

Construction Practices: Contamination Risk Reduction within Ongoing Operations

by Charles Hammond and Steve W. Van Wormer

This article presents good construction practices for work in existing pharmaceutical facilities and encourages further development of construction procedures to prevent product safety issues.

Pharmaceutical manufacturers with facilities in mature markets, such as the United States and Western Europe, have faced varying project implementation conditions as a result of increased emphasis on using existing facilities versus developing greenfield sites. Factors such as economic volatility, relocating manufacturing to emerging markets, changes and improvements to manufacturing efficiency, and outmoded facilities and equipment have contributed to the shift in greater utilization of existing facilities.

Many best practices in engineering and construction developed during the industry's expansion on greenfield sites have been slow to adjust to the differing risks when construction takes place next to active production and shares existing infrastructure. Construction practices implemented in Greenfield conditions, where there is little or no impact on existing operations, do not typically contain the standard of care and rigor that are necessary when working in existing operations.

Significant attention and focus have been given to the best engineering and validation practices in the pharmaceutical industry, while less focus has been given to the methods of construction. Ongoing, large capital investments by the pharmaceutical industry have allowed engineering firms to gain vast experience, and along with owner's input, lead to the development of engineering practices and solutions targeting the project's completed performance. Engineering processes and procedures are objectively defined and simi-

lar, if not shared, by firms across the life science industry. Consistent application of these good engineering practices makes the final physical outcome of the project predictable.

During the key implementation phase; however, construction project execution has not evolved into industry-wide or generally accepted defined processes, procedures and methods to the same degree. Lack of these practices is evidenced by the "surprising frequency" of construction as a source of contamination as reported by the FDA.¹ Good procedures and practices to control construction activities and its byproducts represent a significant opportunity to minimize the risk, if not eliminate, such outcomes.

The increasing percentage of pharmaceutical construction projects taking place within existing facilities, adjacent to ongoing operations, creates significant vulnerability of contamination caused by construction. This can be disproportionately detrimental and extremely costly if manufacturing's work-in-progress is affected, even if the initial capital investment or project budget is not that large.

This lag in the development of construction practices tailored to prevent such issues during renovations may be attributed to traditional engineering practices that do not take means and methods of construction into account. Also, the means and methods needed to construct within an operational pharmaceutical facility are not typically included in construction management curriculum. Rather, construction professionals have to rely heavily on acquired practical experience and exposure to different project environments. Engineering methods, on the other hand, are well shared

through engineering curriculums, industry organizations, and migration of pharmaceutical professionals from one company to another.

Here, the objective is to define currently utilized good construction practices for projects in existing pharmaceutical facilities and to encourage further development of construction procedures to prevent contamination and product safety issues.

Project Life Cycle

The level of effort and extent of practice or procedure definition varies through the project life cycle, usually commensurate with the level of development of detail around the scope of the project. Construction management tasks throughout the life cycle focus on impact and risk identification, from business planning to project closure. As the project moves toward closure, the activities focus on prevention, planning and execution. There are tasks at each life cycle phase that help mitigate risks related to construction. This article is formatted to identify construction management related tasks at each stage of the project life cycle. A “pass gate” approach at the end of each life cycle phase is recommended to ensure that there is no impact by construction and that product safety remains intact.

Business Planning

In response to growing pressures to improve growth and margins, pharmaceutical manufacturers are striving to:

1. Increase research and development productivity, including innovation needed for new drug development
2. Respond to currently untapped or unmet medical needs, particularly due to the increasing prevalence of chronic diseases in aging populations and those with unhealthy lifestyle choices
3. Expand market share to growing populations in developing countries

Concurrent with these activities is the requirement to create, consolidate and maintain pharmaceutical manufacturing facilities that are efficient, technologically cutting-edge, and able to develop products with the highest quality and safety standards in mind.

The owner must involve their operational personnel from the start of the project to ensure that the proposed option will work within the available space and determine any high-level impacts from an operational perspective.

