HUMAN DRUG CGMP NOTES

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

Issued By: The Division of Manufacturing and Product Quality, HFD-320 Office of Compliance Center for Drug Evaluation and Research

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IN THIS ISSUE:

MOTISE'S NOTEBOOK:

Welcome to another issue of Human Drug CGMP Notes, our periodic memo on CGMP for human use pharmaceuticals. Your FAX FEEDBACK responses remain excellent and we especially appreciate your suggested topics for coverage. You need not, however, limit the

dialog to FAX FEEDBACK. Feel free to call, write, or send us e-mail,. We also welcome brief articles FDAers may wish to contribute. Subjects should be CGMP related and would be especially valuable if they address 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'd like to receive an electronic version of this document via electronic mail, let us know (see the check-off line in FAX FEEDBACK).

Thanks!

Paul J. Motise

POLICY QUESTIONS:

How would the CGMPs address the problem of cleanroom operators who are shedders or practice poor aseptic technique?

References: See 21 CFR 211.42(c)(10), Design and construction features; 211.25, Personnel qualifications; 211.28, Personnel responsibilities; 211.113 Control of microbiological contamination; Guideline on Sterile Drug Products Produced by Aseptic Processing, June 1987

To protect exposed sterilized product, personnel are expected to consistently maintain sterile gown quality and aseptic method standards. Investigators can use the referenced sections of the CGMP regulations when they encounter the issues of cleanroom employees who appear to be "shedders" or practice poor aseptic technique. The term "shedders" is popularly used to describe individuals from whom high or frequent counts of microorganisms are recovered, as compared to other personnel. In general, firms can prevent, monitor and solve this problem. Here are some principles to keep in mind.

Cleanrooms are defined by their low levels of both viable and nonviable particulates and these levels need to be monitored and kept under control. Humans are a chief source of particulate contamination in the cleanroom, although these contaminants may originate from a number of other sources.

Firms can take a number of measures to minimize the levels of microbiological contamination introduced by cleanroom operators. Among the widely recognized key measures to control personnel-borne contamination are:

(1) following good hygiene standards;
(2) training in proper gowning techniques;
(3) maintaining gown quality; and,
(4) following proper aseptic technique.

Per CGMPs, firms monitor and observe performance of individuals to detect problematic trends and ensure adherence to these practices. For example, retraining an individual in proper gowning technique can generally resolve the problem of adverse trends or a high spike in personnel monitoring data.

Nonetheless, despite effective execution of the above-listed measures, some individuals are natural shedders whose presence in a cleanroom may compromise product quality. It is not unusual for firms to reassign such employees to duties outside of the cleanroom.

Note that because some people are found to be

shedders, not everyone will be suitable for cleanroom duty. Ultimately, it is such differences among cleanroom personnel which underscore the need to monitor and qualify cleanroom operations on each production shift.

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

Do the CGMP regulations specify how frequently firms must review their SOPs?

References: See 21 CFR 211.180(e), General requirements [Subpart J - Records and Reports]

Yes. At the referenced section, the CGMP regulations call for at least an annual evaluation of each drug product's quality standards to determine the need for changes in product specifications or manufacturing or control procedures. The rule also requires firms to establish and follow written procedures for conducting those evaluations. Such an evaluation would be incomplete if the standard operating procedures for production and process controls were themselves not reviewed.

During your establishment inspections, when auditing for compliance with section 211.180, determine if the firm has established, and is following, those evaluation procedures. Also check to see if the procedures call for reviewing SOPs.

Keeping SOPs current can be a challenging task when manufacturers make frequent changes or have a matrix of SOPs that cross-reference each other. Ensuring that employees are furnished with current versions of SOPs can be problematic. Therefore, during your audits, you might compare dates and version numbers of SOPs that a firm's operators use, against a master list of current SOPs. Discrepancies should be noted as objectionable conditions.

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

On Stability (Policy Questions on Stability)

1) If an annual stability lot fails to meet specifications during testing at the end of the product's expiration dating period, is a failure investigation required?

