

# 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  
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Office of Compliance  
Center for Drug Evaluation and Research

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FAX FEEDBACK  
(Your input requested)

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 still great and we 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, 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 (FOI) 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 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 us by interoffice paper mail, using the above address, by phone at (301) 594-1089, or by electronic mail.

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:

Does FDA enforce USP General Notices?

References: See U.S.P. XXIII

Yes. The USP General Notices provide in summary form the basic guidelines for interpreting and applying the standards, tests, assays, and other specifications of the USP so that these general statements do not need to be repeated in the various monographs and chapters throughout the book. Where exceptions to the General Notices exist, the wording in an individual monograph or general test chapter takes precedence.

This concept is further emphasized in the introduction to the General Information chapters. Here it states, "The official requirements for Pharmacopeial articles are set forth in the

General Notices, the individual monographs, and the General Tests and Assays chapters of this Pharmacopeia." The General Tests and Assays chapters are those numbered lower than 1000.

Contact for Further Info: Robert Rippere, HFD-354, 301-594-0104, e-mail: rippereb@cder.fda.gov

Where are the requirements of current good manufacturing practice (CGMP) stated? How are they applied?

References: See 21 CFR 210 and 211; 21 U.S.C. Federal Food, Drug, and Cosmetic Act, as amended; 21 U.S.C. 331(k)

The Food, Drug and Cosmetic Act establishes the requirement that all drugs must be made under "current good manufacturing practice".

Specific CGMP requirements for human drugs are established in the regulations, "Current Good Manufacturing Practices for Finished Pharmaceuticals" (21 CFR Parts 210 and 211). These regulations state requirements because they are substantive (i.e., they are binding regulations).

What FDA can enforce as CGMP is derived from the general CGMP requirement of the Act, as well as the CGMP regulations. However, if a given practice is not specified in the regulations, FDA has the burden of proving that the practice is, by law, nonetheless CGMP.

During your inspections, be sure that your CGMP related inspectional observations state a failure or an inadequacy against a requirement, i.e., against a provision of the CGMP regulations or CGMP in general.

While the agency publishes a variety of guidance documents (guidance to industry, guides to inspection, etc) containing important recommendations about how to meet individual requirements of the CGMP regulations, the recommendations are neither binding nor the

basis for a CGMP requirement. They are not the only way a requirement may be met. If a firm presents an alternative, it should be evaluated based on its merits.

Other bodies like the USP, trade associations, and individuals publish information on various aspects of drug manufacturing. Such information should not be viewed as the basis for a CGMP requirement by the sole virtue of having been published. No FDA guidance document or external treatise should be referenced in an inspectional observation as the basis for a CGMP requirement unless, by coincidence, the practice at issue is, in fact, required by the regulations or law.

When establishing CGMP requirements, FDA uses the standard of whether a practice is "feasible and valuable" in contributing to assurance of drug safety, quality and purity. Although we consider what is actually done in the industry, before we view a practice as CGMP it need not be predominant in the industry.

The CGMP regulations embody minimum requirements, standards below which products are deemed adulterated.

Only those parts of the CGMP regulations which apply to operations in which a manufacturer is engaged are requirements for that manufacturer.

The CGMP regulations apply to:

- \* both prescription and OTC drug products, including homeopathic drugs;
- \* manufacturing facilities of all sizes, large or small.
- \* the manufacture of drug products in the investigational phase of development when they are produced for clinical trials.
- \* the manufacture of drug products in foreign facilities where the products are distributed in the United States, or otherwise introduced into interstate

commerce.

While the requirements in the Act to observe CGMP apply to wholesales, retailers, pharmacies and hospitals (by the application of Sec. 301(k)), the CGMP regulations don't apply unless such organizations engage in manufacturing operations beyond the usual dispensing or selling of drugs at retail.

The CGMP requirements of the Act apply to the manufacture of active pharmaceutical ingredients (APIs) and other bulk drugs, but the CGMP regulations do not apply. However, there are numerous instances where CGMP for APIs and other bulk drugs parallel the those in the CGMP regulations. For this reason, we use the standards in the CGMP regulations as guidance for inspecting facilities engaged in this type of manufacturing. We are also preparing a specific CGMP guidance document for APIs.