For construction management, the company and selected construction management team must have the experience and background of doing work in a controlled environment, as well as training specific to the site’s access and containment requirements. This knowledge is critical for the team’s input on estimating, logistics planning and scheduling, in

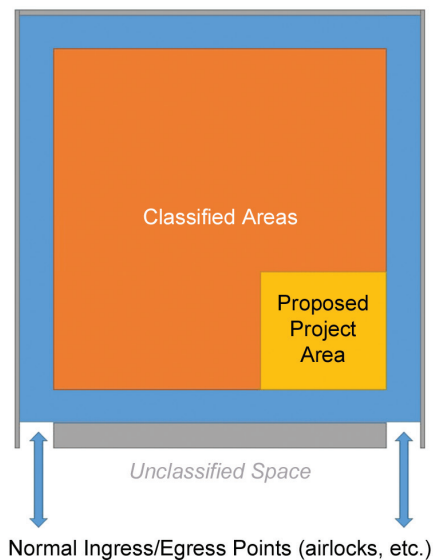


Figure 1. Example high-level logistics review: initial conditions.

addition to overall project success.

A high-level construction logistics plan should be developed during evaluation of site selection alternatives during the business planning phase. Physical layout of an existing facility and availability of area contractors could impact site selection alternatives and Rough Order of Magnitude (ROM) estimates at this phase, so early evaluation is necessary. See Figures 1 and 2 for examples of high-level logistics plan reviews.

This high-level plan considers the logistics of selective

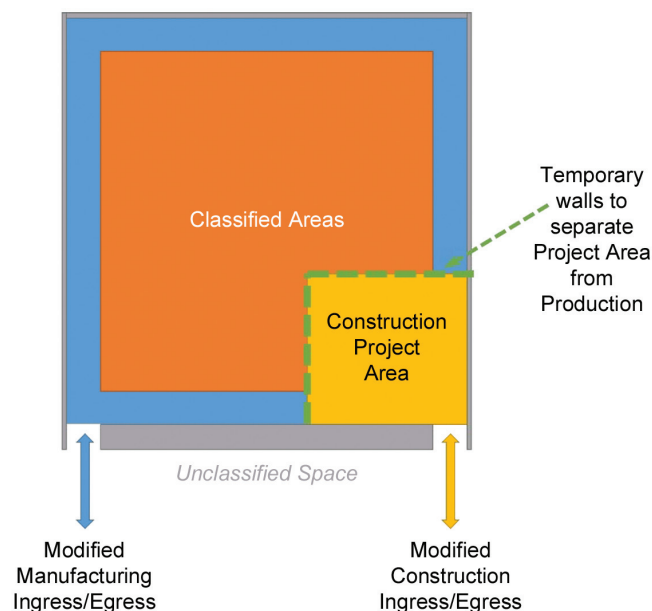


Figure 2. Example high-level logistics review: potential construction conditions.

demolition – for instance, controlling the removal of debris to prevent contamination. Assessment of existing building space without considering construction logistics could fail to discover that the work area is not accessible without construction and operations crossing paths. This can be extremely costly if the area of work is completely surrounded by operational areas that must continue to function. This scenario could later lead to product risk and create additional mitigation costs beyond what was planned for in the contingencies of a ROM.

Many large pharmaceutical construction projects are occurring on sites where a significant project has not taken place in years. A construction project within a pharmaceutical environment needs to be both managed and constructed by knowledgeable and well-trained personnel. The business planning phase should include evaluation of the availability of trained contractors and required training for new contractors. Costs for traveling or specialty contractors need to be included if there are not sufficient contractors that are local or experienced with the facility. Budgets for training programs also should be established at this phase.

Facility Planning, Design, and Preliminary Engineering

The overall space requirements should be considered during programming. As these requirements are defined and preliminary engineering takes place, the construction logistics plan can be developed.

Requirements from operations for both the design as well as the logistics during construction must be determined at this phase prior to implementation. Input for access and shutdowns needs to be provided to help define the logistics plan.

The construction logistics defined during business planning will be expanded upon, creating more detail for the actual effect of construction on adjacent areas and systems. Normally, the project team will define building and user requirements during programming. Figure 3 features a sample of a partial programming questionnaire. In pharmaceutical construction, the same will need to be done for the construction space and process. Schematic or preliminary design follows programming and includes a high-level physical drawing of the area of construction, including planned access routes. HVAC diagrams showing conditions during construction, or each phase of the construction, need to be reviewed for potential impacts on adjacent operations.

