

HUMAN DRUG CGMP NOTES

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(A Memo on Current Good Manufacturing Practice Issues on Human Use Pharmaceuticals)

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Office of Compliance
Center for Drug Evaluation and Research

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(Your input requested)

MOTISE'S NOTEBOOK:

Welcome again to another edition of our periodic memo on CGMPs for human use pharmaceuticals. Your FAX FEEDBACK responses continue to be encouraging and we especially appreciate your suggested topics for coverage. You need not, however, limit the dialog to conveyance by FAX FEEDBACK. Feel free to call, write or send us e-mail, as several of you have done.

Although this document is fully releasable under the Freedom of Information (FOI) Act, our intended readership is FDA field and headquarters personnel. Therefore, for now, we cannot extend our distribution list to people outside the agency. The primary purpose of this communication is to enhance field/headquarters communications on CGMP policy issues and to do so in a timely manner. This document is a forum to hear and address your CGMP policy questions, to update you on CGMP projects in the works, to provide you with inspectional and compliance points to consider that will hopefully be of value to your day to day activities, and to clarify existing policy and enforcement documents.

We intend to supplement, not supplant existing policy development/issuance mechanisms, and to provide a fast means of distributing interim policy.

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 the Policy and Guidance Branch, HFD-323, by interoffice paper mail, using the above address, by phone at (301) 594-1089, or by electronic mail (under the new integrated e-mail addressing system, address the message to the last name of the contact, such as BARR, or MOTISE.

If you would like to receive an electronic version of this document via electronic mail, let us know

(see the check off line in FAX FEEDBACK). In addition, HUMAN DRUG CGMP NOTES is available electronically, by two methods. First, interested persons can send electronic mail to the Internet address DOCNOTES@FDACD.BITNET. There's no need for text in the body of the message, although including a name, address and phone number will facilitate any necessary follow-up. Our system will automatically reply by sending the electronic (ASCII text file) current issue of this document to the requester.

Second, the document can be downloaded from the Internet, via the File Transfer Protocol (FTP), in either ASCII text or WordPerfect (5.1) formats. To download either of these files, connect, using FTP, to CDVS2.CDER.FDA.GOV and log in as ANONYMOUS. Then enter any password. The ASCII file is HDCGMP.TXT, and the WordPerfect file is HDCGMP.WPC. For example, your commands to receive the WordPerfect file would look like this:

```
FTP CDVS2.CDER.FDA.GOV
LOGIN ANONYMOUS
<any password>
BINARY
GET HDCGMP.WPC HDCGMP.WPC
EXIT
```

Thanks!

Paul J. Motise

POLICY QUESTIONS:

When does process scale-up require revalidation (i.e., greater than ten-fold)?

References: Office of Generic Drugs Policy and Procedure Guide #22-90; Interim Policy on Exception to the Batch Size and Production

Condition Requirements for Non-Antibiotic, Solid, Oral-Dosage Form Drug Products Supporting Proposed ANDA's; 9/13/90.

The simple answer is that any process change, including an increase in batch size, requires an evaluation of that change and validation of the modified process.

First, it is important to understand the origin of the "ten-fold" policy. Per the above OGD guide, the biobatch must be at least 10% of the proposed production batch size for solid oral-dosage non-antibiotic ANDA's. The guide also says that one or more batch size increases **that do not cumulatively result in a batch size that exceeds ten times** the size of the biobatch, will ordinarily be acceptable without supplemental approval. There are additional restrictions and even these changes must be validated and reported in the annual report. The policy implies that a scale-up beyond ten-fold, or the maximum **approved** batch size covered in the application, ordinarily **will require** prior approval, but it is the firm's responsibility to evaluate the change to determine if a supplement is required.

The essential point is that the ten-fold policy applies to the need for an approved supplement; it does not apply to the need for validation.

Any process change requires revalidation. A pharmaceutical manufacturer needs to have a change control system to evaluate any process change, including small and large batch size increases. This evaluation of the equipment or process changes resulting from the batch size change will help determine the extent or scope of the revalidation needed.

Division Contact for Further Info: John Dietrick, HFD-325, (301) 594-0098.

What does FDA expect regarding temperature mapping of autoclaves as part

of sterilization validation; must mapping include interior chamber surfaces?

References: 21 CFR ' 211.113, Control of microbiological contamination.

For dry heat ovens and autoclaves we have required empty chamber temperature mapping and minimum and maximum load temperature mapping.

