



U.S. Food & Drug Administration

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Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance - Laboratory Controls

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1. Many leading analytical balance manufacturers provide built-in "auto calibration" features in their balances. Are such auto-calibration procedures acceptable instead of external performance checks? If not, then what should the schedule for calibration be?

The auto-calibration feature of a balance may not be relied upon to the exclusion of an external performance check (211.68). For a scale with a built-in auto-calibrator, we recommend that external performance checks be performed on a periodic basis, but less frequently as compared to a scale without this feature. The frequency of performance checks depends on the frequency of use of the scale and the criticality and tolerance of the process or analytical step. Note that all batches of a product manufactured between two successive verifications would be affected should the check of the auto-calibrator reveal a problem. Additionally, the calibration of an auto-calibrator should be periodically verified--a common frequency is once a year--using National Institute of Standards and Technology (NIST)-traceable standards or NIST-accredited standards in use in other countries.

References:

- 21 CFR 211.68: Automatic, mechanical, and electronic equipment
- 21 CFR 211.160(b)(4): General requirements (Lab Controls)
- USP Chapter <41> Weights and Balances
- See also: ASTM standard E 617: Standard Specification for Laboratory Weights and Precision Mass Standards (this standard is incorporated into the USP by reference; other widely recognized standards may be acceptable)

Contact for further information:

Division of Manufacturing and Product Quality (HFD-320): CGMP Subject Contacts
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm096102.htm>

2. Do CGMPs require that forced degradation studies always be conducted of the drug product when determining if a drug product stability test method is stability-indicating?

No. Drug product stress testing (forced degradation) may not be necessary when the routes of degradation and the suitability of the analytical procedures can be determined through use of the following:

- data from stress testing of drug substance
- reference materials for process impurities and degradants
- data from accelerated and long-term studies on drug substance
- data from accelerated and long-term studies on drug product

Additional supportive information on the specificity of the analytical methods and on degradation pathways of the drug substance may be available from literature sources.

Section 211.165(e) of the CGMP regulations states that the accuracy, sensitivity, specificity, and reproducibility of test methods shall be established and documented. Further, section 211.166(a)(3) requires that stability test methods be reliable, meaningful, and specific, which means that the content of active ingredient, degradation products, and other components of interest in a drug product can be accurately measured without interference, often called "stability-indicating."

The CGMP regulations do not specify what techniques or tests are to be used to ensure that one's test methods are stability-indicating. However, evaluating the specificity of the test methods during forced degradation studies (i.e., exposing drug to extremes of pH, temperature, oxygen, etc.)

of drug substance and drug product often is necessary to ensure that stability test methods are stability-indicating. But in certain circumstances conducting a forced degradation study of just the drug substance may be sufficient to evaluate the stability-indicating properties of a test method. Generally, in determining whether it is necessary to conduct forced degradation studies of the drug product, the specificity of the test method should be evaluated for its ability to assay drug substance, degradants, and impurities, in the presence of each other, without interference. The evaluation also should provide assurance that there is not a potential for interaction between drug substance, degradants, impurities, excipients, and container-closure system during the course of the shelf-life of the finished drug product.

Last, the rationale for any decision made concerning the extent of the forced degradation studies conducted as well as the rationale for concluding that a test method is stability-indicating should be fully documented.

References:

- 21 CFR 211.137: Expiration dating
- 21 CFR 211.165(e): Testing and release for distribution
- 21 CFR 211.166(a)(3): Stability testing
- Compliance Policy Guide, Section 480.100 (7132a.04), *Requirements for Expiration Dating and Stability Testing*

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3. When performing the USP <788> Particulate Matter in Injections test for a Large Volume Parenteral (LVP), is it acceptable to take the average among the units tested to determine if the batch meets its specification for this attribute?

No. It is not acceptable to take the average among the LVP units tested in each batch/lot when following this method because the purpose of this method is to measure and limit intra-batch variability.

"Particulate matter" refers to small, sub-visible particles. USP <788> provides two tests for detecting such particulates--light obscuration and microscopic assay. Both are generally accepted for use in testing LVPs and small volume parenterals (SVP) for the determination of sub-visible particulate matter. Normally, samples are first tested by the light obscuration method; if the sample fails the specified limits, the microscopic assay method can then be used. However, the microscopic method can be the sole test if there is a documented technical reason or interference from the product under test that would make the light obscuration method unsuitable or the results invalid.

