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

Equipment

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?
 2. Is there a list of CDER-approved drug manufacturing equipment?
 3. Can Total Organic Carbon (TOC) be an acceptable method for detecting residues of contaminants in evaluating cleaning effectiveness? (updated 5/18/2005)
 4. A firm has multiple media fill failures. They conducted their media fills using TSB prepared by filtration through 0.2F m-sterilizing filter. Investigation did not show any obvious causes. What could be the source of contamination?
- 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)

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2. Is there a list of approved drug manufacturing equipment?

No. The CGMP regulations neither approve nor prohibit specific equipment for use in manufacturing of pharmaceutical products (with the exception of asbestos and fiber-releasing filters, see 211.72). We do not maintain a list of approved equipment. Firms are afforded the flexibility to select equipment that best satisfies their particular needs and that is capable of meeting the relevant CGMP requirements. Each firm is responsible for selecting all equipment used in their manufacturing process to produce quality product in accordance with CGMP. They are also responsible for selecting the appropriate intended use for the equipment's operation, and are free to modify standard equipment designs to best suit their process and that are compatible with the product under process.

The CGMPs require that equipment be of appropriate design to facilitate operations for its intended use and for cleaning and maintenance (see 211.63 and 211.67) and, that any equipment surface in contact with components, in-process materials, or drug products not be reactive, additive, or absorptive so as to "alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements" (see 211.65).

References:

- 21 CFR 211.63: Equipment design, size, and location
- 21 CFR 211.65: Equipment construction
- 21 CFR 211.67: Equipment cleaning and maintenance
- 21 CFR 211.68: Automatic, mechanical, and electronic equipment
- 21 CFR 211.72: Filters

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3. 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.

TOC or TC can be an acceptable method for monitoring residues routinely and for cleaning validation. 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 an important exercise because 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. 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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4. A firm has multiple media fill failures. They conducted their media fills using TSB (tryptic soy broth) prepared by filtration through 0.2 micron sterilizing filter. Investigation did not show any obvious causes. What could be the source of contamination?

A firm recently had multiple media fill failures. The media fill runs, simulating the filling process during production, were conducted inside an isolator. The firm used TSB (non-sterile bulk powder) from a commercial source, and prepared the sterile solution by filtering through a 0.2 micron sterilizing filter. An investigation was launched to trace the source of contamination. The investigation was not successful in isolating or recovering the contaminating organism using conventional microbiological techniques, including the use of selective (e.g., blood agar) and nonselective (e.g., TSB and tryptic soy agar) media, and examination under a microscope. The contaminant was eventually identified to be *Acholeplasma laidlawii* by using 16S rRNA gene sequence. The firm subsequently conducted studies to confirm the presence of *Acholeplasma laidlawii* in the lot of TSB used. Therefore, it was not a contaminant from the process, but from the media source.

Acholeplasma laidlawii belongs to an order of mycoplasma. Mycoplasma contain only a cell membrane and have no cell wall. They are not susceptible to beta-lactams and do not take up Gram stain. Individual organisms are pleomorphic (assume various shape from cocci to rods to filaments), varying in size from 0.2 to 0.3 microns or smaller. It has been shown that *Acholeplasma laidlawii* is capable of penetrating a 0.2 micron filter, but is retained by a 0.1 micron filter (see Sundaram, et al.). *Acholeplasma laidlawii* is known to be associated with animal-derived material, and microbiological media is often from animal

sources. Environmental monitoring of mycoplasma requires selective media (PPLO broth or agar).

Resolution:

For now, this firm has decided to filter prepared TSB, for use in media fills, through a 0.1 micron filter (note: we do not expect or require firms to routinely use 0.1 micron filters for media preparation). In the future, the firm will use sterile, irradiated TSB when it becomes available from a commercial supplier. (Firm's autoclave is too small to permit processing of TSB for media fills, so this was not a viable option.) The firm will continue monitoring for mycoplasma and has revalidated their cleaning procedure to verify its removal. In this case, a thorough investigation by the firm led to a determination of the cause of the failure and an appropriate corrective action.

References:

- 21 CFR 211.113: Control of microbiological contamination
- 21 CFR 211.72: Filters
- 21 CFR 211.84(d)(6): Testing and approval or rejection of components, drug product container, and closures
- Sundaram, S., Eisenhuth, J., Howard, G., Brandwein, H. Application of membrane filtration for removal of diminutive bioburden organisms in pharmaceutical products and processes. PDA J. Pharm. Sci. Technol. 1999 Jul-Aug; 53(4): 186-201.
- Kong, F., James, G., Gordon, S., Zekynski, A., Gilbert, G.L. Species-specific PCR for identification of common contaminant mollicutes in cell culture. Appl. Environ. Microbiol. 2001 Jul; 67(7): 3195-200.
- Murray, P., Baron, E., Pfaffer, M., Tenover, F., Yolken, R. Manual of Clinical Microbiology ASM Press, Sixth Edition.

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