The National Institutes of Health | Division of Technical Resources | Office of Research Facilities

Design Requirements Manual **News to Use**

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The formulae $\frac{\partial \rho \bar{U}_i}{\partial t}+\frac{\partial}{\partial x_j}(\rho \bar{U}_i \bar{U}_j)=-\frac{\partial \bar{P}}{\partial x_i}+\frac{\partial}{\partial x_j}\left(\mu \frac{\partial \bar{U}_i}{\partial x_j}\right)+g_i(\rho-\rho_0)$ for building $\frac{\partial}{\partial x_j}(\rho \bar{U}_i \bar{U}_j)=-\frac{\partial \bar{P}}{\partial x_i}+\frac{\partial}{\partial x_j}\left(\mu \frac{\partial \bar{U}_i}{\partial x_j}-\rho \overline{u_i' u_j'}\right)+g_i(\rho-\rho_0)$ state of the art $\frac{\partial}{\partial x_i}(\rho \bar{U}_i \bar{H})=\frac{\partial}{\partial x_i}\left(\lambda \frac{\partial \bar{T}}{\partial x_i}-\rho \overline{u_i' h'}\right)$ biomedical research facilities.

Preparing for FDA Pre-Operational Review of APF Projects (Part One of Two)

NIH operates a growing portfolio of Aseptic Processing Facilities (APFs). These designated APFs support patient care and research programs by enabling the effective use of aseptic techniques for the safe processing, manipulating, compounding, or admixture of therapeutic, prophylactic, and diagnostic drugs and medical devices for human use. These facilities include those where the materials handled are bioburden-controlled, aseptically processed, or terminally sterilized, as well as supporting laboratories which provide testing of the environment within these facilities, their processes, and/or products. APFs process materials intended for direct injection (e.g. parenterals), mucus membrane administration (e.g. ocular, inhaled, nasal treatments), or tissue contact administration (e.g. implants). APFs shall be operated in a state of control, as defined by the facility's Quality Management System (QMS).

For new APFs and significant renovation projects, it is the typical practice of the NIH, under the guidance of the Clinical Center's Office of Research Support and Compliance and The Office Of Research Facilities, Division of Technical Resources, in collaboration with the end user and outside subject matter experts, to request a Pre-Operational Review of Manufacturing Facilities by the FDA. The stated purpose of the FDA's Pre-Operational Review is to provide an opinion on whether the work described (facility, process, or both) in the document would comply with current Good Manufacturing Practices (cGMP), per FMD-135. The NIH is not engaged in commercial production, but it shares many of the same concerns as a commercial manufacturer regarding the prioritization of patient safety. NIH retains the responsibility to design, construct, commission, qualify, validate, and operate APFs in a state of control.

There are multiple types of review which may be requested under a Pre-Operational Review. This article covers Design Review; the second article in this series will cover Pre-Construction Review, Construction/Equipment Installation and Qualification Review, and Pre-Production Review.

Design Review

The Design Review meeting generally occurs at or after the end of the design-development phase, 30 days after the submission of a document package to the FDA. This package consists of the User Requirements Specification (URS); flow diagrams, which may include but are not limited to room classifications and pressurization, gowning-level zones, raw material, finished material, personnel, waste, and other diagrams which illustrate the implementation of the contamination/cross-contamination prevention strategies, including segregation, separation, and unidirectional flows; and Risk Assessment (RA) and mitigations. Other technical and illustrative documents may also be included, which describe how the completed facility will meet cGMPs and other regulatory requirements. The FDA has shown keen interest in how construction and maintenance activities may impact ongoing operations nearby, something which should be clearly described in the documents.

The documents must be advanced enough to permit meaningful review and comment and must be provided well in advance of the meeting. The meeting is intended to address NIH's questions to the FDA, but also any questions or concerns the FDA may have about patient risk. These meetings are held at the FDA's offices, and are attended by the end user chief (who submits the documents to the FDA) and representatives of key departments within the user group, ORSC, and FCIS. This small contingent will present and respond as representatives of the NIH's intent during the meeting, then will interface with the larger project team afterwards to develop written responses to any questions or requests for additional information from the FDA.

The intent of the NIH's careful, layered approach to these projects, the engagement of multiple levels of Subject Matter Experts, the FDA's external oversight, and the ongoing NIH-internal oversight of operations and maintenance of each APF in the NIH portfolio is to ensure the Safety, Integrity, Strength, Purity and Quality (SISPQ) of the products being produced. This helps prioritize both patient and worker safety.

'Design Requirements Manual (DRM) News to Use' is a monthly ORF publication featuring salient technical information that should be applied to the design of NIH biomedical research laboratories and animal facilities. NIH Project Officers, A/E's and other consultants to the NIH, who develop intramural, extramural and American Recovery and Reinvestment Act (ARRA) projects will benefit from 'News to Use'. **Please address questions or comments to:** shawm@nih.gov

Further details on this month's topic are available on the DRM website Chapter 13
www.orf.od.nih.gov/TechnicalResources/Pages/DesignRequirementsManual2016.aspxPages/DesignRequirementsManual2016