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
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MOTISE'S NOTEBOOK:

Welcome to another edition of Human Drug CGMP Notes, our periodic memo on CGMP for human use pharmaceuticals. Thanks for your great FAX FEEDBACK and e-mail responses. 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 (FOI) Act, our intended readers are FDA field and headquarters personnel. Therefore, we can't 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 is a forum to address your CGMP questions, update you on CGMP projects, and clarify and help you apply existing policy to your day to day inspectional and compliance activities. This publication does not supplant agency policy development/ issuance mechanisms.

Appended is a FAX FEEDBACK sheet to make it easier for us to communicate. You can also reach us by interoffice paper mail, phone at (301) 594-1089, or electronic mail.

To receive an electronic version of this document via e-mail, see the check-off line in FAX FEEDBACK. We're also on the Internet at http://www.fda.gov/cder/cgmpnotes.htm.

Thanks!

Paul J. Motise

POLICY QUESTIONS:

May repackers assign the same lot number to a lot of solid-oral dosage forms if all of the following apply: (1) there's only one repackaging operation; (2) the products are from the same original manufacturer's lot number; and (3) the repackager receives the lot in multiple shipments?

References: 21 CFR 211.130(c), Packaging and labeling operations; 211.160, General requirements (Subpart I, Laboratory Controls); Compliance Program 7356.002B, Drug Repackagers and Labelers

Yes. In the above scenario, the CGMP regulations permit the repacker to assign the same lot number to the repackaged drug products. The CGMP regulations, at 211.130(c), require that drug products be identified with a lot or control number that permits determination of the history of the manufacture and control of the batch. The fact that the repacker receives the single manufacturer's lot as separate shipments does not make each shipment a separate lot itself. However, the repacker may, at its own discretion, want to further identify each packaging run with a unique number.

Be aware, however, that repackers should be performing an identity test on a representative sample of each lot in each incoming shipment of drug products, regardless of whether identity testing was performed previously on samples from the same lot received during an earlier shipment.

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

May firms omit second person component weight checks if scale weights are automatically recorded to a computer system?

References: 21 CFR 211.101(c), Charge-in of components; and, Compliance Policy Guide 7132a.08, Computerized Drug Processing; Identification of "Persons" on Batch Production

and Control Records, 9/4/87

No. Automatically recording weight alone would not meet the specific requirements of 211.101, if the automated system did not include checks on component quality control release status and proper identification of containers.

Adequate supervision of weighing operations involves a number of quality control measures that are second nature to humans but not necessarily to machines. For example, while identifying containers, operators are likely to alert the quality control unit if the component being weighed is obviously not the color or granularity it's supposed to be, thus preventing a potential mix-up. In addition, people who observe weighing operations ensure that no objects (such as tools, cart wheels, or feet) rest on platform scales so as to cause inaccurate weights.

Per the referenced CPG, an automated system could act as a second "person" if it examines the same conditions a human being would look for, and with at least the same degree of accuracy. Apply this CPG to an automated weighting operation.

Contact for further info: Paul J. Motise, HFD-325, 301-594-1089; e-mail: motise@cder.fda.gov

What cleaning and process validation do the CGMPs require for production of a bio-batch, where only a single lot has been made?

References: 21 CFR 211.67, Equipment cleaning and maintenance; 211.100, Written procedures; deviations; Guideline on The Preparation of Investigational New Drug Products, 3/91

The agency has not articulated its expectations regarding process validation or cleaning validation with respect to bio-batches, per se. The closest relevant document is our Guideline on The Preparation of Investigational New Drug Products. In that document we said:

> At early clinical stages, where a single batch of drug product may be produced, and where significant formulation and processing changes may make batch replication difficult or inexact, only limited process validation may be possible. In such cases, limited validation, especially for such critical processes as sterilization, should be derived, to the extent possible, from product and process analogs. In addition, data obtained from extensive in-process controls and intensive product testing may be used to demonstrate that the instant run yielded a finished product meeting all of its specifications and quality characteristics. It is expected that more comprehensive process validation will be conducted as additional uniform batches are made under replicated conditions.

