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# Steam for Humidification in HVAC Systems: Key Design Considerations

## Introduction

The DRM outlines acceptable humidity ranges for laboratories, Animal Research Facilities (ARFs), and Aseptic Production Facilities (APFs). As the HVAC systems for these facilities utilize 100% outdoor air, significant humidification is necessary to maintain the required design relative humidity within the space(s); NIH uses low pressure steam for humidification in all referenced applications. This article reviews the different types of steam and some of the appropriate applications and design requirements for each.

## Steam Types and Applications

Steam for humidification can be separated into three common types: Clean Steam (CS), Chemical Free Steam (CFS), and utility steam. CS for humidification is produced from high purity water (ASTM D1193, Type III or IV) by reverse osmosis (RO). CFS for humidification is produced from potable water that is filtered and softened without chemical additives (i.e., amines and hydrazines commonly used in plant steam). Utility steam is typically generated from either a central plant or building steam boilers and contains chemical additives to prevent pipe corrosion. The central plant steam at the Bethesda campus is continuously monitored to ensure chemical levels are well below FDA/OSHA limits; it is therefore widely used for most HVAC humidification applications.

Engineers should utilize a risk-based approach early on to determine the appropriate steam type for humidification applications. An approach that considers capital cost, operational cost, and the facility's Critical Quality Attributes (CQA) will help define the risks of humidity to potential product or process contamination and occupant comfort. Generally, when steam is used for indirect humidification (i.e., injected into the HVAC air system), it does not need to be purer than the air that it is being mixed with. While campus plant steam is acceptable for most laboratories and ARFs, there are specialized areas, including APFs, where either CS or CFS is required. Most APFs at NIH are closed-process facilities, with open processing conducted inside ISO 5 biosafety cabinets (BSCs), meaning CFS steam would be adequate. CS steam may be considered for pharmaceutical open processing, higher-grade clean rooms, and other critical applications where risk of volatile contaminants can adversely impact the product and the room's environmental quality.

## Steam System Design Considerations

Applications that use different types of steam have different system design requirements. For instance, in CS systems, the feedwater distribution system shall fully recirculate back to the water production system to prevent stagnation and biofilm growth. In CFS systems, a controlled (slow close solenoid) drain valve shall be located directly adjacent to the steam-to-steam converter's connection to ensure routine water turn-over during periods of low/no demand. Regardless of specific system requirements, Preventative Maintenance (PM) shall include defined cleaning/sanitization schedules of the feedwater piping system and routine/seasonal service of steam-to-steam generator vessels.

Where either CS or CFS is determined necessary for the application, the design should provide a robust production system with redundancies. In general, these steam systems include sanitary design, 316L stainless steel construction, pressurized steam generators (ASME vessels), double wall heat exchangers, properly sloped piping (to low point drains), and sample valves. Independent modulating control and isolation valves for each AHU unit humidification distribution grid are required (per DRM 6.2.6). CS and CFS systems shall be designed so that low pressure steam is continuously available to meet demand, including periods of steam generator vessel filling and blow-down. Dispersion grids in AHUs shall be located directly upstream of cooling coil(s) to ensure efficient distribution and absorption in the air stream. Where jacketed distribution tubes are utilized, provide automatic isolation valve to prevent steam circulation when humidification is not active to prevent unwanted heat gain to the supply air.

## Conclusion

Proper humidification control is necessary to maintain stable relative humidity inside the facility over the full range of outdoor humidity conditions. Evaluation of a recent NIH facility installation confirmed that commercial humidification systems which utilize atmospheric steam and control of the steam generator's heating rate in response to humidification demand changes are incapable of maintaining the DRM-specified relative control range(s). However, incorporating the key design elements reviewed in this article will ensure robust systems that perform as required.

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# Lessons Learned – Pneumatic Tubing Installation for Pressure Monitoring of Critical Rooms

## Introduction

In an Aseptic Processing Facility (APF), differential pressure (dP) is a critical parameter to monitor in order to maintain the facility in a qualified state. The design, installation, and maintenance of dP sensors is necessary for accurate and consistent measurement during operation. At NIH, APF projects typically have two dP systems: The Building Automation System (BAS), which monitors and indirectly controls the room dP; and the validated Environmental Monitoring System (EMS), which only monitors dP and is utilized by the User for regulatory compliance.

## Background

In 2021, the Division of Design and Construction Management (DDCM) opened an investigation to inspect and evaluate problematic dP tubing that was installed in dP monitor displays and pressure pick-ups in two buildings, East Terrace Modular (T10B) and NCI TIL Modular (T-30). In several locations within both buildings, the investigation found dP tubing that was kinked and damaged; connections that were not properly secured; and several instances where incorrect tubing material and connections were used. Additionally, the investigation found that the BAS and EMS dP transmitters shared reference ports and a majority of the dP tubing, which impacted dP readings in affected areas and subsequently caused dP values to shift post-calibration.

In Building T10B, the enclosures that house both the BAS and the EMS were congested, lacking sufficient space for the dP transmitters and associated wiring and tubing. The depth of the enclosure was too shallow to contain all tubing without kinking and bending the tubes. These issues were only discovered post-installation due to inefficiently detailed design documents and lack of review and inspection both prior to and during installation.