The CGMP regulations do not apply to OTC products if those products and all their ingredients are ordinarily marketed and consumed as human food ( e.g., some candy cough drops).

Where a class of drugs is exempt from a given section of the regulations, the exemption is stated in the section. For example, homeopathics, some allergenics, and some OTCs are exempt from section 211.137 as stated in that section.

Contact for Further Info: Nicholas Buhay, HFD-325, 301-594-0098; e-mail: buhay@cder.fda.gov

Is it acceptable for a firm to use drug components, drug product containers, or drug product closures simultaneously with testing and/or prior to determination of conformity to all specifications?

References: Federal Register Vol.43 No. 190, 9/29/78, 45013 [at 45045].

No. It is not acceptable to use drug components,

containers, or closures prior to completion of all testing to determine conformance to established specifications. The above preamble to 21 CFR 211.84, clearly states that the use of drug components, containers, or closures prior to completion of testing for conformity to specifications violates the precept of good quality control because untested and possibly noncomplying materials would be used in drug product processing. This type of procedure substantially increases the risk to the consumer that an unsatisfactory lot might erroneously be released.

Contact for Further Information: Luann Pallas, HFD-325, 301-594-0098, e-mail: pallasl@cder.fda.gov

Is there an acceptable substitute for DOP to integrity test HEPA filters?

Reference: 21 CFR 211.46, Ventilation, air filtration, air heating and cooling, and 211.67 Equipment cleaning and maintenance.

Yes. Dioctyl phthalate aerosols also called Di (2-ethylexyl) phthalate, di-sec octyl phthalate, DOP, or DEHP, have long been used to test the integrity of high efficiency particulate air (HEPA) filters. Concern about the potential health effects to people working with DOP test aerosols has led to a search for a safer equivalent replacement.

The prime candidate from U.S. Army testing with assistance from various private companies was a Henkel Corporation (Emery Group) product called Emery 3004 PAO. This product is a polyalphaolefin (POA) in the 4 centistoke (4 cSt) viscosity grade, used primarily as a lubricant base stock for oils, lubricants, and electrical/hydraulic fluids.

As cited in the March 1994 Human Drug CGMP Notes, based on data submitted to FDA we have concluded that Emery 3004 (POA) can replace DOP in HEPA integrity testing.

The original manufacturing site which produced the Emery 3004 (POA) for the data submitted has changed since the study and Emery 3004 (POA) is now manufactured at a different site. Discussions with the Army and the companies involved in the original studies indicate the product remains the same from the new site of manufacturing. CDER has also compared the original specifications and the new site specifications along with data from the Material Safety Data Sheets and agrees that there is no significant difference in the product from either site.

The Chemical Abstracts Service (CAS) number which identifies this product also remained as 68649-12-7.

Other reported alternatives used in the industry include DOS ( Di (2-ethylhexyl) sebacate ) and Ondina Oil. However, no manufacturer has yet submitted all the necessary data to evaluate these alternatives.

As such, Emery 3004 POA with the CAS number 68649-12-7 still remains an acceptable replacement for DOP.

Contact for further information: Michael J. Verdi, HFD-322, 301-594-0095; e-mail: [verdim@cdcr.fda.gov](mailto:verdim@cdcr.fda.gov)

When do the changes in USP water monographs chemical testing take effect?

Reference: USP XXIII/NF XVIII, Supplement 5.

In Supplement 5, the USP published changes in testing water covered by several monographs, including Purified Water and Water for Injection, effective November 15, 1996. The revisions include: 1) a new test for Total Organic Carbon (TOC) <643> which will ultimately replace Oxidizable Substances (OS); and 2) a Water Conductivity <645> analysis, replacing several wet chemistry tests. The test for pH remains. These changes in testing were made to take advantage of modern analytical technology and

for better cost effectiveness. The changes do not tighten standards for pharmaceutical water.