Empty chamber studies are designed to show temperature uniformity in the chamber. The difference between the lowest and highest temperatures in an empty autoclave should be less than 0.5 degree C. In an empty dry heat oven the difference between the highest and lowest temperature should be less than 5.0 degrees C.

The load studies are designed to determine the cold spot or the slowest to heat area. The cold spot is used to control the depyrogenation or sterilization cycle. Thermocouples are placed in the product containers in the case of autoclaves, and inside the components or glassware in the case of dry heat ovens.

The number of thermocouples to be used in empty and loaded chamber studies will depend on the size of the chamber. During the inspection the investigator will want to audit the data generated from these studies.

We have never required temperature mapping of chamber surfaces in dry heat ovens or autoclaves. The only time that we would want to see surface temperature studies is temperature mapping of the cooling/heating shelves in lyophilizers.

Division Contact for Further Info: Terry Munson, HFD-322, (301) 594-0095.

Does CGMP inspectional coverage extend to contractors who produce clinical supplies?

References: Compliance Program 7346.832, Pre-Approval Inspections, Part IIIB

Yes. The referenced compliance program requires that NDA biobatch(s) be compared with the clinical supplies which are used in pivotal clinical trials (phase III trials). The intent is to assure equivalence between the manufacturing process intended for use in commercial production and that used in production of clinical supplies. In some cases, these clinical supplies are produced by contract manufacturers. The pre-approval program also requires that these contract manufacturers be audited for CGMP compliance.

If contract manufacturers are found to have produced phase III clinical supplies, we are requesting that you check the GWQAP (Government Wide Quality Assurance Program) profile and determine the compliance status of the manufacturer involved. If the contract manufacturer is not profiled or has not been inspected in the profile class or is not in compliance, please notify the Division of Manufacturing and Product Quality, Investigations and Compliance Evaluation Branch, HFD-324, as soon as possible.

Division Contact for Further Info: Bruce Hartman, HFD-324, (301) 594-0098.

Would a manufacturer of empty hard gelatin capsules be inspected for CGMP compliance when identified in an NDA/ANDA as a supplier?

Reference: 21 CFR ' 211.1, Scope.

No. Where an NDA or ANDA identifies a firm as a supplier of empty hard gelatin capsules, FDA would initiate an inspection of that supplier only on a for cause basis. This is because the empty hard gelatin capsules are regarded as inactive ingredients, and our follow up inspections of

component suppliers to new drug product manufacturers generally extends only to makers of active ingredients. The empty capsules are still legally defined as drugs, considering their intended use in this case, rather than as food additives.

Our Current Good Manufacturing Practice (CGMP) regulations, at 21 Code of Federal Regulations Parts 210 and 211, do not apply to the preparation of the empty hard gelatin capsules because the capsules are considered bulk drug components rather than finished dosage forms. The manufacturing standards to which we hold producers of empty hard gelatin capsules have not been codified, but are the general statutory standards within the broader meaning of current good manufacturing practice, as identified in the U.S. Food Drug and Cosmetic Act, at Section 501(a)(2)(b). The CGMP regulations may be used as guidance, however, in determining what controls, procedures and documentation would be acceptable to the agency.

Division Contact for Further Info: Paul Motise, HFD-323, (301) 594-1089, or Mark Lynch, HFD-324, (301) 594-0098

If a manufacturer of a new drug changes its granulation process from slugging to chilsonating, is a supplement needed? What's the difference between the processes?

Reference: 21 CFR 314.70, Supplements and other changes to an approved application.

Both the slugging and chilsonating (compacting) processes are a form of dry granulation. Slugging involves compression of powders into tablets and re-milling them into granules of desired sizes before final tablet compression.

Chilsonating makes use of two rollers revolving toward each other through which powder

materials are fed in. Rollers are pressurized by hydraulic rams and force of compaction may be adjusted by them. The compacted material will come out the other end in thin chunks, which then may be milled to the desired size. Factors that are associated with chilsonating are hydraulic pressures, material feeding speed, and roller rotational speed.

They are similar processes in that dry granules are formed to improve tablet compressibility. However, as with any other process changes, comparability of the processes using the two different techniques may not be generalized or process concerns limited to equipment being used. For example, excipients, which were added for specific purposes in one process, may not behave the same way in another. So, the change may bring about another change in formulation.

In light of the process and formulation changes that may result from switching from slugging to chilsonating, a supplement would be needed.