Programming Questionnaire

Construction Logistics

Renovation and Compliance Upgrade Project Planning

Anytown, USA

September 01, 2013

The objective of this programming study questionnaire is to identify operational adjacencies, analyze workflows and requirements. Your input will be used to develop a preliminary construction logistics and controls plan. The preliminary plan will be used to evaluate the feasibility of contiguous construction while maintaining operational GMP conditions.

Your input is important to us and to the successful development of this project. This questionnaire is intended to help us obtain your direct input on the following areas:

- A floor plan of the existing formulation area with current personnel, material, and product flow has been included. The project area of work has also been included.
- It may be helpful if specific people fill out the specific sections: General, Operational/Manufacturing, and Facilities.
- This will be a continuing process for data gathering.
- We will review this questionnaire and other info with you during the Kick-Off/Data Gathering Meeting.

DEPARTMENT: Formulation Area

- Does the attached floor plan and workflow accurately represent current operations?
- What are the current shifts and work hours?
- What are the projected shifts and work hours?
- What are the current gowning requirements?
- Are there any planned shutdowns of your area?

Survey Completed by:

NAME	_____
DEPARTMENT	_____
TITLE	_____
DATE	_____
OFFICE PHONE	_____
CELL PHONE	_____
FAX	_____
E-MAIL	_____

Figure 3. Programming questionnaire.

The criticality of the project and number of people expected to be working on it drives the number of field-staff needed to manage the project; however, subcontractor selection can have a huge influence on the ability to contain any construction impact. If the site or project doesn't maintain trained, knowledgeable subcontractors that regularly work in pharmaceutical facilities, the management team size must be increased and significant training of all subcontractor personnel must be planned before the project starts to maintain product safety. An evaluation of an area's contractors can determine if this is a risk factor for a particular project.

Programming for construction logistics must include:

1. The anticipated flow of construction personnel to and from the worksite, including definition of:
 - a. Expected gowning and Personal Protective Equipment (PPE) requirements at different points
 - b. Expected containment and isolation requirements for personnel traffic
2. The flow of construction materials in and out of the space, including identification of:
 - a. Expected inspection and cleaning points and requirements for incoming materials
 - b. Expected containment requirements for outgoing materials; for example, sealed debris containers that are cleaned prior to leaving the construction area
3. HVAC requirements during construction, so that these can be built into the design documents. Many times, HVAC demolition and new installations are phased, in order to:
 - a. Separate construction from operations, including the

- construction pressurization plan
- b. Complete construction modifications
- c. Reconnect the completed construction area to turn back over to operations

This approach could require three or more sets of drawings showing the work to be completed in each phase, which engineering must anticipate in its planning.

The deliverable in this phase is a written description of the requirements of construction, which allows for project execution without impacting or contaminating adjacent production space.

Design, construction management and adjacent operations members of the project team should thoroughly examine the project description and drawings to confirm that requirements to construct adjacent to operations have been met. In addition, adjacent production schedules should be revisited at this point, to account for changes in production that could impact construction.

Once the above tasks are completed, isolation, containment and construction logistics requirements will have been sufficiently defined to allow for cost estimating and detailed engineering. The budget, or scope of work, can then be

adjusted and reviewed to confirm the final site selection and project value. An example of a simplified checklist that can be used to confirm your logistics plan is completed can be seen in Table A.

The level of effort and detail applying these practices will be determined by the complexity of the project and amount of risk to adjacent operations. Tools such as the Ishikawa diagram (fishbone diagram) can be used to help identify risks that need to be controlled - *Figure 4*.

Detailed Engineering

During detailed engineering, the design is completed with full detail to allow the project to be accurately bid and constructed.

