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

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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 Two)

NIH operates a growing portfolio of Aseptic Processing Facilities (APF). 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. The stated purpose of the FDA's Pre-Operational Reviews of Manufacturing Facilities is to provide an opinion as to whether the work described (facility, process, or both) in the documents would comply with current Good Manufacturing Practices (cGMP), per FMD-135. For a full description of the APF program and the FDA's Pre-Operational Review Program, please see Part One of this article.

The various types of post-design review may occur at any or all the following stages, depending on the project:

Pre-Construction Review

At this stage, the review involves studying and commenting on the complete design package, including drawings; specifications; URS (updated); Basis of Design (BOD), which includes updated and expanded facility diagrams; RA (updated); System Level Impact Assessment (SLIA), which establishes system and facility boundaries as well as robustness, resiliency, and redundancy requirements; and Project Validation Master Plan (PVMP). The comments at this phase tend to delve into materials of construction and construction detailing; drainage and water systems; product systems; compressed air systems; heating ventilation and air-conditioning (HVAC) systems; and process equipment configurations, along with their associated piping systems and controls.

Construction/Equipment Installation and Qualification Review

The FDA will respond to requests for an on-site review of specific portions of the construction while it is in progress. Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ), and validation and control data are collected and stored under document control during and after this phase. They will be available for FDA review upon request.

Pre-Production Review

At the pre-production phase, the FDA generally follows the guidance of the applicable Compliance Program and their Investigations Operations Manual (IOM). At this point, the NIH will have produced a large volume of facility documents that are validated per Good Documentation Practice (GDP). Many of these documents are currently in, or are in the process of migrating to, the Document Management System (DMS), where they will be maintained as current throughout the life of the facility. The users will complete the development of the facility's other establishment files and preoperational memo in coordination with the Office of Research Support and Compliance (ORSC) prior to beginning production at the facility.

The facility documents described above are generally developed by outside subject matter experts (SMEs) and contracted directly by the users, or under the umbrella of the design and construction project contracts. These documents are prepared in coordination with the end user, ORSC, and Facility Compliance and Inspection Section (FCIS). In a highly collaborative and integrative process, the user and ORSC tend to focus on process and regulatory compliance associated with the products to be produced, while the user and FCIS tend to focus on assuring that the facility being designed meets or exceeds the acceptance criteria as described in the User Requirement Specification (URS), which can be traced back to regulation and risk analysis.

The intent of the NIH's layers of internal oversight and the FDA's external oversight is to ensure the Safety, Integrity, Strength, Purity, and Quality (SISPQ) of the products being produced in order to minimize the risk to our patients as part of an overall quality system. The NIH Quality Management System (QMS) is a formalized system of interacting documents, processes, procedures, resources, and responsibilities for achieving quality policies and objectives that promote patient and worker safety, in accordance with all applicable guidelines and regulations. The QMS requires appropriate quality management personnel to oversee the use of the facility, as well as the development and maintenance of documents.

The FDA's review on cGMP compliance can reveal defects or vulnerabilities, especially early in the facility development process. These faults could lead to costly corrective action or risk of contamination, increasing the risk to patient safety – the avoidance of which is the shared goal of both the FDA and the NIH.

'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