## Design and Installation Requirements

Pneumatic tubing conveys air from both a room of interest and a reference room to a sensor for the purpose of monitoring the dP in critical rooms, particularly across doorways, which often delineate the boundary between zones of different air quality (e.g., ISO-8 on one side of the door and controlled not classified (CNC) on the other, etc.). To reduce the risk of contamination of the product being produced, the design and operation of the APF must ensure that air only moves from cleaner areas to dirtier ones, never vice versa.

Since there are countless pneumatic tubing types on the market, engineers should always specify Type FR (fire retardant) polyethylene in accordance with DRM Section 7.6.7. This pneumatic tubing is relatively low cost and is rated for its resistance to kinking and a wide range of chemicals and solvents. To ensure a good seal with polyethylene tubing, project installation specifications should require the use of barb fittings for connections. Enclosures should be generously sized to reduce risks of bends and kinks in pneumatic tubing.

It is good engineering practice to have the BAS and EMS systems fully segregated and operating independently from one another (inclusive of all transmitters, probes, wiring, tubing, etc.) to minimize dP reading errors, reduce the impact between systems, and improve overall system reliability. However, unless pressure monitors have built-in pressure transmitters, pressure transmitters for both the BAS and EMS should be located remotely in a common panel where they can be easily accessed and serviced. There are multiple advantages to segregating BAS and EMS systems: ease of maintainability; the ability to calibrate one system without impacting the other; and the ability to eliminate a single point of failure, where one failed sensor or transmitter would cause data from both systems to be compromised and result in the affected facility operating at risk. There are, however, disadvantages to fully segregating the BAS and EMS: SOPs are necessary to provide constant comparison between system dP readings, and each system's sensors require concurrent calibration to ensure that the readings vary within the same tolerance.

## Remediation

Post investigation, all non-conforming tubing inside the BAS and EMS enclosures for Buildings T-30 and T10B was replaced with polyethene tubing, and elbow-type fittings were installed to minimize bends and kinks.

In Building T-30, isolation valves were added to the tubing from pressure pick-up enclosures to segregate the BAS from the EMS while calibrations are being performed. This solution allows for one sensor to be operational during calibration. For future installations, full segregation between the BAS and EMS tubing and remote transmitters is necessary.

In Building T10B, the BAS and EMS enclosures were too small to accommodate additional isolation valves to facilitate calibration. The tightness of the back box housing remains an issue that could cause further problems in the future. The back box where the EMS Setra Transmitter is located is narrow; ideally, a larger (and deeper) back box should have been provided to allow adequate room for parts, tubing, and wiring.

## Conclusion

For optimal dP measurement installation, designers should follow both NIH's DRM requirements and manufacturer's installation procedures and inspect all materials before and after installation. It is also good practice to provide detailed engineering design drawings with in-situ mockups of pneumatic tubing, wiring, and differential pressure device locations for BAS and EMS to NIH for review and approval prior to installation.

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# Alarm Management

## Introduction

In a plant, an **alarm** acts as an intentional interruption to an operator indicating an abnormal condition. Meaningful alarms notify the operator to take action to prevent or mitigate the impact of an occurrence with an associated negative consequence, such as a forced equipment outage.

Active alarms are presented to a human operator by an alarm display, which may be located on a computer monitor or an annunciator panel. The operator's ability to view, acknowledge, and respond to each alarm is limited by the human factor of cognition, notably the individual's ability to filter out data that is extraneous to making appropriate decisions. This cognitive ability may become overloaded during an **alarm flood**, which is a period of excessive and rapid alarm rates, resulting in an operator unintentionally missing or ignoring important alarms because they are overwhelmed by the number of alarms. Alarm floods can grow in intensity and frequency if the system is configured with poor alarming practices – such as bad actor alarms and poor alarm prioritization – which hinder the operator in assessing and resolving the source of the abnormal situation.

**Alarm management** addresses the flaws in alarm system controls, processes, and designs to allow the plant to promote good stewardship and usability by the operations staff. The concepts can be applied in plants as well as building operations or other processes where alarm use is critical.

## Alarm Philosophy

An alarm philosophy is an alarm management handbook developed by the plant's alarm team and customized specifically for their site. This comprehensive document provides guidance to ensure that the alarm system is developed, implemented, and maintained to effectively help the operator take the correct action at the correct time. The handbook compiles the rules for alarm selection, priority setting, configuration, response, handling methods, system monitoring, roles and responsibilities, and system maintenance.

## Benchmarking/Reporting/Analysis

The data collected by the alarm system is used to build analyses that reflect the system's health and performance as an operator tool. These analyses are compared to target performance metrics and the alarm management program's initial benchmarking to identify critical issues and gauge the effectiveness of mitigations and improvements.

## Alarm Change Management

Alarm reporting may highlight alarms with behaviors that are categorized as a nuisance or are irrelevant to the operator. These are interchangeably classified as **nuisance alarms** or **bad actor alarms**.