In addition to standard engineering documents, the design documents for pharmaceutical work must include floor plans showing isolation barriers, sequenced drawings showing HVAC changes for construction pressurizations and final conditions, and utility diagrams reflecting the sequence of construction for demolition and tie-ins. A typical engineering design will have a demolition drawing and a new, finished installation drawing. The utilities sequence is not typically taken into account, as it is considered a means and

Construction Separation/Logistics Checklist		Completed?	N/A?
HVAC modifications and balancing completed to separate construction from operations?			
	Pre-balanced and pressurization checks completed prior to any work taking place		
	Additional filtration or removal of return air from construction area that feeds into operational areas		
	All supply air and exhaust air balanced to keep construction area negatively pressurized to surrounding GMP spaces		
	Balancing & Airflow Diagrams (showing pressurization) checked for compliance prior to re-starting operations and/or construction		
Construction Access defined and separated from Operations?			
	Material/Debris access locations, cleaning and inspection plans in place		
	Personnel access locations, gowning, and PPE plans in place		
	Personnel training plans in place before allowed access		
	Physical barriers in place for each use/classification		
	Changes to operational procedures or additional cleaning defined		
Electronic Disconnections/Shutdowns traced and planned for separation of operations from new construction?			
	All affected feeds defined and planned for modifications		
	All material available prior to modification/shutdown		
Piping disconnections/shutdowns traced and planned for separation of operations from new construction?			
	All affected piping systems defined and planned for modifications		
	All materials available prior to modification/shutdown		

Table A. Construction separation/logistics checklist.

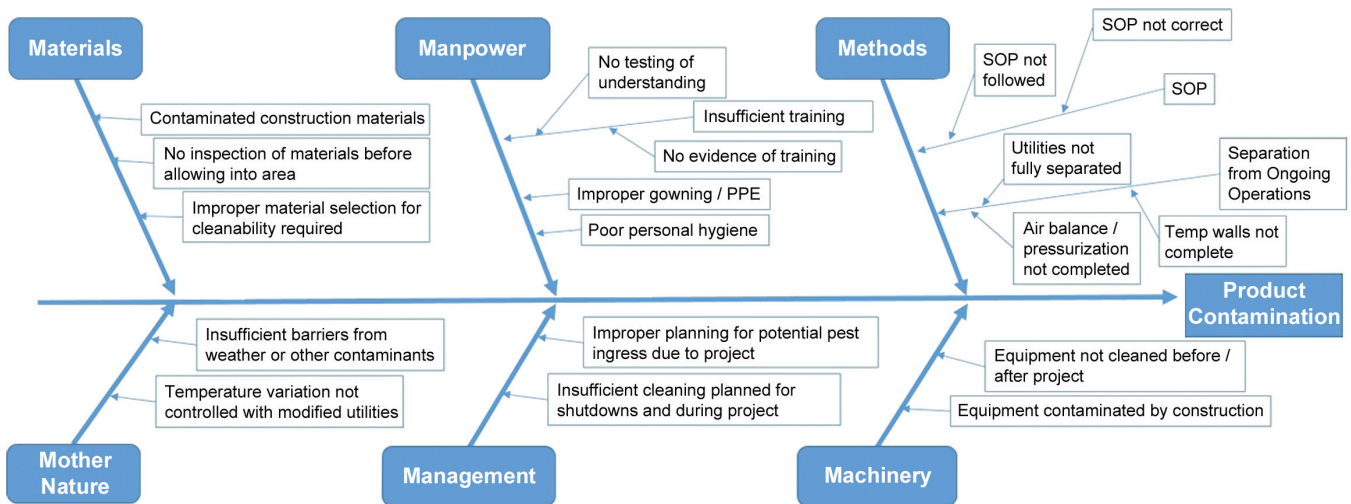


Figure 4. Ishikawa diagram.

methods issue to be resolved by construction management in the field. However, the sequence is clearly defined in the scope of work to support and clarify the isolation sequence and allow for quality assurance planning.

Standard Operating Procedures (SOP) must be referenced, revised or created to address the isolation plan specific to the project. The SOP documents must be incorporated into the scope of work to ensure that bidders and contractors are clear on the requirements for the specific project.

All engineering documents must incorporate material selections and design requirements, providing specific information and two-way communications between the construction team and quality assurance.