Confusion about when averaging data is and is not acceptable is probably due to the sample preparation method for the light obscuration test (USP <788>). At least 2, 5-mL aliquots from each sampled unit or the pooled sample (see below) are to be used in the particulate count determination, and the results from these aliquots are to be averaged for comparison with the specification. Note that the average is of the results from examining each aliquot and not between units. (The results of the first aliquot examined by light obscuration are to be discarded, and the subsequent aliquots--2 or more--are retained.) Pooling units prior to analysis is permitted only if the volume in each unit is less than 25 mL, in which case 10 or more units may be pooled. If the volume in the SVP or LVP is 25 mL or more per unit, single units are to be examined by this method (USP <788>).

Results **among** the test units cannot be averaged because particulate matter is assumed to be non-uniformly dispersed throughout the lot. The intent of assessing results from each individual unit is to ensure adequate representation of the lot and to detect potential variation within a lot.

As to the number of individual units to be tested for LVP and SVP units having a volume of 25mL or more, the USP states that the number of units tested depends on "statistically sound sampling plans," and "sampling plans should be based on consideration of product volume, numbers of particles historically found to be present in comparison to limits, particle size distribution of particles present, and variability of particle counts between units." The USP also suggests that the total number of units tested for any given batch may be less than 10 units (for LVP and pooled SVPs) with proper justification. This is consistent with the CGMP requirement for statistical sampling plans (see 211.165).

Reference:

- 21 CFR 211.160: General requirements (laboratory controls)
- 21 CFR 211.165(c),(d): Testing and release for distribution
- USP <788> Particulate Matter in Injections
- For information only: Draft Guidance: Guidance for Industry: Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production

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Division of Manufacturing and Product Quality (HFD-320): CGMP Subject Contacts
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm096102.htm>
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4. Can Total Organic Carbon (TOC) be an acceptable method for detecting residues of contaminants in evaluating cleaning effectiveness?

Yes. Since the publication of the inspection guide on cleaning validation in 1993, a number of studies have been published to demonstrate the adequacy of TOC in measuring contaminant residues.

We think TOC or TC can be an acceptable method for monitoring residues routinely and for cleaning validation. But in order for TOC to be functionally suitable, it should first be established that a substantial amount of the contaminating material(s) is organic and contains carbon that can be oxidized under TOC test conditions. This is not a trivial exercise because we know that some organic compounds cannot be reliably detected using TOC.

TOC use may be justified for direct surface sample testing as well as indirect (rinse water) sample testing. In either case, because TOC does not identify or distinguish among different compounds containing oxidizable carbon, any detected carbon is to be attributed to the target compound(s) for comparing with the established limit. Thus, a firm should limit 'background' carbon (i.e., carbon from sources other than the contaminant being removed) as much as possible. The established limit, or the amount of residue detected for comparison to the specification, should correct for the target material's composition of carbon. As for any cleaning method, recovery studies are necessary (211.160(b)). If TOC samples are being held for long periods of time before analysis, a firm should verify the impact of sample holding time on accuracy and limit of quantitation.

References:

- 21 CFR 211.67: Equipment cleaning and maintenance.
- 21 CFR 211.160(b): General requirements (Laboratory Controls)
- USP <643> Total Organic Carbon
- *Guide to Inspections of Cleaning Validation, 1993*

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5. Would a paramagnetic or laser oxygen analyzer be able to detect all possible contaminants or impurities in a medical gas?

No. Although, paramagnetic and laser oxygen analyzers are very accurate and reliable when calibrated correctly, these types of analyzers can only detect the identification and strength of oxygen. They are unable to detect contaminants or impurities that may be present, such as hydrocarbons or arsenic compounds. According to the USP General Notices, Foreign Substances and Impurities section, "it is manifestly impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present." The USP monograph test for oxygen does not include an impurity screen and other analyzers may need to be used. For example, assays for hydrocarbon impurities are routinely conducted during the oxygen manufacturing process even though the USP does not list hydrocarbons as an impurity. Also, alternative methods may be needed to test high-pressure cylinders for cleaning solution residues.

References:

- 21 CFR 211.160: General requirements (Laboratory Controls)
- 21 CFR 211.165: Testing and release for distribution
- United States Pharmacopoeia

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6. Can up to twelve month expiration-dating be assigned to oral solid and liquid dosage forms repackaged into unit-dose containers based on guidance in the May 2005 draft revision of Compliance Policy Guide, Section 480.200 (7132b.11), "Expiration Dating of Unit Dose Repackaged Drugs"?