Bad actor or nuisance alarms are notifications that don't meet the definition of an alarm (such as alarms without a required operator action) and are thus not meaningful; those that are triggered by normal operations (e.g., status alarms); or those that are chattering (rapidly repeating) or fleeting (occurring and clearing in very short intervals). Once identified, these bad actors may be resolved by the alarm management team through the introduction of one or several control tools – primarily deadbands (which prevent alarms from returning to normal until the alarm condition is cleared by a defined increment, preventing successive alarms), process filters, and delays.

As nuisance alarms are controlled, valid alarms are prioritized through documentation and rationalization (D&R). D&R is the methodology of alarm rationalization by which alarms are determined to be valid, assigned meaningful priority and setpoint values, and then documented to ensure consistent alarm configuration in accordance with the alarm philosophy. The most frequent method of alarm rationalization is the grid-based method, which combines the severity of the alarm's consequences with the maximum time available for response and mitigation.

## Real Time Alarm Management

Advanced alarm capabilities may be necessary to resolve certain alarming issues. Equipment may have different operating modes (e.g., running, startup, tripped) where a static alarm configuration would produce inconsistent results; a static configuration can result in an alarm triggering despite the condition being normal for the equipment's current state. To rectify this, **state-based alarming algorithms** dynamically alter equipment alarm configurations (e.g., alarm setpoint and priority) based on changes to the equipment's detected operating state. **Alarm flood suppression** temporarily eliminates expected and distracting alarms from a unit trip or forced outage, displaying only the most relevant alarms to assist the operator in managing the post-trip resolution.

## Conclusion

Alarm management is a continuous improvement process that requires an ongoing – and frequently automated – program of system analyses and monitoring by a dedicated alarm management team. Effective alarm management helps maintain an improved level of performance and prevent various alarm problems from being reintroduced into the alarm system.

## Additional Reading

Hollifield, Bill R., and Eddie Habibi. *Alarm Management: A Comprehensive Guide: Practical and Proven Methods to Optimize the Performance of Alarm Management Systems*. International Society of Automation, 2011.

ANSI/ISA-18.2-2016, Management of Alarm Systems for the Process Industries Copyright: 2016

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# Disinfection Efficacy Validation for Architectural Finishes – Preliminary Study Results

## Introduction

This article reviews the study "Disinfectant Efficacy Validation Summary Report for National Institutes of Health's (NIH) Aseptic Processing Facilities (APF)," which was developed by the Division of Technical Resources/Facilities Compliance and Inspection Section (DTR/FCIS) in cooperation with the Office of Research Support and Compliance (ORSC) and the Clinical Center Department of Laboratory Medicine (DLM) and executed under contract by Boston Analytical. This report was based on the execution of "PRO-0968-BA Disinfectant Efficacy Surface Coupon Evaluation for National Institute of Health (NIH)." The study was principally intended to validate the use of various cleaning materials and processes for cleanroom surfaces, but this article explores how that same data can be leveraged to improve the selection of materials of construction for use in cleanrooms based on cleaning efficacy.

## Scope and Rationale

The study design was based on United States Pharmacopeia (USP) Chapter <1072>, "Disinfectants and Antiseptics," and AOAC Chapter 960.09, "Methodology for Surface Disinfectant Efficacy Testing." DTR/FCIS was responsible for analyzing the architectural finishes installed throughout the Aseptic Processing Facility (APF) cleanroom portfolio as well as designing the coupon requirements to represent the most typical architectural finishes and mounting specifications to ensure they would be testable. The coupons represented epoxy-coated gypsum board, manufactured panels (smooth finish uPVC and Fiberglass-reinforced plastic with gel coat finish), welded sheet vinyl, epoxy resin flooring, cleanroom acoustical ceiling tile, 304 stainless steel, and glass. DLM was responsible for identifying microorganisms of concern from environmental monitoring of the NIH cleanroom portfolio, including spore forming and non-spore forming bacteria, yeasts, and molds. DLM provided isolates of the 20 identified challenge microorganisms derived from species collected in the cleanrooms. ORSC provided the disinfectant protocols for the use of specific products identified by the APF cleaning protocol, which is executed by contractors under ORSC's control. The disinfectants included Vesphene® III, LpH® III, and Peridox RTU®.

## Testing

All coupons were cleaned and prepared following a protocol developed between NIH and Boston Analytical. All isolates were prepared using methodologies approved by NIH. Each surface coupon was inoculated with 200 µL of the microbial suspension in a drop-wise fashion. The inoculated coupon was allowed to dry in a biosafety cabinet (BSC) and then sprayed with the appropriate disinfectant. The coupon was saturated with the disinfectant for the required contact time. After the required contact time, the coupons were inverted over a deep petri dish and rinsed with 20 mL of sterile buffer solution. The resulting test solution was then used to prepare subsequent plating. The test samples and positive and negative controls were inverted (i.e., media side up) and incubated per the approved protocol. Post-incubation, the samples were assayed, including positive and negative controls, and colony purity was determined (a pure colony is defined as macroscopically uniform and consistent with that of the intended challenge microorganisms).