Planning After Design Completion

After the design is completed, but before construction begins, the impact assessment should be finalized with appropriate controls planned for the work to take place. In order to maintain adjacent production, enforced shutdowns are often phased to minimize the duration that production areas need to be shutdown. The phases of manufacturing operations to be maintained are critical in deciding the requirements needed.²

A logistics plan must be finalized with approvals from quality assurance, operations, maintenance, engineering and construction. The causes and effects of potential contamination must be reviewed and planned for using methods such as an Ishikawa Diagram.³

Logistics plan considerations include:

1. Planning and implementation of all personnel routes, gowning and PPE
 - a. Example: gowning may be required to be worn to get to the construction area, then removed and new gown-

ing worn to return through classified spaces.

2. Consideration of material ingress and egress, as well as the level of containment required for the materials
 - a. Example: when materials pass through a classified area, they may need to be inspected prior to entry and/or put in sealed or enclosed containers that are cleaned.
3. Determination of temporary barrier requirements and locations, and planning for their installation to isolate the construction area from production
 - a. Example: temporary walls may be constructed of a simple plastic curtain, or may need to be more rigid and constructed of metal, drywall or plastic and caulked in, due to potential damage or pressurization requirements.

Next, finalize all SOPs governing the work to take place, in addition to any modifications to operational SOPs for the surrounding production areas. Finally, determine verification requirements for the construction area and surrounding production areas before work takes place. This could include:

1. Additional particle and/or viable monitoring instituted in surrounding areas to continually confirm that construction is not impacting production
2. Periodic or continual testing of construction area pressurization to ensure that the area stays negative to the surrounding production

If it is possible to physically access the area of work, the final design documents should be fully reviewed in the field to ensure that the existing conditions match the planned design. A construction project's contamination plan and overall project plan can be completely derailed if unplanned issues exist that were not fully realized until after work begins. If

unplanned systems are accidentally modified or changed, product contamination could result.

By following the steps outlined and defined in the business planning, facility planning and engineering phases of the project life cycle above, the phased impact on utilities and timing of shutdowns should be well understood, and can then be planned for work completion.

Project Execution

Once the design, logistics and appropriate containment plans are in place and fully approved by quality assurance and operations, the project can start.

Prior to the work taking place, each individual worker must be trained on all SOPs and routes for construction. This could include different routes and containment plans for each phase of construction in a multi-phase implementation. Emphasis on minimizing bio-burden, both during shutdowns and construction, must be fully understood by every worker.⁴

The importance of this is highlighted by a 2005 case study from the *PDA Journal of Pharmaceutical Science and Technology*, where it was reported that contaminants discovered in media fill vials had migrated from the area of construction activity.¹

Particularly in a pharmaceutical environment, it is crucial to understand and remember the bigger picture and broader implications for protecting the people, products and property. The whole job site should be regularly reviewed for any hazards that could potentially cause ingredient or product contamination, research animal disturbance, product manufacturing disturbance, production delays that could affect ingredient lifespans and quality, or any other issues that could possibly harm the manufacturer's product quality or reputation.

The following are examples of items that must be completed at the start of work:

1. All systems and facilities that will be modified should be pre-tested to confirm that acceptable parameters were maintained while production was underway.
2. Systems that will be modified for construction must be shut down.
 - a. Install barriers to isolate the project area from production. Barrier installation must be coordinated with pressurization requirements.
 - i. The construction of the barriers varies depending on the level of cleanliness of the adjacent production.
 - ii. Example: in classified spaces, it is critical to have barriers that are constructed of non-organic cleanable materials, are sealed to adjacent spaces, and are sufficiently tamper-resistant to avoid damage that could contaminate adjacent production.
 - b. Disconnect and isolate systems that will be brought

back online for production to continue while the construction takes place. Complete all validation and testing to ensure that these systems are performing within acceptable parameters for production after the modifications.

- i. Example: isolate HVAC branches or systems and re-balance operational areas to their requirements, in addition to the construction area to maintain negative pressure to adjacent spaces for contamination control.
 - c. Complete cleaning and validation of adjacent areas to confirm that they are back to acceptable levels to return to production.
3. Once the work area is separated, construction can proceed on the project. All previously developed plans and SOPs must be followed to ensure that the work progresses without affecting other areas.
4. At the completion of the project or following each phase, another shutdown of production is needed. Similar steps should be followed to put all systems and utilities into their next or final configuration. All systems and facilities should then have post-testing and cleaning to confirm readiness to return to production.