Reference: 21 CFR 211.137, Expiration dating; 211.166, Stability testing; 211.192, Production record review.

Yes. Because the failure was discovered at expiry, there no longer would be concern about the failed stability lot in market channels. However, the failure at expiry signals that the product may not be stable through the end of its expiration dating period (i.e., testing indicates the product went out-of-specifications at some time between expiry and the preceding passing stability test). Consequently, the failure has implications for unexpired lots in commercial channels. CGMPs require a thorough failure investigation to include the extent to which other lots of the same and other products are affected by the failure. The investigation should prompt appropriate corrections, which may include recall of affected lots and/or shortening of the product's expiry period.

Similarly, if stability testing that is supposed to be performed prior to the end of the expiration dating period is delayed past the stability lot's expiration date, it would not be appropriate to ignore an out-of-specification test result. As above, the out-of-specification test result should be thoroughly investigated to determine its implications for lots in market channels. Such an investigation may entail testing other lots to ensure the product's stability throughout the expiration dating period.

Investigators also should be aware that a firm's recall of a stability lot that fails prior to its expiry is not a sufficient correction if the firm has not thoroughly investigated the extent to which other marketed lots are affected, and has not made corrections accordingly. Normally, not every lot of a product is monitored on stability; therefore, stability lots are intended to be representative of the product, not just the lot being tested.

To ensure that stability testing is performed at the

assigned test intervals in an approved stability testing protocol, SOPs should specify a reasonable and justifiable time frame for testing each product relative to the assigned intervals. Failure to test at the assigned intervals in an approved protocol is a CGMP deviation. Moreover, it may delay uncovering a product that falls out-of-specifications.

2) Notice of Availability of draft guidance for industry, "Stability Testing of Drug Substances and Drug Products," published in June 5, 1998 Federal Register (63FR31224)

The Federal Register availability notice states that the new draft guidance is intended to update and supersede the February, 1987 FDA guideline, "Submitting Documentation for the Stability of Human Drugs and Biologics." The new draft guidance incorporates the relevant International Conference On Harmonization stability guidances. It represent the agency's current thinking and recommendations on stability testing on human drugs and biologics. The guidance is available on the Internet at http://www.fda.gov/cder/guidance/index.htm or http://www.fda.gov/cber/guidelines.htm.

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

CGMP Sorites

The last edition of HUMAN DRUG CGMP NOTES (June 1998) introduced a particular form of deductive reasoning known as sorites. This was applied to CGMP regulations. Again, a sorites is an elliptic series of propositions arranged so that the predicate of the first premise is the subject of the next premise, and so on, until a conclusion can be obtained by uniting the subject of the first with the predicate of the last. You may find this helpful to expand your knowledge of CGMPs and simultaneously test and improve your reasoning skills. Here is another CGMP sorites:

Any building or buildings used in the manufacture, processing, packing or holding of a drug product shall have adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials and drug products and to prevent contamination. [21 CFR 211.42(a) & (b)]

The necessary prevention of mixups or contamination during drug manufacturing, processing, packing or holding of a drug product shall be assured by separate or defined areas or other control systems. [21 CFR 211.42(c)]

Separate or defined areas or such other control systems shall provide for the following operations: [21 CFR 211.42(c)]

1) Receipt, identification, storage and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging;

2) Holding rejected components, drug product containers, closure, and labeling before disposition;

3) Storage before and after release and during processing;

4) Manufacturing and processing;

5) Packaging and labeling;

6) Quarantine:

7) Control and laboratory operations; and,

8) Aseptic processing

The conclusion appears after the final article of this issue.

Toward The Electronic Government:

Can a firm that creates batch production records in electronic form archive them as

paper only?