## Results

Table 1: Cleaning Efficacy Study Summary, below, provides a simplified summary of the study's results. The results are color-coded to indicate whether the required Log10 reduction in viable microorganisms was met. Green indicates that the criteria was consistently met by all three disinfectants against that microorganism on that coupon (e.g., architectural finish); Yellow indicates that some of the disinfectants demonstrated efficacy (typically always included Peridox RTU®); and Red indicates that none of the disinfectants demonstrated efficacy against the combination of that microorganism and coupon type.

## Conclusions

There are multiple ways to interpret the findings of this study. Routine environmental monitoring is performed across the APF portfolio. The vertical axis then lists various isolates; detection of isolates of special concern (as in columns #4, 10, or 18-20) indicate that the cleaning SOP should be modified to prompt re-cleaning with a product that has a higher demonstrated efficacy, including Peridox RTU®. The horizontal axis shows various materials. Certain rows (including epoxy resin flooring, cleanroom acoustical ceiling tiles and epoxy-coated gypsum board) performed poorly. Micrographs of these materials show an unavoidable degree of surface texture which may provide harborage and protection for microorganisms from adequate exposure to the disinfectants, as applied. This suggests that the use of such materials in cleanrooms requires very careful consideration.

While Peridox RTU® is highly effective at achieving the required Log kill of these microorganisms, it contains peracetic acid, which is particularly aggressive towards certain long-chain polymers. It has been associated with the accelerated failure of certain architectural finishes, particularly epoxy-coated drywall. Extra care is necessary when specifying and detailing such materials, and preference should be given to those which function to better support the efficacy of disinfectants, where possible.

## Additional Reading

1. NIH Design Requirements Manual, CH-13

## Table 1: Cleaning Efficacy Study Summary

| Surface | Micrococcus luteus (Facility Isolate 1) | Staphylococcus hominis (Facility Isolate 2) | Kocuria flava (Facility Isolate 3) | Bacillus megaterium (Facility Isolate 4) | Janibacter spp. (Facility Isolate 5) | Mycolicibacterium mucogenicum (Facility Isolate 6) | Rhodococcus spp. (Facility Isolate 7) | Streptomyces spp. (Facility Isolate 8) | Corynebacterium jeikeium (Facility Isolate 9) | Paenibacillus species (Facility Isolate 10) | Rosemonas mucosa (Facility Isolate 11) | Sphingomonas paucimobilis (Facility Isolate 12) | Pantoea septica (Facility Isolate 13) | Moraxella species (Facility Isolate 14) | Filobasidiella neoformans (Cryptococcus neoformans) (Facility Isolate 15) | Candida parapsilosis (Facility Isolate 16) | Phaeoannellomyces elegans (Facility Isolate 17) | Aspergillus fumigatus (Facility Isolate 18) | Cladosporium spp. (Facility Isolate 19) | Talaromyces spp. (Facility Isolate 20) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Acrovyn – Pebbly Finish) | | | | | | | | | | | | | | | | | | | | |
| (Acroplast – Smooth Finish) | | | | | | | | | | | | | | | | | | | | |
| Polymer Panel | | | | | | | | | | | | | | | | | | | | |
| Welded Sheet Vinyl | | | | | | | | | | | | | | | | | | | | |
| 304 Stainless Steel | | | | | | | | | | | | | | | | | | | | |
| Glass | | | | | | | | | | | | | | | | | | | | |
| Epoxy Resin | | | | | | | | | | | | | | | | | | | | |
| Clean Room Acoustic Ceiling Tiles | | | | | | | | | | | | | | | | | | | | |
| Epoxy Coated Gypsum Board | | | | | | | | | | | | | | | | | | | | |
| | **ALL PASS** | **ALL PASS** | **ALL PASS** | **All fail except** - Peridox RTU® / 5 Minutes | **FAIL** - Vesphene® III / 10 Minutes | **ALL PASS** | **ALL PASS** | **All pass except** - Vesphene® III / 10 Minutes | **ALL PASS** | **All fail except** - Peridox RTU® / 5 Minutes | **All pass except** - Vesphene® III / 10 Minutes | **ALL PASS** | **ALL PASS** | **ALL PASS** | **ALL PASS** | **ALL PASS** | **ALL PASS** | **All fail except** - Peridox RTU® / 5 Minutes | **All fail except** - Peridox RTU® / 5 Minutes | **All fail except** - Peridox RTU® / 5 Minutes |

(GREEN) Criteria was met by all disinfectants

(YELLOW) Criteria was met by some disinfectants

(RED) Criteria was met by none of the disinfectants

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# HEPA Air Filtration in Cleanrooms – Design, Construction and Testing Requirements

## Introduction

NIH maintains a portfolio of cleanrooms that are designed, built, and operated as Aseptic Processing Facilities (APFs). Supply Air (SA), delivered via terminal High Efficiency Particulate Air (HEPA) filters, is the primary method of reducing airstream contaminant levels in these facilities to maintain the specified ISO classifications. HEPA filters and their housings have specific design, construction and testing requirements that must be followed to ensure that the integrity of these filters is maintained throughout the life cycle of the facility. Maintaining certified HEPA filters in APF spaces ensures the safety of patients, workers, and the environment, as well as the integrity of research at NIH.

