

# HUMAN DRUG CGMP NOTES

(Volume 1, Number 4)

December, 1993

(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-323  
Addressee Database Manager: William C. Crabbs, HFD-323

## IN THIS ISSUE:

Motise's Notebook

Policy Questions On:

- ***What component impurity testing must a dosage form manufacturer perform for precursors, synthetic intermediates, and degradants either known to the firm or identified by the drug supplier? Must impurity limits, if specified, be verified by quantitation?***
- ***Is a firm required to set finished product limits or specifications for degradants identified by them or their drug supplier? Should they quantitate the degradant(s)?***
- ***Do all impurities detected in routine stability testing need to be identified and quantitated?***
- ***Do USP criteria apply throughout the shelf life of a compendial article, and, if so, must a firm do full compendial testing at each stability point?***

- ***Considering that the CGMPs require a specific identity test be performed on raw materials, if a firm uses an identity test in the current edition of the USP/NF that is known to be non-specific, is an additional specific test required?***
- ***Will the new cut labeling controls apply to inserts, cartons, and pre-printed containers?***
- ***Must raw laboratory data be maintained in bound books?***
- ***In what period of time should a firm complete a failure investigation?***

New Technology Emerging:

- ***Near Infrared (non-destructive) Analytical Methods***

Published In Final:

- ***Regulations Covering:***
  - Abbreviated New Drug Applications;  
Preapproval Inspection Requirements
- ***Compliance Policy Guide Covering:***

## HUMAN DRUG CGMP NOTES

DECEMBER, 1993

- Process Validation Requirements for Drug Products Subject to Pre-Market Approval:

### ***. Inspectional Guide Covering:***

- Liquid Injectable Radiopharmaceuticals Used in Positron Emission Tomography (PET)

Attachments:

Index of Topics Covered in the 1993 **HUMAN DRUG CGMP NOTES**

### ***FAX FEEDBACK***

(Your input requested)

---

MOTISE'S NOTEBOOK:

This is the fourth issue of a periodic memo on CGMPs for human use pharmaceuticals. Judging from your response via *FAX FEEDBACK*, I am pleased that our prior editions were so well received. We especially appreciate your suggested topics, which we will cover in this publication. You need not, however, limit the vehicle for your inquiries to *FAX FEEDBACK*. Feel free to call, write or send us e-mail.

Folks outside of FDA continue to ask to be put on our distribution list. Again, we must stress that, although the 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.

This document is intended 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*).

Thanks!

*Paul J. Motise*

### **POLICY QUESTIONS:**

***What component impurity testing must a dosage form manufacturer perform for precursors, synthetic intermediates, and degradants either known to the firm or identified by the drug supplier? Must impurity limits, if specified, be verified by quantitation?***

References: See 21 CFR 211.84 (Testing and approval or rejection of components, drug product containers, and closures) and 211.160 General requirements (for Laboratory Controls).

The nature and extent of component testing (by

## HUMAN DRUG CGMP NOTES

DECEMBER, 1993

or for the dosage form manufacturer) depends upon the applicable component specifications. The specifications may be stated in the USP/NF, an applicable NDA/ANDA, or in the firm's own records. Some of those specifications, like impurities, may be related to how the raw material was made. However, the reason for the tests do not necessarily have to be presented in terms of precursors, synthetic intermediates, and degradants. Instead, they may simply be presented at face value. For example, a USP heavy metals specification needs to be met, but the relation of the test to how the component was synthesized becomes academic at the point when the dosage form manufacturer receives the material. Thus no component test re: precursors and synthetic intermediates would be expected.

Where component specifications include limits, there are generally associated upper and lower numerical values. In these cases we expect test results to be quantified. The USP has a general 2% impurity limit where tests are performed by thin layer chromatography (TLC). As discussed below, an impurity specification and quantitative impurity testing, may be necessary if the impurity will interfere with analytical testing.

In addition, a dosage form manufacturer may accept the supplier's certificate of analysis, provided the supplier's reliability has been verified and the dosage form producer conducts at least one specific identity test.

Division Contact for Further Info: Barry Rothman, HFD-325, (301-594-0098), and Paul Motise, HFD-323, (301-594-1089).

***Is a firm required to set finished product limits or specifications for degradants identified by them or their drug supplier? Should they quantitate the degradant(s)?***

References: 21 CFR 211.160, as above, and 211.165, Testing and release for distribution.