You may apply these principles to the bio-batch process and cleaning validation. We would expect adequate cleaning to have been performed and documented and that in-process and end product testing would show instant lots to meet specifications.

Contact for further information: John Dietrick, HFD-325, 301-594-0098; e-mail: dietrickj@cder.fda.gov

Does FDA have any guidance regarding the color of ink used to prepare CGMP production records?

Reference: 21 CFR 211.180, General requirements, Subpart J, Records and Reports

No. However, whatever ink is used should permit the records to meet the inspection, review and archiving requirements in section 211.180 of the CGMP regulations. For example, for a record to be maintained for one year past the expiration date of the related lot, per 211.180(b), one needs to be able to read the record throughout the retention period. Likewise, per 211.180(c), the records are subject to FDA photocopying or other means of reproduction. In addition, paragraph (e) of this section requires that production records be maintained such that firms may review them at least annually to determine if production and control changes

need to be made. Keeping these needs in mind, the ink that fades, can't be copied or otherwise obscures information would be troublesome.

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Are firms required to use HEPA filters in the manufacture of tablets and capsules?

References: 21 CFR 211.46, Ventilation, air filtration, air heating and cooling; 211.42, Design and construction features

No. The CGMP regulations do not specifically require tablet and capsule manufacturing facilities to maintain high-efficiency particulate air (HEPA) filtered air. The regulations, at 211.46, do require use of equipment for adequate control over air pressure, microorganism, dust, humidity and temperature when appropriate. In addition, this section calls for use of air filtration systems, including prefilters and particulate matter air filters on air supplies to production areas, as appropriate. These provisions speak to measures to prevent cross contamination, and the key phrase is "as appropriate".

Do not confuse the 211.46 provisions with 211.42(c)(10)(iii) which calls for aseptic processing areas to be equipped, as appropriate, with an air supply filtered through HEPA filters. Whereas such filtration is the norm for aseptic areas, tablet and capsule production rooms seldom need the same level of air filtration.

Despite the lack of an explicit CGMP requirement, some firms may elect to use HEPA filtered air systems as part of their dust control procedures. For example, firms may perform dust containment assessments and decide that such filters are warranted to prevent cross contamination of highly potent drugs that, even in small quantities, could pose a significant health hazard when carried over into other products.

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On Stability (A Special Report)

"Guidance for Industry Expiration Dating and Stability Testing of Solid Oral Dosage Form Drugs Containing Iron," Notice of Availability published in 7/9/97 Federal Register (62 FR 36836)

To address the hazards of acute iron poisonings, including deaths, in children less than six years of age resulting from accidental overdose of iron-containing drug products, on January 15, 1997, the Agency published in the Federal Register (62 FR 2218), a final rule for solid-oral dosage form dietary supplements and drug products containing 30 mg or more of iron per dosage unit. The rule requires that such drugs be labeled with certain warning statements and requires that they be packaged in unit-dose packaging only. The rule went into effect on July 15, 1997.

As the final rule was published only six-months before its effective date, some firms indicated they were unable comply with the unit-dose packaging requirement because the six-month period was not sufficient time to complete stability studies on the new packaging. Accelerated stability testing was not practical because the drugs containing iron, mostly multi-vitamin products, generally are not stable when exposed to the elevated temperatures used in accelerated stability testing.

Rather than delay the effective date of the unit-dose packaging requirement in the new rule, and thus delay measures that are intended to reduce the hazards of poisonings in children, the new guidance for industry was developed to provide regulatory relief from the provisions in 211.137 and 211.166. This is a temporary guidance which includes provisions for conducting concurrent stability testing through July 15, 1999, on marketed drugs containing 30 mg or more of iron. The guidance can be obtained via the CDER Internet home page (http://www.fda.gov/cder/guidance/1807fn1.pdf) or by phoning CDER's Drug Information Branch at 301-827-4573.