## Design and Construction Requirements

HEPA filters are rated by their minimum particle removal efficiency of 99.97% of 0.3-micron (µm) diameter sized particles. Velocity and filter thickness and/or density impact filter performance (higher filter velocity means more particles will pass, and a thicker or more dense filter media will impact pressure drop). Terminal HEPA filters are generally designed with a face velocity not to exceed 0.5 m/s (100 fpm). Within the cleanroom, HEPA filter selection and placement should minimize areas of stagnation and turbulent airflow, avoid short cycling to exhaust and return grilles, and not disrupt the air curtain at the sash of any primary engineering controls (PEC) in the room, such as a biosafety cabinet (BSC).

A HEPA filter has a gel seal that forms a positive seal when the filter is properly installed in its housing, eliminating air bypass around the filter edge. Filter housings are fully welded stainless steel or aluminum with an exposed stainless-steel trim. They should be equipped with room-side accessible aerosol challenge and pressure test ports as well as a damper adjustment. HEPA filters designed to be replaced room-side are preferable, except where there is sufficient service space above the ceiling, which is atypical. Filter housings must be cleaned prior to filter installation using IPA, Vesphene, or other pre-approved cleaning chemical(s).

HEPA filters must be handled with care during shipping and inspected for damage both upon arrival and immediately prior to installation. Damage can occur due to rough handling, touching the face with hands or tools, or even storage in the wrong orientation. Filters must be stored per the manufacturer's requirements: indoors, protected from damage (including water intrusion), and between 4.4°C and 37.8°C (40°F and 100°F) and 25% to 75% relative humidity. Despite best efforts to protect the filters from damage, some filters will fail the test during the initial installation, so keeping at least 20% additional spare filters on hand will help avoid project delays.

## Testing Requirements

The FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – cGMP (also known as Filter Integrity Testing) mandates HEPA filter leak tests. This test applies to all HEPA filters in the cleanroom suite, including filters located in the pass-through chambers and PECs. ISO standard 14644-3 and the Institute of Environmental Science and Technology's (IEST) standard IEST-RP-CC034.5 provide additional guidance on this testing. Leak testing is performed initially at the factory and then in situ to verify the integrity of the filter and its installation. Individual leaks should not exceed 0.01% of the upstream challenge. It is important that the airflow rate through the filters is verified prior to testing to ensure that airflow velocity and volume are within specified limits.

HEPA filters are tested with a challenge media, typically Poly Alpha Olefin (PAO), aerosolized through the injection port of the filter housing upstream of the HEPA filter at a concentration between 20-80 ug/l. Per ISO 14644, scanning is performed by using a series of overlapping strokes with the probe, holding it approximately 1 inch from the filter face and moving it at a maximum velocity of 10 linear feet per minute. An appropriate scanning velocity of the probe used across the face of filter is important to provide sufficient time to detect any leak.

Unless approved otherwise, HEPA filters are tested at minimum once every 12 months, except those installed in ISO Class 5 facilities, which are tested every 6 months. If testing detects a leak in the HEPA filter, repairs must follow an approved patching procedure based on the IEST RP-CC034.5 standard, which states, "Fill repair should not block or restrict more than an additional 3% of the filter face area, and no single repair should have a dimension exceeding 3.8 cm (1.5 in)." After the repair is complete and suitable cure time of the approved silicone patching material has passed, the repair area is rechecked for leaks. Patching along the edges of the HEPA filter is not acceptable. If a leak exceeds the allowable limit (> 0.01%), then filter replacement is required. Field repair is not allowed for HEPA filters in ISO 5 environments (typically found inside PECs).

## References

Institute of Environmental Sciences and Technology. (2022). *HEPA and ULPA Filter Leak Tests* (IEST-RP-CC034.5). IEST. https://www.iest.org/

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# Managing cGMP Documents Under a Document Management System (DMS)

## Introduction

Most organizations can greatly benefit from utilizing a system to manage documents. In current Good Manufacturing Practice (cGMP) facilities, a validated Document Management System (DMS) is an essential tool to help a facility maintain a state of compliance. A DMS platform supports the quality management processes that allow for electronic document storage and retrieval, workflow management, and effective safeguarding against unauthorized revisions, deletion, or alteration of records. This also serves to minimize potential compliance and audit problems.

Per ISO 19475, a DMS must meet the "requirements necessary to maintain the authenticity, integrity and readability of documents managed by an electronic document management system." A DMS uses the following features to manage documents in an effective manner.

## Access Permissions

A DMS should use access permissions that assign specific user roles to ensure information and document security. Some of the most common roles in a DMS are creator/revisor, reviewer, document control, training coordinator, and approver. This is especially important for cGMP facilities, where any alteration of data could result in an adverse regulatory finding for failure to maintain a DMS that conforms with GMP regulations. A DMS is also often used to restrict document access to only those needed for the performance of an individual's assigned job duties, which limits the potential for exposure of intellectual property, Patient's Personally Identifiable Information (PII), and other sensitive data. A DMS should also be configured to retrieve documents in a manner which clearly identifies versions which are effective/released, marking current documents in a manner which clearly distinguishes them from earlier versions to minimize the likelihood of mix-up.