No. In May 2005, a Notice of Availability of the draft revision of FDA's Compliance Policy Guide Section 480.200 (CPG 7132b.11), "Expiration Dating of Unit-Dose Repackaged Drugs," was announced in the Federal Register. The draft CPG specifies certain conditions when it may be possible to assign up to twelve month expiration-dating to non-sterile solid and liquid oral drug products repackaged into unit-dose containers without conducting new stability studies to support the length of expiration-dating on the repackaged products. The draft CPG was prompted by United States Pharmacopoeia (USP) standards for assigning up to a twelve month "beyond-use date" to non-sterile solid and liquid oral dosage forms dispensed in unit-dose containers. ("Beyond-use date" is USP's pharmacy dispensing term for specifying a date on a prescription container beyond which a patient should not use the product.) If finalized, FDA's draft CPG would replace the current version of CPG Section 480.200. The current version of CPG Section 480.200 was finalized in March 1995 and provides conditions under which FDA will not initiate action for assigning up to six month expiration dating for drug products repackaged into unit-dose containers without conducting new stability studies.

FDA is conducting a stability study of certain commercially repackaged drugs to determine the suitability of the draft revision of CPG Section 480.200. Until the stability study is complete and FDA evaluates all comments submitted to the public docket in response to the May 2005 Federal Register Notice of Availability, the agency does not intend to make a final decision on the draft revision of CPG Section 480.200. Consequently, at this time and until FDA announces a final decision on the draft CPG, the current CPG Section.480.200, which was finalized in March 1995, is in effect.

References:

- Compliance Policy Guide section 480.200 (CPG 7132b.11)
- Federal Register: May 31, 2005 (Volume 70, Number 103) pages 30953-30954
- CFR 211.137 and 211.166

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7. Is it ever appropriate to use an unvalidated method to test a drug component or product?

The CGMP regulations require the use of validated methods when performing routine testing of raw material, in process material, and finished product (21 CFR 211.160, 211.165(e), and 211.194) for manufacturing finished drug products. Method validation studies establish proof that a method is suitable for its intended purpose. The purpose is generally to measure a particular material's conformance to an established specification (see FDA Guidance for Industry, ICH Q2 (R1)).

FDA recognizes, however, that test methods developed based on scientifically sound principles (e.g., sufficient accuracy and precision) but which are not fully validated may be suitable for use in certain instances during an investigation of a potential quality problem or defect. For example, investigation of an atypical impurity or possible contaminant of a drug product or any of its components (e.g., OSCS in heparin) may indicate the need for additional methods beyond routine quality control tests. Such testing may be critical to promptly and adequately evaluate the problem and protect public health. Full evaluation of a method's robustness and reproducibility may not initially be feasible or appropriate when conducting tests in certain investigations.

When a company, for whatever reason, tests drug components or products using an unvalidated method, it is important to recognize the possibility of greater uncertainty in the test results derived from these unvalidated test methods, as compared to validated test methods. Nevertheless, the resulting data may yield important information indicating the need for prompt corrective action. Accordingly, we expect all such test results on drug components or products to be reviewed to assess the need for follow-up action (211.192 and 211.180(e)).

References:

- 21 CFR Part 210 <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=210&showFR=1>
- 21 CFR Part 211 <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211>
- ICH Q7, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129098.pdf>
- Guidance for Industry, ICH Q2 (R1), *Validation of Analytical Procedures: Text and Methodology*

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065005.htm>

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8. Did the FDA withdraw the 1987 Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human Parenteral Drugs, Biological Products, and Medical Devices?

Yes, the FDA withdrew the 1987 Guideline. The 1987 Guideline is considered obsolete and does not reflect the Agency's current thinking on the topic.

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9. Where can drug manufacturers find information regarding endotoxin testing?

The United States Pharmacopeia (USP) publishes endotoxin testing recommendations and acceptance criteria in General Chapter <85> *Bacterial Endotoxins Test*. USP <85> provides methods and calculation of limits for drugs. FDA may, as needed, provide additional guidance to clarify the Agency's current thinking on use of LAL, recombinant LAL, and other endotoxin testing methods.

References:

- United States Pharmacopeia, General Chapter <85> *Bacterial Endotoxins Test*. United States Pharmacopeial Convention: Rockville, MD.

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