The test for OS has not been deleted with the addition of the test for TOC. The intent of the USP is to accommodate the interim use of OS while firms phase-in TOC. It is expected that the deletion of the OS test from the USP will become official in May 1998. At present either of these tests is acceptable to CDER and CBER. CDER and CBER expect compliance with the Water Conductivity test.

On-line meters for testing water conductivity or TOC should be installed in a location in the water system which reflects the quality of the process water. If worst-case placement is not used, laboratories should continue performing these USP water monograph tests as part of a routine sampling program which covers each point-of-use.

Contact for Further Information: (for CDER) Richard L. Friedman, HFD-322, 301-594-0095; e-mail: [friedmanr@cdcr.fda.gov](mailto:friedmanr@cdcr.fda.gov); or, (for CBER) Walter Lange, Division of Establishment Licensing, HFM-205, (301) 827-3031

On Stability (Policy Questions on Stability)

1) Is it proper to cite a firm on an FDA-483 for not demonstrating that its stability test methods are stability indicating? What if the method is the approved assay method in the firm's new drug application?

Reference: 21 CFR 211.166(a)(3), Stability testing

CGMPs require the use of stability-indicating methodology for stability testing. In general, it would be appropriate to cite firms if they don't comply with this requirement. However, because the technology may not have been available, older applications lacking stability-indicating methodology may have been approved. Absent documentation that the methods are stability indicating, districts should

contact HFD-320 and the appropriate review division to coordinate resolution of the matter before determining if an FDA-483 citation is appropriate.

2) Is it appropriate to cite a firm on an FDA-483 when a product passes a regulatory release specification but not a firm's more stringent internal release limits?

Reference: 21 CFR 211.160(b), General requirements; 211.165(a) Subpart I--Laboratory Controls

An FDA-483 observation would be appropriate if failure to meet the tighter internal specification means that at some point in its expiry period the drug product may not meet the wider regulatory specification.

For a variety of reasons, firms may set internal product release specifications that are more stringent than such regulatory specifications as those in the USP or approved new drug applications. For example, the tighter specifications may be established in anticipation of product degradation over time. Thus, if a product meets those tighter specifications upon release for distribution, it is likely to still meet the less stringent regulatory specifications throughout its shelf life.

In other instances, a firm may set tighter internal release specifications, not for reasons of stability described above, but as a process control indicator -- an alert limit that signals attention to potential problems but that does not necessarily indicate process or product failure. Absent an indication of such failure, deviation from internal release specifications would not be grounds for an FDA-483 observation because the CGMPs do not require a firm to establish such tighter controls in the first place, and we would not want to discourage firms from adopting measures to improve their process controls. We would expect, however, that firms follow written procedures regarding those tighter specifications that they do set and how the firm responds to deviations from such limits.

Therefore, in assessing whether deviation from an internal specification is objectionable, be sure to determine and consider why the firm established the tighter internal release specification initially.

Division contact for stability matters: Barry Rothman, HFD-325, 301-594-0098, e-mail: rothmanb@cder.fda.gov

#### Active Pharmaceutical Ingredient (API) Issues

1) Should APIs be tested solely for those impurities, if any, named in their USP monographs, or must batches be sufficiently characterized for purity?

Reference: USP XXIII, General Notices (p.6 and 7), and Supplement 5; Guide to Inspections of Bulk Pharmaceutical Chemicals (Sept. 1991)

Some specific ordinary, related compound, and organic volatile impurity tests are included in USP drug substance and dosage form monographs. API producers should establish analytical methods and specifications to test for other impurities potentially found in the drug substance, but not named in the USP. We expect that prior to being used in dosage form production, APIs will have met both groups of tests.

"Impurity" is a broad term essentially meaning anything present in the drug substance that is not the chemical entity itself (other than water). The profile of drug substance purity at release, developed over the course of process development and process validation studies, is known as an "impurity profile." Regarding monographs published in USP XXIII, the Pharmacopeia's General Notices Section states:

"It is manifestly impossible to include in each monograph a test for each impurity, contaminant, or adulterant that might be present, including microbial contamination. These may arise from a change in the

source of material or a change in processing, or may be introduced from extraneous sources. Tests suitable for detecting such occurrences... should be employed in addition to the tests provided in the individual monograph."