## Workflows

A workflow is a series of orderly steps that a document must follow before it can become effective and/or released, depending on the type of document. Workflows also prescribe how documents are changed. These steps may include creation, collaboration, training, and approval. A short workflow can be used for documents that require minor changes; however, documents such as a new Standard Operating Procedure (SOP) may require a more comprehensive workflow before being released for a first-time use. This is because a new procedure would require staff training as well as additional layers of approval. Other types of documents, including batch records, may only require a review-and-release workflow.

## Collaboration

Throughout the control process, collaborators are assigned to work together on documents that are being developed or revised. The system keeps a complete revision history of comments, which includes revision dates and the identities of editing parties. This allows for transparency, efficiency, and adequate collaboration, as all comments will be visible to collaborators. Throughout the collaboration process, only the most current version of a document is available for general user access.

## Revision Control

Document revision control plays a vital role in adhering to GMPs. The system automatically keeps track of document expiration dates and sends notifications to advise document owners when revisions are necessary. The system also supports the tracking of all controlled copies that are in effect so that, when a revision is made to a document, the users will know where to update these copies. If a document is needed for a short period of time, an uncontrolled copy may be retrieved with an expiration date automatically printed on the document to ensure its disposal after use. A DMS can manage the archiving and deletion of outdated documents.

## Electronic Signatures

Critical documents may have an approval phase in the workflow which requires final review and approval from authorized parties. An electronic signature is created using personal credentials and used to sign and date documents to indicate review and approval. After all the required e-signatures are complete, the document becomes effective and is ready for general use. Once the document is approved, the system can automatically provide a signature manifest, if required.

## Conclusion

Document management is often overlooked, which can lead to issues during audits and inspections. Good document management is beneficial for all facilities and especially critical for maintaining cGMP facility compliance. A DMS provides an effective way to reduce the risks of incomplete documentation, incorrect forms, forms without signatures, and inconsistent audit trails. It also ensures that documents are suitable and readily available for decision making and facility operation purposes.

## References

International Standards Organization. (2021). *Document management – Minimum requirements for the storage of documents.* (ISO 19745-2021). ISO. https://www.iso.org/home.html

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# Design/Build-Bridging (D/B-B) Documents

## Introduction

There are various delivery methods for executing the successful design and construction of projects. This article explores one of the more common methods, Design/Build-Bridging (D/B-B[1]), though the method selected should be appropriate for the scale, complexity, and constraints of the project. D/B-B combines elements of the traditional Design-Bid-Build (DBB) method, with its separate contracts for design and construction, and the Design-Build (D/B) method, with its unified contract that typically gets the design services from a subcontractor to the construction contractor. The objective of D/B-B is to retain the best features of both, including better control of the final design and tighter cost and schedule constraints due to fewer unknowns within the proposal, while allowing for innovations in approach.

## Bridging Documents

Bridging documents differ from typical architect and engineer (A/E) submission requirements described in DRM Appendix E[2] in that each discipline needs to be developed to a level necessary to define and design, and there must be sufficient coordination between disciplines to reasonably demonstrate fit and function within any known constraints. The Contracting Officer's Representative (COR) must develop Scope of Work (SOW) language to convey to the designers responsible for creating the bridging documents that each discipline should be sufficiently developed to demonstrate design feasibility. Under-definition increases the risk of increased initial cost and schedule, change orders, post-award with additional cost, and schedule impacts. A D/B-B submission package generally consists of:

- **Basis of Design (BOD):** This document describes the technical requirements and constraints of the project, including the design intent of the users and their acceptance criteria for the work. These parameters must, through narrative and graphical content, adequately describe the rationales and methodologies used in feasibility studies (whether informally integrated into the bridging documents or formally submitted through a stand-alone document with the D/B-B package). The BOD should be organized to address each discipline and must have a description of the significant products used in the design described in the feasibility study.
- **Drawings and Specifications:** Drawings and specifications demonstrate the technical approaches for meeting the user's design intent, mitigating identified risks, and providing a constructable, commissionable, operable, and maintainable model for the final design to be executed by others. Higher resolution modeling is provided for the most critical aspects and lower resolution for the less critical. They must be sufficiently advanced to convey the design intent of the project.
- **Calculations:** The D/B-B documents describe the capacities, limitations, and assumptions that their authors have determined. The A/E of record may develop a significantly different approach, but this demonstrates the ability to meet the requirements and accommodate project constraints, establishes a baseline for future comparison, and provides a basis for evaluating D/B pricing and scheduling.
- **Other Documents:** Additional documents may be required to establish the reliability of the bridging documents, including feasibility studies, risk assessments, special studies, surveys, commissioning and/or validation plans, cost and schedule estimates, etc.