Division Contact for Further Info: Charles Ahn, HFD-325, (301) 594-0098.

Gas What? (Policy Questions on Medical Gases):

1) Is it acceptable for a medical gas filler to assign a single lot/batch number for the entire day's production?

Reference: 21 CFR 211.130(b), Packaging and labeling operations

No. A manufacturing operation, such as the filling of high pressure cylinders on a multi-outlet manifold, is governed by a set of manufacturing procedures or conditions which when performed from the beginning to the end of a process provides assurance that the batch is uniform and consistent. Further, each batch is in itself a separate entity with little resemblance to the

previous batch other than the use of the same incoming materials with subsequent batches exhibiting their own uniqueness. According to the CGMP, each manifold filling sequence, each uninterrupted filling sequence, each cryogenic vessel filled, and each storage tank filled is considered a new batch and is required to be assigned a new lot/batch number.

This does not apply to cryogenic home vessels filled at a patient's home.

2) What is the accuracy of the USP methodology for the analysis of Oxygen USP? What oxygen analyzers are acceptable?

Reference: 21 CFR 211.165(e), Testing and release for distribution; 211.194(a)(2), Laboratory records; and, Compressed Medical Gases Guideline, Rev. 2/89.

The accuracy of the USP method, the Orsat burette is plus or minus 0.1%. Analytical equipment accuracy is required to be equivalent to or greater than this value.

Analyzers that operate on the paramagnetic susceptibility principle, and have the above accuracy would be considered acceptable. Some of the oxygen analyzers commonly encountered and found to be acceptable are the Servomex 570A and the 244OA - upper scale only; Western Enterprise's TR104 and MADA Medical's OAP640 (These two are actually Servomex 570A); Rosemount Analytical and Siemen. Paramagnetic analyzers provide both a strength/potency and an identification test in one result.

Handheld analyzers operating on the fuel cell, electrochemical cell, polarographic cell or the galvanic cell, such as the Hudson RCI, Catalyst Research's MiniOx, etc. are capable of providing a specific oxygen identification test result only. These analyzers have an accuracy between plus or minus 1% to 3%.

Division Contact for Further Info: Duane Sylvia,
HFD-322, (301) 594-0095

NEW TECHNOLOGY EMERGING:

Osmotic Membrane Controlled Release Dosage Form System:

A relatively new type of controlled release dosage form that is coming into wider use in the pharmaceutical industry utilizes ALZA's osmotic membrane technology. Its trademark is OROS⁷. OROS⁷ systems may also be referred to as gastrointestinal therapeutic systems (GITS). This is a more general term that includes various types of osmotic controlled-release oral dosage forms. As ALZA licenses more pharmaceutical companies to market OROS⁷ products manufactured with this technology, field investigators are more likely to encounter processes related to it.

GITS products have different designs. For example, the elementary osmotic pump, has a single-layer core containing the active ingredient (typically water soluble) enclosed in a semipermeable membrane with one or more minute laser-drilled orifices. (Some GITS products also have an overcoating.) In the gastrointestinal tract, water is drawn in through the membrane at a controlled rate, gradually dissolving the active ingredient; the resulting drug solution flows out through the orifice at the same rate that water is flowing in. Examples of products utilizing this system are Acutrim⁷ (phenylpropanolamine hydrochloride), Efidac/24⁷ (pseudoephedrine hydrochloride), and Volmax⁷ (albuterol sulfate).

Another design found in GITS products, the push-pull system, is typically used with active ingredients of limited water solubility. In this system, the semipermeable membrane encloses a two-layer core, one layer containing the active ingredient and the second layer containing a

water-swellable osmotic agent. As water flows into the core through the rate-controlling membrane, the osmotic agent expands. This expansion causes the aqueous drug formulation being formed in the drug layer to be pushed out through the laser-drilled orifice(s). Examples of products utilizing the push-pull system are Procardia XL⁷ (nifedipine) and Minipress XL⁷ (prazosin hydrochloride).

Field investigators should be alert for the following:

- One of the more critical aspects of this technology is the coating operation and a company's means of controlling coating thickness. The weight of the semipermeable membrane affects release rate. (Increased membrane thickness, as measured by weight, slows release rate.) Therefore, it is important that any applicant developing a GITS dosage form determine and control the weight of the semipermeable membrane during the coating operation. This consideration is important in pre-approval inspections.

