaired, or replaced to resolve a product problem caused by Y2K before that problem is manifest, the action will be considered a market withdrawal (21 CFR 7.3(j)), not a recall. Conversely, the action will be considered a recall (21 CFR Part 7, Subpart C) if the regulated product manifests the problem before the correction or removal is completed. For example, the action would be a recall where a drug product labeled with the wrong expiration date is recovered from the market.

3. The agency may exercise enforcement discretion and consider unusual or extenuating circumstances bearing on each enforcement decision.

4. Factors to consider in pursuing regulatory actions include:

(a) Public health risks;
(b) impact on product quality;
(c) availability of critical use products and their substitutes to meet public health needs;
(d) the adequacy of the firm's Y2K mitigation plans and efforts; and,
(e) where violative products enter the market, identification of those firms that hold responsibility for taking Y2K preventive measures before the products were released for distribution.

5. Districts should, as appropriate, consult with respective center program monitors before recommending regulatory actions, and should get monitor concurrence for warning letters regarding Y2K.

6. Regulatory citations should reference the underlying regulations and statutes involved in the product or process deficiency.

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

Conclusion to CGMP sorities:

All batch to batch uniformity shall be assured by written procedures that are followed.

Notice the form - all BBU is PMP; all PMP is WP; therefore all BBU is WP.

P. Motise 06/01/99
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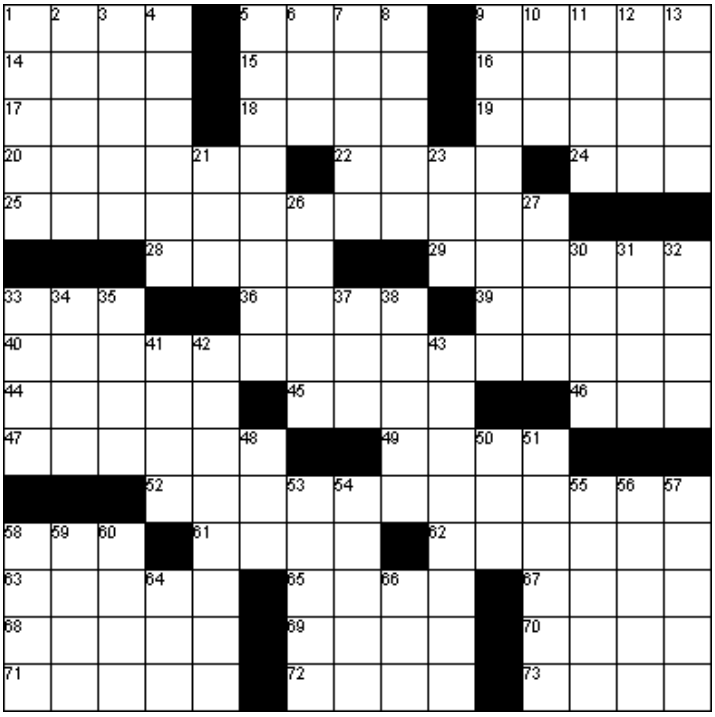
CGMP Puzzle #2



Across

1 Cookie man
5 Photosynthesis organ
9 Kind of pepper
14 Controlled area cover up
15 Sailor's patron saint
16 Practice
17 Quechua
18 Arabian gulf
19 Ponder
20 Soviet dictator
22 HFR-MW3594's turf
24 Kind of recall, briefly
25 They surround gelatin
28 Body fluids
29 Core garment
33 Partners to p/ws
36 Russian parliament
39 It's drainless at core
40 210/211 apply to them
44 Macabre
45 First name in scat
46 D.C. in March
47 It could be hidden
49 Hence
52 Beneath the surface
58 Hood's home
61 Type of culture
62 Snuggle
63 High
65 Scratch
67 Ms. Ferber
68 Two time Nobelist (chemistry and physics)
69 With 12 down, cleanroom garb characteristic
70 Kind of ticket
71 Revise
72 Sampling ports
73 War god

Down

1 Anabaptist sect
2 Horse blanket, in Madrid
3 Movie prize
4 Viking poets
5 Mona's man?
6 Shade tree
7 Gather
8 Hot dip
9 Suffocate
10 Chance
11 Egyptian flyer
12 Navel collection?
13 483 follower
21 Cool
23 Cleric robe
26 It's sometimes pregnant
27 Alone
30 Pulled apart
31 Field refs.
32 Formerly, formerly
33 It could be bright or big
34 Fermentation sediment
35 Positive
37 Bad in Paris
38 Part of 58 down
41 Deseeds cotton
42 Took away
43 Otological woes
48 He's on 64 down
50 Antelope
51 Swelling
53 Split
54 Extreme
55 More unusual
56 Arm bones
57 They could be official
58 It's generally not on 29 across
59 Astringent ingredient
60 Caliber
64 Two make ten
66 Mushroom

FAX FEEDBACK

TO: Paul Motise, HUMAN DRUG CGMP NOTES, HFD-325
FAX: 301-5942202 (Phone 301-594-0098)

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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 regarding _____
_____
_____

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