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

DRM Chapter 13: Aseptic Production Facilities

A major DRM revision, Revision 1.0, was published on February 13. The major addition is Chapter 13, *Aseptic Production Facilities*. This new chapter addresses the complexities and unique processes needed in design, construction, operations and maintenance of an Aseptic Production Facility (APF).

Successful APF projects require continuous and collaborative effort from project initiation to the end of the facility life cycle. NIH's APFs produce therapeutic and diagnostic products for human use, inclusive of those required to follow current Good Manufacturing Practice (cGMP) regulations, aseptic processing (for those manufacturing biological products) and for the production of Phase-I and II clinical trial products (including pharmacy compounding of sterile products). Chapter 13 references sections of the DRM when the criteria are the same as other NIH facilities; however Chapter 13 contains requirements specific to APFs which do not directly fit within the scope of other DRM sections.

The purpose of Chapter 13 is to establish minimum criteria for NIH APFs to ensure that patients receive products of appropriate strength, identity, quality, purity, and other factors related to patient safety. Chapter 13 provides requirements to mitigate risks where the facility can have a direct or indirect impact.

Risks

Failure to adequately design, build, and operate APFs under-control can result in the contamination of products, threatening patient and worker health and safety. Due to the level of risk, there are significantly higher and more stringent requirements for APFs compared with typical research laboratories.

Statutes, Regulations, Standards and Guidelines

APFs are highly regulated facilities with specific statutes, codes, standards, regulations, and guidelines based upon the product being produced and the locations where the products are administered (e.g. extra-jurisdictional enforcement may be applicable).

Above and beyond these requirements are Good Engineering Practice (GEP) and cGMP which are, at their core, driven by risk analysis.

Process Changes

APFs are challenging to design, build, commission, validate (qualify and certify) and operate. Unlike much of the DRM, which focuses on basic design requirements, Chapter 13 includes the exhaustive and highly prescriptive documentation requirements that APFs demand. Extensive attention is given to the context-specific definitions of Statement of Requirement (SOR), User Requirement Specification (URS) and Basis of Design (BOD). Commissioning, qualification and validation requirements take on new dimensions in APF projects through the Validation Master Plan (VMP). Many of these documents are subject to change control, which is a formalized process for authorizing changes to specific documents.

Robustness, Resilience and Readiness

The purpose of the heightened scrutiny under which APFs are designed and operated is patient protection. APFs in which drugs and biologics are manufactured must achieve and maintain the requisite cleanliness and operating environments. APFs are subject to regular, thorough cleanings with a protocol of aggressive chemical agents which require all material used in construction be appropriately selected, detailed and installed to resist degradation. Typically a cleaning may involve a process called a triple cleaning, involving three successive applications, each with a different chemical agent.

Due to their critical nature and cost of operation, APFs are uniformly intolerant of downtime and disruption of operations. Risk assessments and Standard Operating Procedures (SOPs) must identify and address points of failure and scenarios which have an impact on operations. An example of failure is a pressure reversal, which allows less clean air to migrate towards areas which have more stringent ISO classifications or induces cross contamination. If this was to occur the APF would have to be taken off-line for triple cleaning and testing before being allowed to resume operations.

These facilities are regularly monitored by specially trained, dedicated staff to identify out of specification conditions, and then, in accordance with SOPs, develop and institute Corrective and Preventative Action Plans (CAPAs).

Contents of Chapter 13

Chapter 13 includes the following sections:

'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 DRM Chapter 13 Aseptic Production Facility Requirements
https://www.orf.od.nih.gov/PoliciesAndGuidelines/BiomedicalandAnimalResearchFacilitiesDesignPoliciesandGuidelines/Pages/default.aspx