- Weights of total cores--and of the active layer in two-layer products--should be monitored as part of in-process quality control.

Division Contact for Further Info: Randy Woods,
HFD-324, (301) 594-0098

TOWARD THE ELECTRONIC GOVERNMENT:

Videoconferencing Brings CDER to You!

Reference: 59 FR 9488 No. 39, 2/28/94; Notice: Videoconferencing Facility; Availability

On March 29, 1994 CDER supplied 7 speakers to the DIA (Drug Information Association) Conference held in Dallas, TX. What makes this unique was that they gave their talks by video link. CDER can now support more field district

and industry conferences by using this technology. Here's how it worked at our initial videoconference with Dallas.

The conference format was straightforward. After the local intro and welcoming to the Dallas audience by Mr. Leroy Gomez and Ms. Marie Falcone, the program was turned over to us here in headquarters. We came "on the air" with 2 speakers, a break, and 2 more speakers; we then hosted a round-table question & answer period with all 4 speakers before lunch break. The afternoon session was similar.

The equipment in Dallas consisted of a pair of 54" large screen monitors positioned along the aisles, a smaller monitor front center, and a large standard screen on the wall in front on which the visual aids were displayed. The audience could thus watch the speaker or the visual aid, like a standard in-person presentation. Two sets of visual aids were used: one for live display in Dallas, the other for live prompting of speakers in Rockville. A separate phone link between the visual aid operator in Texas and the facilitator allowed slides to stay in sync. In one speaker's case the duplicate slides didn't arrive in Dallas, so we had to toggle between transmitting the slide and speaker. The feedback on this was that the audience preferred to view the slide up front on the large screen.

The round table question & answer periods went off exceptionally well. Due to audio limitations, the audience was asked to write issues on 3x5 cards which Marie read, and the appropriate speaker responded. In some cases, members of the audience walked up to the microphone and asked their questions directly, or asked for clarification of a point. The advantage was an instant response to questions from the headquarters person best suited to answer.

Video Conferencing has several advantages over on-site presentations:

- Centers can provide more speakers.
- Attendees hear speakers who are most familiar with the subjects.
- Speakers spend minimal time away from their normal duties.
- Travel costs are minimized.

We anticipate using this technology in the future as a standard means for providing speakers to smaller conventions and group conferences. If you are interested in learning more about the mechanics of videoconferencing, would like more information on equipment requirements, or would like to arrange a demonstration, meeting, conference etc, get in touch with the contacts named below. Let us show you the possibilities!

Contacts for Further Info:
Russ Rutledge, HFD-323, (301) 594-1089;
Angie Youngblood, HFD-057, (301) 443-0724

FDA Phone Directory on Internet

For you savvy Internet surfers, there is a file (FDADIRECT.DAT) available on CDER's FTP node that we think you may find useful. The file is an FDA directory of 9837 employees (as of 3/94), in ASCII format. Fields are fixed length, without delimiters other than the carriage return that denotes the end of a record. To obtain the file use the following commands:

```
FTP CDVS2.CDER.FDA.GOV
LOGIN ANONYMOUS
<any password>
BINARY
GET FDADIRECT.DAT FDADIR.TXT
EXIT
```

The phone directory file is updated regularly and can be imported into a database program which enables searches and sorts to be made on the database records in the resulting database file.

For example, a sort can be made on the mailing symbol field to get a listing of all personnel in a given unit such as a resident post or review unit.

Division Contact for Further Info: William Crabbs, HFD-323, (301) 594-1089.

FAX FEEDBACK

TO: Paul Motise, HUMAN DRUG CGMP NOTES, HFD-323
FAX: 301-594-2202 (Phone 301-594-1089)

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This FAX consists of this page plus _____ page(s).

Please have the HFD-320 information contact person get in touch with me regarding:

| |
|--|
| <p>I found this issue of HUMAN DRUG CGMP NOTES to be [check as appropriate]:</p> <p>___not very; ___ somewhat; ___ very; ___ extremely informative, and</p> <p>___not very: ___ somewhat; ___ very; ___ extremely useful to my inspectional/compliance activities.</p> |
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- Autoclave Temperature Mapping _____ Clinical Supplies _____
- Bulk Inactive CGMP _____ Dry Granulation _____
- Osmotic Membrane Technology _____ Videoconferencing _____
- Medical Gases _____ Other _____

Future editions of HUMAN DRUG CGMP NOTES should address the following CGMP

questions/issues:
