good manufacturing practices

Comprehensive equipment and utility change control for GMP production facilities

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This article provides a systematic process for designing utility change control procedures for new equipment in GMP production facilities.

Annex 15 of the "EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use" defines "change control" as: "A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes" [1]. The FDA's own guidances refer to change control as "…managing change to prevent unintended consequences" [2].

In practice, many companies limit change control to documentation such as batch records, standard operating procedures, protocols, and specifications, while handling equipment and facilities change control in isolation, if at all. As a result, new equipment is often installed and connected to utilities without prior input and approval from facilities, engineering, validation, and quality personnel.

While many in the pharmaceutical industry may conceptually understand change control for equipment and facilities, most lack the knowledge to apply this control to highly sophisticated equipment and the utilities to which the equipment connects. This article provides a detailed framework that companies can use to design compliant equipment change control procedures.

Scope of change control

Equipment change control (ECC) applies to all GMP and non-GMP equipment that connects to a facility's GMP utilities. Utilities include electrical, water systems, drainage, clean gases, venting/exhausting of heat and fumes, equipment cooling, clean steam, GMP servers and networks, HVAC, and any system that has direct or indirect impact on cleanroom operations. Non-GMP equipment is included in ECC because the utilities are shared.

If you are fortunate, your company's R&D departments are located in buildings with utilities dedicated to research activities. However, many companies must share buildings and utilities between R&D and GMP operations. In such cases, any time a piece of equipment (R&D or GMP) is connected to a shared utility, it has the potential to affect the performance of other equipment connected to the utility or even damage the utility. This is why ECC is so important and where it shows its value. One of the biggest errors you can make is to assume that the utility you intend to connect to is dedicated to R&D.

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ECC can be grouped into six primary stages: (1) determining the new equipment's utility/IT requirements; (2) comparing the new equipment utility requirements to existing utility capabilities; (3) assessing the new equipment's impact on utility validations; (4) equipment installation, validation/calibration; (5) review/approval of turnover packages, executed validation data/reports, and release of equipment for GMP use; and (6) evaluation of the effectiveness of the equipment change control.

1. Determining the new equipment's utility/IT requirements

The starting point for ECC, and one of its most important steps, is to determine the new equipment's utility and IT requirements. It's critical to detail the equipment's utility requirements *before purchasing* the equipment because the cost of purchasing the equipment can often double when you include utility upgrades and other related equipment purchases required to ensure the desired equipment's proper operation.

You can find the utility requirements in the owner's manual or directly from the equipment manufacturer. The manufacturer can often provide specification sheets detailing the equipment's requirements for electrical, venting/exhausting, heat dissipation or cooling, water quality, clean gases, clean steam, drainage, and explosion proofing. The specification sheet should also include a list of materials of construction that is critical for product-contact equipment used in GMP manufacturing. It's important to determine the requirements for each utility when the equipment is operating at full capacity. Your company's engineers and facility mechanics can be a great resource in helping you come up with an exhaustive list of impacted utilities.

The need to connect new equipment to GMP servers and networks is often overlooked. Equipment configured with outputs that can be connected to GMP servers is now the norm for new instruments and represents one of several methods for ensuring the integrity of electronic data. However, companies often encounter problems when purchasing used and refurbished equipment that the manufacturer originally designed as stand-alone equipment without networking capabilities. Data integrity compliance doesn't vanish when equipment is unable to connect to validated networks. Such equipment creates compliance issues that your company must develop a plan to address.

2. Comparing the new equipment utility requirements to existing utility capabilities

Electrical. To determine if an electric utility is capable of meeting the needs of your new equipment, facilities personnel will first need to know where it will be installed. This seems obvious, but too often those who purchase equipment don't know exactly where the new equipment will be installed. A common response is that the equipment "will be put in one of the cleanrooms." That can be a problem because it's unlikely that each cleanroom is configured exactly the same in terms of the type of power available and the number of connections.