Degradants and impurities can be problematic in two areas -- their direct effect on product quality, and their ability to interfere with analytical methods. These potential problems will govern whether or not a dosage form producer needs to quantitate degradants and impurities.

Regarding product quality, per se, where degradants/impurities are known to be toxic or otherwise adverse, limits are usually specified in the relevant compendial monograph or new drug application, and lot release testing would include quantitative tests for their presence. If there are no limits for degradants specified in the relevant compendial monograph, or new drug application, a firm would not have to set limits or quantitate degradants for purposes of product release testing.

Regarding interference with analytical methods, some impurities (at certain levels) can interfere with analytical test methods to the point of yielding a false perception of drug quality. We expect firms to know what the expected levels of impurities are, where they are detected in the analytical system, and whether or not they will interfere with quantifying active ingredients. This information is normally obtained during analytical methods validation.

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

***Do all impurities detected in routine stability testing need to be identified and quantitated?***

Reference: 21 CFR 211.166 (Stability testing), and 211.160 (as above).

There is normally no reason to identify and/or quantitate all impurities during post approval drug product stability testing. A firm only has to identify and quantitate impurities if required by a drug application or a compendial monograph. Barring any compendial or application

## HUMAN DRUG CGMP NOTES

DECEMBER, 1993

requirement, a firm only has to demonstrate that its assay methods are not subject to interference by impurities.

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

***Do USP criteria apply throughout the shelf life of a compendial article, and, if so, must a firm do full compendial testing at each stability point?***

USP drug products are required to meet all USP criteria throughout their shelf lives. However, this does not mean that stability testing protocols must include testing for all USP criteria. Stability testing protocols should require testing for those characteristics that may be affected by physical or chemical degradation over the life of the product. Those USP criteria which are not normally considered indicative of product degradation, such as identification and uniformity, are not normally included in a stability testing protocol.

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

***Considering that the CGMPs require a specific identity test be performed on raw materials, if a firm uses an identity test in the current edition of the USP/NF that is known to be non-specific, is an additional specific test required?***

Reference: 21 CFR 211.84(d)(1) (Testing and approval or rejection of components, drug product containers, and closures.)

Specific identity tests must be used only if they exist. If a given USP/NF monograph lacks a specific identity test AND no other specific identity test exists, then a non-specific test may be used. If you have a particular component in mind and are unsure as to whether or not a specific identity test is available, let us know and

we will try to find out.

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

***Will the new cut labeling controls apply to inserts, cartons, and pre-printed containers?***

Reference: Federal Register of 8/3/93, pg. 41348, Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; Revision of Labeling Controls; Final Rule.

The new cut labeling controls, effective August of 1994, will apply to all labeling that meets the definition of cut labeling. Therefore, we expect the rule to apply to inserts and cartons, and other elements of labeling, which are not applied from a roll. The new provisions do not apply, however, to pre-printed immediate drug containers such as silk-screened tubes or vials. These pre-printed items will still be subject to existing general labeling controls to prevent mix-ups.

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

***Must raw laboratory data be maintained in bound books?***

Reference: Guide to Inspections of Pharmaceutical Quality Control Laboratories, issued July, 1993

Bound notebooks are an easy and desirable way to avoid problems with data manipulation. However, this is not the only way to facilitate data security and auditing by FDA and the firm. Other acceptable methods include the use of prenumbered analytical sheets for which there is accountability. In addition, electronic systems for the storage of such data are also acceptable provided that the raw data is identified, is not subject to tampering, and if the system has been validated.

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

### ***In what period of time should a firm complete a failure investigation?***

Although the above inspectional guide indicates that such investigations should be performed within 20 business days, this (or any other uncodified) time period should not be viewed as a requirement. The CGMP regulations do not specify a time frame for investigation because what is appropriate depends on the circumstances. Any investigation, however, must be timely, based on the nature, scope, and consumer impact of the problem.

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

### **NEW TECHNOLOGIES EMERGING:**

#### ***Near Infrared (non-destructive) Analytical Methods***

The development of Near IR as an analytical tool has been a recent subject of interest to both academia and industry. As such, it is a technology which you may encounter. It is a non-destructive technique, applicable to solids, liquids, and gases. In addition, it can be used to test some products contained within blister-packs and other final packaging.

How can Near IR be used? In the near term, we expect to see this technology used for in-process controls and as a supplement to traditional analysis; examples include:

- monitoring a mixing operation to determine when a uniform blend is achieved; and
- use as an end point monitor to signal when a reaction is complete.