## Review of Bridging Documents

A bridging document is traditionally described as an A/E's 35% Construction Document level submission. While this may be appropriate for a simple project, complex projects may require more advanced development for some disciplines to identify gaps and conflicts, assure full incorporation of lessons learned and best practices, prove or disprove assumptions, holistically describe scope, and attain other benefits inherent to D/B-B. Reviewers should be aware of the potential for unequal development across disciplines. The COR needs to communicate the level of development of each discipline so that reviewers apply appropriate Appendix E level of development expectations to a submission on a by-discipline basis, rather than assuming a uniform level. The COR should also ensure that a full D/B-B document package is provided to the reviewers, inclusive of the documents described in this article, with the SOW to help provide an appropriately calibrated level of review. It is also crucial that sufficient time and appropriate discipline-specific specialist reviewers be provided to perform their reviews.

## Conclusion

A D/B-B package can determine the viability of a project before investing in a full design; control project costs and duration by minimizing the bidder's need to build in as much "padding" in cost and schedule proposals to account for unknown risks; and greatly increase the likelihood that the final product will meet the user's requirements, particularly in large and/or complex projects. D/B-B package review can create challenges, but when the COR properly communicates the scope, much of the friction between the COR, designers, and reviewers can be avoided and the benefits of this approach can be more fully realized.

## Additional Reading

1. There is a lack of industry consensus on the abbreviations used regarding this topic. Due to space constraints, the author has elected to conform to the typical usage of the General Services Administration (GSA) here, including Design/Build (D/B) and Design/Build-Bridging (D/B-B).
2. The National Institutes of Health (NIH). *Design Requirements Manual,* https://www.orf.od.nih.gov/TechnicalResources/Pages/DesignRequirementsManual2016.aspx

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# Using Machine Learning to Forecast NIH Campus Cooling Load

## Introduction

Today, machine learning is widely used to provide valuable information by identifying patterns within large volumes of data. At NIH, the Division of Technical Resources (DTR) uses machine learning to optimize the operation of the Central Utility Plant (CUP), which continuously supplies the campus with electricity, chilled water, and steam. One of the machine learning engines that DTR developed is the "Campus Cooling Load Forecaster," which forecasts the campus' chilled water demand for the next four days. With this information, CUP management can plan and optimize the chiller plant's operation and maintenance.

## Overview

We start by assuming that the future campus load nonlinearly depends on past campus load and local weather, which can be described by a nonlinear autoregressive exogenous (NARX) model that is written as:

$$\hat{y}(t+1) = F[y(t), y(t-1), \dots, y(t-n_y),$$

$$X(t), X(t-1), \dots, X(t-n_x)] \qquad (1)$$

where *y(t)* and *X(t)* represent campus load and weather variables at time *t* and *F* represents a nonlinear function that predicts future campus load $\hat{y}(t+1)$. The differences between the NARX model and linear autoregressive model are the nonlinear function *F* and the exogenous terms *X* in addition to autoregressive terms y. Ending terms $n_y$ and $n_x$ in equation (1) represent the autoregressive order and exogenous order, respectively.

The nonlinear function *F* is modeled by a feed-forward artificial neural network (ANN). The ANN was trained on campus cooling load data and weather data (dry bulb and wet bulb temperature) collected over four years (2018 to 2021). The training process determined optimal ANN hyperparameters, such as the number of network layers and neurons at each layer, and neuron weights that minimize forecast errors.

After function *F* is determined, it is recursively applied to forecasting campus load for future hours. For example, once the campus load for the first hour $\hat{y}(t+1)$ is predicted with equation (1), it is fed into function F to forecast the campus load at the second hour as shown in equation (2).

$$\hat{y}(t+2) = F[\hat{y}(t+1), y(t), \dots, y(t-n_y-1),$$

$$X(t+1), X(t), \dots, X(t-n_x-1)] \qquad (2)$$

This procedure is repeated until all 96 hours of campus load are forecasted.

## Model Improvement

A major issue with the standard NARX model is error accumulation. As the forecasted value $\hat{y}$ is fed into the function, the forecast error is added into the ANN and passed to the next prediction. This error accumulation will negatively impact the result as the forecast horizon expands. One way to stop this error propagation is to train a single model for each hour of campus load forecast and employ 96 distinct models to forecast campus load for the next four days.

## Results

DTR tested the campus cooling load forecaster of 96 ANN models using recently collected data. Figure 1 shows a comparison of true campus load with five forecast results that were forecasted one hour and one through four days in advance. While the forecast of the next one-hour campus load achieved the most accurate result, all forecasts captured the trend of the true campus load. The forecast for the past 10 months shows that the overall average forecast error is under 2000 tons, which is less than the capacity of one standard 5000-ton chiller. This forecaster can therefore assist in operation planning for the 10 chillers at the NIH CUP.

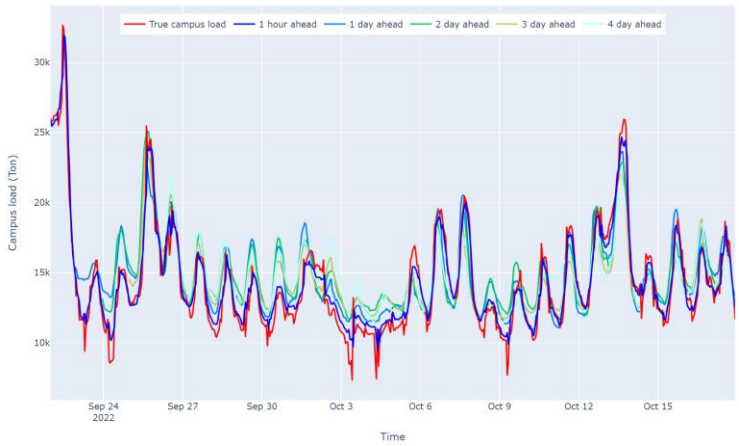


**Figure 1: Campus load and forecasting results**

## Conclusion

The machine learning model developed here can be used to forecast campus cooling load with a reasonable confidence interval to allow accurate, efficient operation planning for the NIH chiller plant without impacting campus reliability.