Field observations completed by *Controlled Environments* identified an organization faced with cleanroom start-up delays following a construction shutdown, because *Streptomyces* bacterial spores were found even after triple-cleaning the facility.⁵

Cleanroom processes must be successfully cleared at each stage of construction before products are able to move on to the next stage. Closely monitoring cleanroom sterility at all stages will help ensure product quality and safety.

Project Closure

At the completion of the construction work, after the final shutdown is completed, the new area is turned over to operations for final cleaning. At closure, all documents are turned over to quality assurance for review and approval. Once reviewed and approved, the project is complete.

Case Study: Filling Line Installation

A recent project created a space for a new filling line with Grade-A filling space, inside Restricted Air Barrier Systems (RABS), surrounded by Grade-B personnel space. The new Grade-A/B filling space was adjacent to existing to Grade-C and Grade-D space and built in what was previously controlled-non-classified space. Access to the new Grade-A/B filling space was through controlled-non-classified space during construction. See Figures 5 to 7 showing the configurations of the space throughout the project.

This particular project required the following:

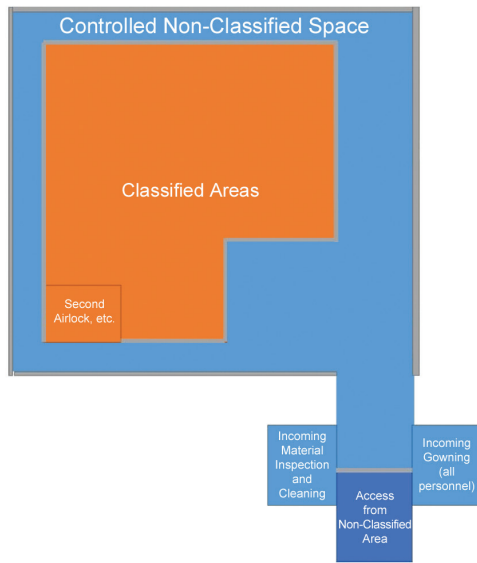


Figure 5. Case Study: existing conditions.

1. HVAC modifications

- a. Pre-balance and pressurization checks validated the HVAC system for prior production.
- b. Temporary exhaust was installed to keep construction area negative to the surrounding space.
- c. The existing supply, return and exhaust were disconnected from the area.
- d. Operation areas were re-balanced and confirmed for the pressurization of the construction area to return to service.
- e. Complete construction of all new duct and HEPA banks was completed while operations were in pro-

duction in adjacent spaces. The new systems don't connect to existing systems at this stage.

- f. One final, short shutdown was needed to connect and startup the new equipment to bring the space into use. Final balancing and pressurization was completed to turn the area over to operations for use. Smoke studies and equipment testing were able to take place post-construction.

2. Construction Access

a. Material Access and Egress

- i. Incoming materials were required to be inspected, cleaned and wrapped at the in-going material airlock to contain anything being dropped while moving through controlled-non-classified areas.
- ii. Outgoing debris and excess materials were inspected, cleaned (or placed in carts that had their exterior cleaned) and wrapped at the temporary construction airlock to contain anything being dropped while moving through controlled-non-classified areas.

b. Personnel Access and Egress

- i. Incoming personnel put on gowning in a similar fashion to operations personnel. The gowning was then removed when they entered the temporary construction airlock.
- ii. PPE in the construction space followed standard OSHA requirements for the work being performed.

c. Personnel Training

- i. All workers went through training covering all of the containment and construction requirements for the project. This was led by operations with workers tested for understanding at the completion of training, before starting work.

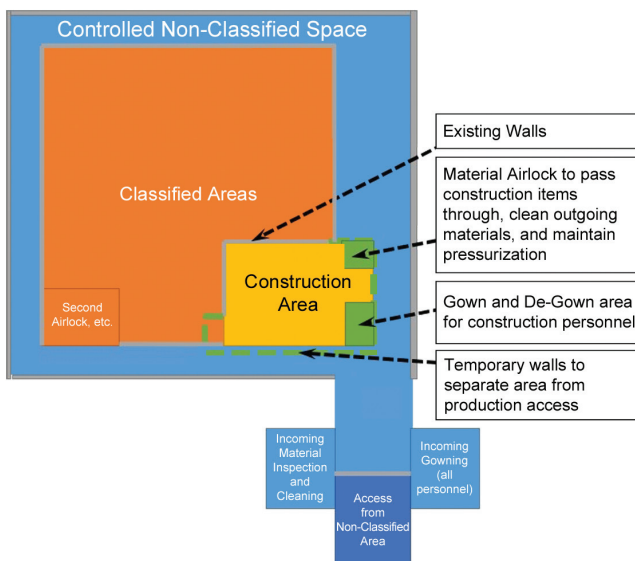


Figure 6. Case Study: construction conditions.