Note that the above applications involve a

change in components or ratios of ingredients, a lack of uniformity. The most likely near term uses will be qualitative in nature; quantitative analysis requires refinement before Near IR can be considered useful as a parallel method.

Unlike UV/Vis and IR spectra, which exhibit strong absorption at specific wavelengths leading to identification and quantification of drug substances, Near IR displays only weak absorption with a corresponding low signal to noise ratio. It therefore requires a significant amount of computing to extract useful data from these signals. Thus, Near IR has been virtually ignored until the recent development of fast, powerful, and inexpensive microcomputers.

How does Near IR work? In general, a signal is introduced onto the sample surface via optic fibers, with the reflectance, transmittance, and scattering measured. Properties which can be determined are particle sizes, density, identification, quantitation. From these properties research is centering on predicting dissolution rate, tablet hardness, assay value, impurity profile, and individual lot signatures (fingerprinting). The hoped for goal from this research is development of one analytical method that could be used to obtain an entire monograph of test results.

Division Contact for Further Info: C.D. Rutledge, HFD-323, (301) 594-1089.

### **PUBLISHED IN FINAL:**

The following CGMP related documents have been published in final form:

Abbreviated New Drug Applications;  
Preapproval Inspection Requirements; Final Rule: Federal Register of 9/8/93, pg. 47340 (Contact: Mark Lynch, HFD-324, 301-594-0098)  
This rule, effective 10/8/93, requires industry submission of a third copy of the chemistry section of applications.

## **HUMAN DRUG CGMP NOTES**

**DECEMBER, 1993**

Compliance Policy Guide 7132c.08, Process Validation Requirements for Drug Products Subject to Pre-Market Approval, issued 8/30/93 (Contact: William C. Crabbs, HFD-323, 301-594-1089).

Guide to Inspections of Liquid Injectable Radiopharmaceuticals Used in Positron Emission Tomography (PET), issued November, 1993 (Contact: John Levchuk, HFD-322, 301-594-0095).

P. Motise 12/15/93  
DOC ID CNOTES51.D93

## Index of Topics for the 1993 Issues of HUMAN DRUG CGMP NOTES

TOPIC	MONTH	PAGE
Antibiotic Monographs	February	2
Bioretention Samples	February	3
Blend Uniformity	May	5
Cut Labeling Controls	December	4
Degradant Testing	December	3
Electronic Records	February	4
	May	6
Electronic Signatures	February	4
End Product Testing	May	3
Ethylene Oxide Sterilization	February	2
Failure Investigations, Time Frames	December	5
Identity Tests, Specificity	December	4
Impurity Testing	December	2
	December	3
Impurity Testing, Stability	December	3
Labeling Regulations	February	3
Laboratory Notebooks	December	4
Metrification, Clean Rooms	May	5
	September	4
Near Infrared Analytical Method	December	5
Orange Book, Electronic	September	6
Plastic Containers, Recycled	May	4
Product Development Reports	February	2
Publications, Available List	February	5
Recycled Plastic Containers	May	4
	September	5
Repacking	February	4
Retrospective Review	February	3
Retrospective Validation	May	3
Solid Dosage Form Inspection	February	5
Speeches, Available List	February	5
Stability Pilot Batches, Antibiotics	September	2
Stability Pilot Batches, Non-antibiotic	May	2
Stability Testing, Compendial Standards	December	4
Stability, Unit Dose Repacking	September	3
Storage Temperatures	May	4
Tablet Weight Check Controls	September	4
Third Copy of NDA	February	3
Topical Drug Products	February	5
Validation Documentation	February	4
Warehouse Storage Temperatures	May	4
Warehousing CGMPs	September	3

**FAX FEEDBACK**

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

FROM: \_\_\_\_\_

AT: \_\_\_\_\_ MAIL CODE: \_\_\_\_\_

PHONE: \_\_\_\_\_ FAX: \_\_\_\_\_

E-MAIL ADDRESS: \_\_\_\_\_

To receive the electronic version of HUMAN DRUG CGMP NOTES via E-mail, check here \_\_\_\_.

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.

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

Component Impurity Testing \_\_\_\_ Laboratory Records Management \_\_\_\_  
Stability Testing \_\_\_\_ Failure Investigations \_\_\_\_  
Specific Identity Testing \_\_\_\_ Near IR Analysis \_\_\_\_  
Cut Labeling Controls \_\_\_\_ Other \_\_\_\_\_

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

\_\_\_\_\_  
\_\_\_\_\_