Reference: 21 CFR 11.10(b) and (c); Federal Register, 3/20/97 (62 FR13429) at comment 71

No. Part 11 requires that electronic records be archived in electronic form. The electronic records must be protected to enable their accurate and ready retrieval throughout the relevant retention period set by the rule that applies to those records. In this case, 21 CFR 211.180 requires batch records to be kept for at least one year past the batch expiration date, or, for certain OTC products, three years after batch distribution. Part 11 also requires that firms be able to generate accurate and complete copies of electronic records in electronic as well as human readable form suitable for agency review, inspection, and copying.

It is important to note that paper printouts are seldom accurate and complete copies of electronic records (paper records lack meta-data information such as time and date stamps, audit trails, and other information not intended to be printed.)

Moreover, a major principle in part 11 is that for FDA to be able to protect and promote public health it must function on the same technological plane as the regulated industry. We couldn't do that if firms were allowed to destroy their electronic records and present to FDA investigators only paper archives because investigators would not be able to apply information technology based tools such as search and sort techniques when reviewing those records.

Finally, considering that industry urged FDA to develop part 11 in large measure to reduce the burdens of paper recordkeeping, it is unlikely that firms would want to fall back to paper for archiving purposes.

Contact for further info: Paul J. Motise, HFD-325, 301-594-0098; e-mail: motise@cder.fda.gov, or Richard Lev, HFD-325, 301-594-0098; e-mail: levr@cder.fda.gov

Where can I get a copy of the FDA "Guide to Inspections of Validation of Cleaning Processes"? Is this guide available on the FDA web page?

Reference: FDA Guide to Inspections of Validation of Cleaning Processes, July 1993

The "Guide to Inspections of Validation of Cleaning Processes" is available on the FDA web site. The following web page address provides a listing of other guides to inspections: http://www.fda.gov/ora/inspect_ref/igs/iglist.html

Follow the heading of "Drugs" and the "Guide to Inspections of Validation of Cleaning Processes" is the sixth guide. A single click on the name of the guide will give you access to the guide.

You can also order a paper copy of guide from the National Technical Information Services (NTIS) at 5285 Port Royal Road, Springfield, Virginia, USA 22161. NTIS will charge for a copy of the guide. Any questions regarding NTIS and its services can be answered by calling (703) 605-6000.

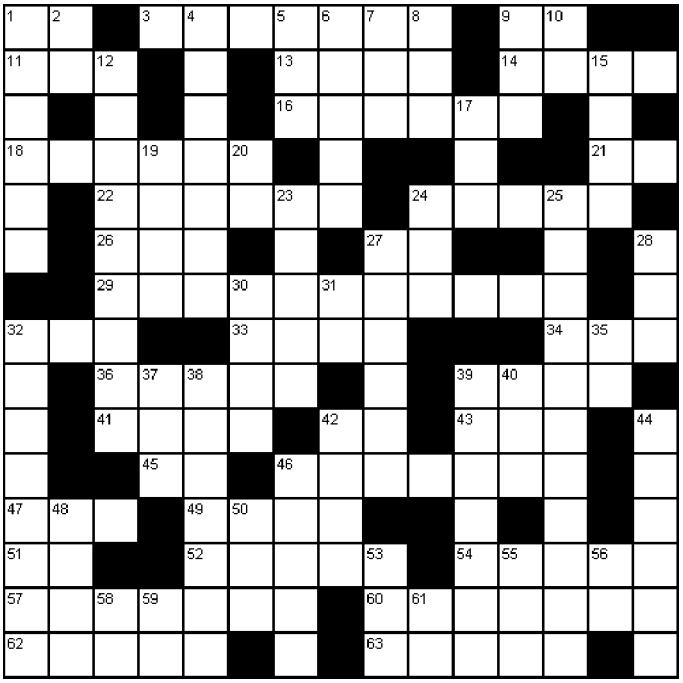
Contact for further information: Patricia L. Alcock, HFD-322, (301)594-0095; e-mail: alcockp@cder.fda.gov

Answer to CGMP Sorites:

Any building(s) used in the manufacture, processing, packing or holding of a drug product shall have adequate space for the operations listed in 21 CFR 211.42(c).