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# Engineering Change Management (ECM) for Aseptic Processing Facilities (APFs)

## Introduction

The International Society for Pharmaceutical Engineering (ISPE) defines change as anytime a system is "modified, altered, added to, removed, or improved in the way that make its functions, physical features, or performance different from what they were before the change." Engineering Change Management (ECM) is a Good Engineering Practice process to effectively manage creating, reviewing, and documenting formal approval for engineering change requests, ensuring such changes do not adversely impact the facility, system, or equipment. This article concentrates on facility infrastructure and utility change, in particular the engineering change management process for NIH Aseptic Processing Facilities (APFs), and is not meant to cover changes to the manufacturing process and product.

## Background

All facility infrastructure and utility systems supporting APFs are operated and maintained by the NIH Office of Research Facilities (ORF) Division of Facilities Operations and Maintenance (DFOM). The ORF Division of Technical Resources (DTR) Facilities Compliance and Inspection Section (FCIS) provides quality assurance (QA) oversight to ensure that changes to APF systems and equipment are planned, executed, managed, and approved following a controlled process. The ECM Standard Operating Procedure (SOP) for APFs[1] is applicable to all ORF-owned facility systems, equipment, computer systems, instruments, and utilities (i.e., those which create, maintain, and monitor an APF's environment, excluding the User's scientific and environmental monitoring systems and equipment) supporting operational APFs.

## ECM Process

The ECM process is designed to use a risk-based approach and involve Subject Matter Experts (SMEs) and End User QA. Whenever there is a change with potential quality impact, the ECM could provide traceability and documentation to support change control that is processed by the End User. There are five primary steps in the ECM SOP procedure,[2] which are described below. An APF-specific, task-specific change management board (CMB) is established to review and approve or deny each request and to provide guidance to change requesters for the development and implementation of the proposed changes. The CMB is made up of representatives from DTR/FCIS, the Office of Research Support and Compliance (ORSC), DTR/Technical Services Branch (TSB), DFOM, APF End User QA, SMEs and other stakeholders as required.

**Step 1 - Change Control Screening Assessment (CCSA):** A CMB will determine if the proposed change needs to be managed through the ECM process. The CCSA is developed by the requester to capture the Current Situation, Proposed Change, Justification of Change, Impact to Facility and Documents, and whether the proposed change is related to a System Deviation (SD), Corrective and Preventive Action (CAPA), or audit observation. The FCIS change coordinator performs a completeness review prior to submittal for review by a CMB.[3]

**Step 2 - Change Request Form (CRF):** This form captures the Current Situation, the Proposed Change, and Justification; identifies any Post Implementation Requirements; identifies all affected change-controlled documents; and enumerates the results of the Risk Assessment (RA) which is performed to identify and assess the impact of the change. The FCIS change coordinator performs a completeness review prior to submittal for review by a CMB.[3]

**Step 3 - Pre-Execution Review and Approval of the CRF by the Change Management Board (CMB):** During this step, the CMB will review and approve or deny the CRF.

**Step 4 - Implementation and Completion of the Change (Execution):** The change requester shall follow up to ensure that required changes have been completed and documented in the CRF accordingly.

**Step 5 - Post-Approval and Close-out of the Change (Post Execution):** The FCIS change coordinator performs a completeness review prior to submitting the documents for CMB review. After verifying all post-implementation testing has been completed, all affected documents have been updated, and all applicable attachments have been completed, the CMB approves and closes the CRF. The approved document is then archived.

## CMB Meetings

Each week, CMBs are scheduled to meet separately by APF to review and discuss change request documents. CMB members and the change requester are required to attend this meeting, as well as other individuals and groups as needed, so that all comments and concerns can be effectively discussed and resolved.

## Conclusion

The ECM process can be time-consuming and complicated. The DTR SOP is therefore designed to manage change requests for ORF-owned facility systems and equipment supporting operational APFs. The SOP utilizes a risk-based approach and collaboratively engages all stakeholders to ensure both that their concerns are reviewed and mitigated prior to execution and that there is sufficient post-execution assessment and documentation to demonstrate whether the cause(s) of the change request have been satisfied.

## References

1. DTR-SOP-10004: Engineering Change Management for Facility Operation and Maintenance of Aseptic Processing Facilities.
2. DTR-SOP-10004, Appendix 1, Engineering Change Management Flow Diagram
3. Currently under development, this step is being updated in DTR-SOP-10004 (rev. 3) and will be automated via FCIS CCSA application (https://dtrdata.orf.od.nih.gov/ccsa).