Sufficient analytical methods should be in place to detect and quantify any impurities which may result from the production of an API batch. These impurity testing methods, employed on a batch-by-batch basis, allow for assessing process consistency by impurity profile comparisons. The results of these tests are, in turn, the impetus for an appropriate investigation when atypical levels of individual or total impurities are obtained.

It is noteworthy that USP Supplement 5, official November 15, 1996, includes an addition to the General Notices Section referenced above. This revised section further underscores the need for manufacturers to monitor impurities beyond those named in the USP product monograph. It essentially states that, for most APIs, "major impurities" (0.1% level or greater) which are not listed in the product monograph and cannot be reliably analyzed by its methods should be named, quantified, and included on the certificate of analysis of the official substance. In contrast to "major impurities," a lower qualification threshold, with specialized test methods and more stringent specifications, should be performed for those impurities for which toxicity is a concern.

We'll address the issue of API impurities, including impurity profiles, in future editions of HUMAN DRUG CGMP NOTES.

Contact for Further Information: Richard L. Friedman, HFD-322, 301-594-0095; e-mail: [friedmanr@cderr.fda.gov](mailto:friedmanr@cderr.fda.gov)

## 2) API Guidance Document Update

A draft of the Guidance for Industry; Manufacture, Processing or Holding of Active Pharmaceutical Ingredients, was released for

discussion purposes only at a September 23 - 24, 1996 meeting in Canberra, Australia, sponsored by the Pharmaceutical Inspection Convention to discuss world harmonization of GMP standards for active pharmaceutical ingredients. It was later distributed to several industry trade associations. By the time you read this article, the document should have been posted to CDER's Internet world wide web site at <http://www.fda.gov/cder>.

The discussion draft does not represent a final agency position on any matter concerning active pharmaceutical ingredients.

Comments to the guidance document may be submitted to CDER's Division of Manufacturing and Product Quality, HFD-320, API Comments, 7520 Standish Place, Rockville, MD 20855, until December 11, 1996.

## 3) API Guidance Document Fundamental Concepts

The industry guidance document incorporates two fundamental concepts: (1) Application of CGMP controls to all manufacturing steps, beginning with starting materials; and (2) validation of critical process steps. This approach recognizes that the level of control in a multi-step active pharmaceutical ingredient process increases throughout the synthesis as you proceed from early intermediate steps to final isolation and purification steps. For example, early processing steps may require less frequent and less comprehensive in-process monitoring, tests and documentation, whereas more complex steps in later isolation and purification stages would require more sophisticated controls, in-process evaluation, and documentation. The control needed is also highly dependent on the manufacturing process itself.

Under this approach manufacturers should identify, control, and validate critical process steps that could affect the critical quality attributes of the active pharmaceutical ingredient. Critical process steps would be

determined by sound scientific judgement and are not limited to final stages. They may, for example, include intermediate steps that introduce an essential molecular structural element, result in a major chemical transformation, or introduce or remove significant impurities from the product. In general, data to identify critical process parameters/steps are derived from research or pilot scale batches. This early data and work are confirmed or refined during manufacturing scale-up, and consistency of the process is shown by data generated from production size batches.

Contact for Further Information: Edwin Rivera, HFD-322, 301-594-0095; e-mail: rivera@cder.fda.gov

Gas What? (Policy Questions on Medical Gases):

1) Has FDA modified the federal caution statement requirement for medical oxygen?

Reference: Section 503(b)(4) of the Food, Drug, and Cosmetic Act; 21 CFR Sections 201.(b)(1) and 211.130.

Yes. On September 19, 1996, FDA informed the Compressed Gas Association that a final decision had been reached on its citizen petition. The label for medical oxygen should bear the statement, "For emergency use only when administered by properly trained personnel for oxygen deficiency and resuscitation. For all other medical applications, Caution: Federal law prohibits dispensing without prescription."