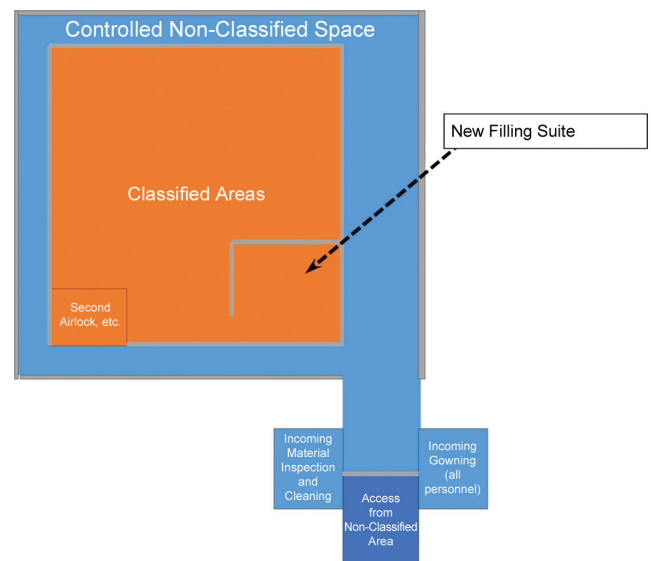


Figure 7. Case Study: final (turnover) condition.

- d. Temporary Walls
 - i. At all points where the work area joined to classified spaces, walls were constructed of metal studs, plastic sheeting and caulked hard-plastic for damage protection and cleanability.
 - ii. At all points where the work area affected the controlled-non-classified space, a metal stud and plastic sheeting wall was constructed for pressurization. Plastic sheeting was installed on both sides to minimize the effect of small amounts of damage.
 - iii. To create construction area airlocks (both personnel and material-pass-through) inside the construction footprint, a metal stud and plastic sheeting wall was constructed to control contamination migration from the construction area.
 - iv. All activities that created a large amount of particulates in the construction area were required to drape plastic sheeting around their specific area to minimize migration of dust particles even inside the construction space.
- e. Cleaning Requirements
 - i. Operations reviewed the impact of the additional personnel and material traffic through their access points. They increased the frequency of floor cleaning and wipe downs around the construction area.
 - ii. Construction was required to clean both the material and personnel airlock multiple times daily.
3. Electrical System Changes
 - a. Power feeds were reviewed on the site to confirm their impacts prior to starting work.
 - b. New work was installed as much as possible to prepare for the shutdowns.
 - c. Affected electrical systems had shutdowns coordinated with operations to allow for modifications to the electrical system.
4. Piping and Utility Changes
 - a. Each of the many utilities that were installed for this project (water for injection, purified water, pharmaceutical nitrogen, etc.) were verified in field for their actual existing condition to confirm plans for shutdowns.
 - b. New work was installed as much as possible to prepare for the shutdowns.
 - c. Each utility had a shutdown to tie-in the new systems and reconfigure the existing systems as required.
5. Summary of Case Study
 - a. These practices listed in this case study allowed construction to complete while operations continued in adjacent space. With the additional controls and procedures, no contamination or product issues occurred. The shutdown of operations was limited to two short operational stoppages for separation and reconnection of the space to operational areas.

Conclusion

This article outlines and defines practices to be followed to minimize risks during construction in an active pharmaceutical environment. These steps allow for planning and input from the appropriate parties to account for additional actions that are needed for pharmaceutical construction. As the project progresses through the life cycle, the level of detail increases until the project is finalized and fully approved for project execution. This allows all parties to understand and follow the strategy that is in place to avoid risk of product contamination.

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