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Laboratory Issues

1) In the performance of system suitability, do all replicate standard injections have to be completed before any analyte sample injections are made?

References: USP 23 <621> Chromatography: - System Suitability; 21 CFR 211.160(b), General requirements, Subpart I, Laboratory Controls

Standard practice in the pharmaceutical industry, regarding this subject, is the performance of five replicate injections for an RSD (relative standard deviation) of 2.0%, or six replicate injections for an RSD of 3%, prior to any analyte sample injections. The referenced USP chapter states: "...To ascertain the effectiveness of the final operating system, it should be subjected to a suitability test prior to use and during testing ...." This indicates that the replicate standard injections should be made, and all system suitability test parameters determined prior to analyte sample injection.

However, while the information provided above would indicate that the answer to the question is a resounding "YES," and the general preference within the agency is for sequential standard injections, the agency recently agreed to an alternative system suitability test procedure with respect to replicate standard injections, as follows:

- A minimum of three replicate standard injections should be made prior to making any analyte sample injections. The remaining two [for a 2% RSD] or three [for a 3% RSD] standard injections can be made during or at the end of the analyte sample injection run.

- The analyte sample results obtained are accepted only if the RSD of the individual standard injections is $\leq$2% for five standard injections or $\leq$3% for six standard injections.

CDER's Analytical Methods Technical Committee reviewed the alternative system suitability test procedure, and accepted it based on the following:

1. It presents a harder or more challenging test to meet statistically.

2. It does not relieve the user of meeting system suitability requirements, in that the sample results obtained may only be used if the RSD of all the standard injections meets the system suitability requirements.

This alternative procedure for standard injections in the performance of system suitability tests may provide a benefit to analysts doing assays which have long run times or sample solutions with short "shelf lives." However, the maxim "caveat emptor" is applicable to this alternative procedure as "let the user beware," in that the time spent on sample analysis may be wasted, and the sample results may be worthless, because they should not be used if the system suitability requirements with respect to RSD are not met.

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When analyzing a sample by HPLC to determine variance within a batch, such as content uniformity or dissolution, and the result for one tablet is out of specifications (OOS), if there is clearly an HPLC malfunction, does the whole test need to be re-run, or only the one solution?

References: USP 23, p. 1791 (Dissolution), p. 1838 (Uniformity of Dosage Units); 21 CFR 211.160(b), General requirements, Subpart I, Laboratory Controls

In general, when the intent of the test is to measure variance within the batch, retesting is not an option. The reason is there are multiple stages of this testing. For example, the Dissolution test starts with stage S1 where 6 tablets are analyzed under wide limits, but if

these 6 don't pass S1 limits, then a second stage (S2) allows for 6 additional tablets to be tested with even broader limits. If needed, there is a third stage for 12 more tablets (S3). All stages actually used in the test (i.e., S1 , S2, and S3) are used in the evaluation, and the sample must fail all stages to be considered OOS. Content Uniformity likewise has multiple stages.

However, if the analytical instrument was clearly shown to give unreliable results by the laboratory investigation, then the test results must all be invalidated and the entire test run again, using the original sample solutions if possible. The new results are substituted for the invalidated results, and only these are used in the batch evaluation. To merely re-run the one sample solution is inadequate because the rejection of data is based on instrument malfunction. Thus, all results from this test should be considered unreliable.

Contact for further information: Russ Rutledge, HFD-325, 301-594-1089, e-mail: rutledgec@cder.fda.gov

Toward The Electronic Government:

1) Information Technology (IT) Acronymn Database On-Line

CMP Media, Inc., publishers of Information Week magazine and other IT publications, have established a web site defining some 10,000 information technology acronyms. Located at http://www.techweb.com/encyclopedia, you'll find this database to be an excellent supplement to the August 1995 Office of Regional Operations "Glossary of Computerized System and Software Development Terminology". The on-line database includes many terms, such as MIME and POP, that the 1995 glossary lacks but that you're likely to encounter.