P. Motise 9/1/98
DOC ID CNOTES98.wp6

CGMP Lexicon, Some Basics



Across
1. Auditing unit
3. Lifeless
9. Musical note
11. Home for 211
13. Basic route of administration
14. Canal zone descriptor
16. Pad
18. Paper or linen
21. Qualifications doc.
22. Memory skill
24. Uniform quantity
26. FDA enforcement unit
27. Lobster state
29. Adjustment to equipment
32. Charge
33. 360s
34. Written method
36. Stainless, commonly
39. Hot stuff, in London
41. Without, in Paris
42. Iron, briefly
43. Rabbit's favorite test
45. Fast car
46. The big "C"
47. Make lacework
49. Love god
51. Western alliance
52. Harder to find
54. Waltz or tango
57. Holding
60. Not adding microbes
62. Part of TQM
63. Skin imperfections

Down
1. Key organization
2. Pilots' org.
4. Superficial dosage form?
5. Mickey's big brother
6. All ___
7. Testing place
8. Pipe shape
9. Smaller than 24 across
10. Where it's ___
12. Put through it again
15. Pruritus
17. Airport stat.
19. Chadic language
20. Briny element
23. Immediate container printing
24. Wager
25. Hired guns
27. Original recipe record
28. Compendia
30. Angers
31. Fun conveyance
32. Graphite analysis
35. Computer program
37. Identification label
38. Common route of admin
39. Mixer
40. Ecru
42. Meld
44. Fate of non-conforming stuff
46. Hearts of aseptic areas
48. Immune leader
50. Tattered cloth
53. Unprocessed
55. Likely
56. Radioactivity unit
58. You may need to work this
59. Sun god
61. Western hemisphere grp.

(The answer will be in the HTML edition on the NOTES web site: http://www.fda.gov/cder/dmpq/cgmpnotes.htm.)

DIVISION OF MANUFACTURING AND PRODUCT QUALITY, HFD-320
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		(All numbers in area code 301)
Active Pharmaceutical Ingredients	Edwin Rivera	594-0095
	Rick Friedman	"
Application Integrity Policy		
Implementation/Removal	LuAnn Pallas	594-0098
Data Integrity Cases	Bruce Hartman	827-0062
Aseptic Processing	Rick Friedman	594-0095
	Joyce Bloomfield	"
	Tracy Roberts	594-0098
Barrier Isolators	Rick Friedman	594-0095
	Joyce Bloomfield	"
Botanicals Manufacturing	Brian Hasselbalch	594-0098
CGMP Guidance Documents	Paul Motise	594-0098
Cleaning Validation	Russ Rutledge	594-2455
	Pat Alcock	594-0095
Clinical Supplies/IND CGMP	Paul Motise	594-0098
	Bruce Hartman	827-0062
Computer Validation	Paul Motise	594-0098
Content Uniformity	Monica Caphart	594-2458
	Russ Rutledge	594-2455
Electronic Records/Signatures	Paul Motise	594-0098
	Richard Lev	"
Facility Reviews	Russ Rutledge	594-2455
Foreign Inspections	John Dietrick	594-0095
Impurities	Rick Friedman	594-0095
Inspections/ Investigations	Randall Woods	827-0065
(For Cause)	John Singer	827-0071
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	Russ Rutledge	594-2455

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Medical Gases	Duane S. Sylvia	594-0095
NDA/ANDA Pre-Approval Inspections	John Singer Randall Woods Mark Lynch	827-0062 " "
Packaging	Edwin Melendez	594-2454
Penicillin Cross Contamination	Edwin Melendez	594-2454
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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
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Transdermals	Brian Hasselbalch	594-0098
Videoconferencing	Russ Rutledge Paul Motise	594-2455 594-0098
Water Quality	Rick Friedman Joyce Bloomfield	594-0095 594-0095

FAX FEEDBACK

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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:
_____
_____
_____