A firm may meet this requirement by applying an additional sticker to the label which contains the above statement, until new labels are ordered.

2) What are FDA requirements for opening an oxygen spa bar in the U.S.? Can industrial grade oxygen or oxygen concentrators be substituted for medical oxygen in such use?

Reference: Section 503(b)(1)(B) of the Food, Drug, and Cosmetic Act

Oxygen spa bars have been around in Japan for many years, and are starting to show up in Canada. These establishments don't administer oxygen for medical or emergency use in the traditional sense. We have received inquiries as to FDA's requirements regarding this type of operation. This is a very interesting business concept; however, medical oxygen is defined as a prescription drug which requires a prescription in order to be dispensed, except as described above, for emergency use.

Oxygen spa bar advertising that makes unproven medical claims, e.g., a skin care treatment, anti-aging, hangovers, fatigue, migraine headaches, etc. would render the oxygen a new drug.

Further, we would strongly discourage the use of industrial grade oxygen due to the lack of control exercised over industrial high pressure cylinders and the possibility of contamination occurring. As for the use of oxygen concentrators, these are prescription devices and as such would require a prescription.

Division Contact for Further Info: Duane Sylvia, HFD-325, 301-594-0095; e-mail: sylvia@cder.fda.gov.

Toward The Electronic Government:

Year 2000, a potential CGMP Problem?

Much has been written about the year 2000 (y2k) problem regarding how some software performs date related computations. Be aware of potential y2k problems firms may face in the context of CGMP records and computations. Here's why.

When mainframe computers were in the majority and computer memory was at a premium, software frequently represented dates in formats (such as DDMMYY) that used only two digits to represent the year. Date related computations were calculated reliably using this format. For

example, if you were born in 1960 the software might calculate your age by subtracting the last two digits of your birth year from the last two digits of the current year (for example, 96-60=36). However, using this method when the current year is 2000 would yield a negative number (00-60=-60), with unpredictable consequences. Date sorting, too, can be erroneous. The years 1965, 1905 and 1966 would, for example, correctly sort in ascending order as 05, 65 and 66, but adding 2015 would incorrectly yield 05, 15, 65, and 66.

Some firmware may also have difficulty with y2k. Basic Input and Output Systems (BIOSes) may, by ignoring the century indicating bit, not accurately read or set some older real-time clock chips. In addition, some firmware reportedly "wraps" back to 1994 from 1999.

To test your machine, set its clock to 11:58 p.m., December 31, 1999. Turn off your computer and, after waiting a few minutes, turn it back on and see if the date and time crossed the millennium correctly.

Drug establishments should know how their software calculates dates and, in particular, if their systems are susceptible to the y2k problem. Although we don't expect many such systems to exist in what is essentially a very progressive industry, you may nonetheless encounter some

older systems, or newer CGMP related software, that use two digits to represent the year. Vulnerable programs will likely need to be changed to retain the accuracy of such CGMP computations as determining: expiration dates, equipment calibration and maintenance dates, records and reserve sample retention intervals, and trends to assess the need for manufacturing changes.

During your inspections watch out for signs of y2k errors that may begin to show up, even now. However, remember that an important element of software validation is establishing specifications based on defined needs. As long as software date related specifications meet a firm's "current" needs and you find no signs of date computation related CGMP errors, the y2k matter would not be appropriate for FDA-483 citations. However, the converse holds true -- when a firm's previously validated CGMP software no longer meets its current needs, or when y2k derived errors occur.

For more on y2k, see the General Services Administration Internet site at <http://www.itpolicy.gsa.gov>.

Division Contact For Further Info: Paul J. Motise, HFD-325, 301-594-1089; e-mail: [motise@cder.fda.gov](mailto:motise@cder.fda.gov).

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FAX FEEDBACK

TO: Paul Motise, HUMAN DRUG CGMP NOTES, HFD-325  
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FROM: \_\_\_\_\_

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

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

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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:

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

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