When you enter an acronym, the site returns a concise definition, related terms that are hyperlinked, and a listing of entries that are immediately before and after the target term. Moreover, the site links selected terms to related articles (up to 200, maximum) that appeared in the publisher's magazines, enabling you to learn more about the subject and give it context to your work.

By the way, a MIME in this database is not a silent street performer, but rather "Multipurpose Internet Mail Extensions." Check the site for the full definition and links to explanatory articles.

2) Air Travel Information Web Site

If your work involves frequent air travel or you're expecting business visitors who are flying in for an important meeting, you'll want to check out this web site: http://www.thetrip.com

The site offers information about airports (maps and guides), ground transportation (taxis, car rentals, shuttles, etc.), hotels, and cities, as well as maps of nearby regions. Also offered for major cities around the globe are general facts and advisories (e.g., weather, health alerts, taxes, holidays, and embassy locations).

The most unique feature of this site is its dynamic flight status database. Once a flight is airborne, the service tracks its status by background feeds from Federal Aviation Administration databases. By entering a flight number you can determine its last recorded location, speed, altitude, nearest city, and -- most importantly -- estimated arrival time, all updated every few minutes.

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P. Motise 9/1/97
DOC ID CNOTES97.w6

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

		(All numbers in area code 301)
Applications Integrity Policy		
Implementation/Removal	LuAnn Pallas	594-0098
Data Integrity Cases	Bruce Hartman	827-0062
Botanicals Manufacturing	Brian Hasselbalch	594-0098
Bulk Drugs	Edwin Rivera	594-0095
	Rick Friedman	"
Case Management	Joseph Famulare	594-0098
CGMP Guidelines	Paul Motise	594-1089
Civil Litigation Guidance	Nick Buhay	594-0098
Cleaning Validation	Pat Alcock	594-0095
Clinical Supplies/IND CGMP	Paul Motise	594-1089
	Bruce Hartman	827-0062
Computer Validation	Paul Motise	594-1089
Content Uniformity	Monica Caphart	594-0098
	Russ Rutledge	594-1089
Criminal Litigation Support	Nick Buhay	594-0098
Electronic Records/Signatures	Paul Motise	594-1089
Facility Reviews	Russ Rutledge	594-1089
Foreign Inspections	John Dietrick	594-0095
Impurities	Rick Friedman	594-0095
Inspections/ Investigations	Randall Woods	827-0065
(For Cause)	John Singer	827-0071
Labeling Controls (CGMP)	Paul Motise	594-1089
Laboratory Issues	Monica Caphart	594-0098
	Russ Rutledge	594-1089

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

		(All numbers in area code 301)
Medical Gases	Duane S. Sylvia	594-0095
NDA/ANDA Pre-Approval Inspections	John Singer Randall Woods Mark Lynch	827-0062 " "
Packaging	Edwin Melendez	594-0098
Penicillin Cross Contamination	Duane S. Sylvia	594-0095
Pharmacies, CGMP	LuAnn Pallas	594-0098
Pre-Approval Program	Melissa Egas	594-0095
Process Validation, General	John Dietrick Paul Motise	594-0098 594-1089
Recycling Plastic Containers	Paul Motise	594-1089
Repackaging	Barry Rothman	594-0098
Salvaging	Paul Motise	594-1089
Stability/Expiration Dates	Barry Rothman	594-0098
Sterility Issues	Rick Friedman Tracy Roberts	594-0095 594-0098
Topical Drugs	Randall Woods	827-0062
Transdermals	Brian Hasselbalch	594-0098
Videoconferencing	Russ Rutledge Paul Motise	594-1089 “
Water Quality	Rick Friedman	594-0095

FAX FEEDBACK

TO: Paul Motise, HUMAN DRUG CGMP NOTES, HFD-325
FAX: 301-594-2202 (Phone 301-594-1089)

FROM: _____

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