If the equipment requires a significant power draw, the circuit panel will need to be evaluated to ensure that the panel is not only fed by the right power supply but is also balanced, meaning that the total amperage requirements of the electrical equipment in a shared-neutral installation is distributed equally among the number of available electrical circuits servicing the installation. Obviously,

the equipment purchaser is not the right person to make this determination, so an important element of change control is enlisting subject matter experts (in this case an electrician or competent facilities technician) to make technical assessments on critical parameters.

Emergency generators. Emergency power generation is the most ignored utility. Emergency generators are typically installed during facility construction, and their size reflects only the equipment that was on-site or projected to be on-site at that time. If the new piece of equipment must be connected to an e-power circuit and the equipment's power requirements are high, you should evaluate the emergency generator capacity in comparison to the current load.

You should not rely solely on the architectural as-built drawings, because new equipment and power connections are frequently added without redlining the drawings. A qualified electrical contractor can install monitors at the power source to the facility and trend the power draw over a few weeks or a month. You can then compare the results of this test to the emergency generator's load rating to determine whether the generator has the capacity to meet the new equipment's power needs.

Exhausting of solvents. In pharmaceutical and biopharmaceutical cleanrooms, removing any trace of hazardous vapors from the room or equipment is essential. The hazards of exhausting solvents include fire or explosion as well as the resulting contamination of production, storage, and cleanroom areas by smoke or other substances released by a fire. Solvents should be exhausted through non-corrosive and non-flammable ducting. Fluoropolymer coated stainless steel ducting can be safer and more effective than traditional piping. Additionally, cleanroom exhaust, fume hoods, snorkels, walk-in reactor enclosures, and biological safety cabinets used to store chemicals with corrosive fumes, can all benefit from the use of fluoropolymer coated stainless steel duct, rather than pipe. Refer to the National Fire Protection Association's "Standard for the Protection of Semiconductor Fabrication Facilities" (NFPA 318) and local requirements for materials of construction for ducting in your area.

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Heat dissipation. While it doesn't usually receive much attention, heat generated by production equipment can impact temperature control in GMP production suites and make it difficult for the HVAC system to maintain temperature set points and operate within validated ranges. Rooms with heat-generating equipment such as product drying ovens or pan coaters for tablet coating should be configured with insulated ducting to remove the heat.

Cooling. Some types of production equipment, such as large production spray dryers, require connections to chilled water or stand-alone chillers that use specialized refrigerants for cooling. This equipment often requires installation of process piping wrapped with non-shedding insulation to deliver the chilled water to its point of use in cleanrooms. Process piping installation requires that the affected cleanrooms be shut down for pipe penetration through the cleanroom walls as well as testing for refrigerant leakage.

Water quality. Pharmaceutical manufacturing uses a variety of grades of water, four of which are typically produced and used on-site at manufacturing facilities: purified, water for injection, pure steam, and water for hemodialysis. Confirm the quality of water required for new equipment as well as the required pressure, flow rate, and temperature (as applicable). Some types of equipment, such as autoclaves, require clean steam directly but also typically require reverse osmosis/deionized water (RO/DI) indirectly as feed water for the clean steam generators. When considering adding an autoclave or replacing an existing autoclave with a larger-capacity unit, it's important to add the consumption rates of all equipment using clean steam and equipment that uses only RO/DI.

Clean gases. Pharmaceutical production settings often require nitrogen, oxygen, argon, carbon dioxide, clean compressed air and other specialty high purity gases to operate production equipment; in spray drying applications; to fill head space in product containers; and for fermentation, extraction, and purification. A wide variety of utilities generate gases onsite and distribute them throughout a production facility to points of use in cleanrooms. Alternatively, some facilities use stationary tanks that can store 6,000 liters or more of gas (in liquid or vapor phase) and are configured with telemetry devices to alert service providers to refill the tanks before the gas runs out. In either case, introducing new equipment that uses specialty gas requires an assessment to ensure the utility can meet the requirements of all connected equipment.

In addition to the gas-generating and storage capacity, you must also evaluate the length and internal diameter of gas distribution piping to ensure that the gas flow will be able to keep up with the demand of adding another piece of equipment. Determine the flow rate, pressure, and volume requirements of each piece of equipment currently installed and compare them with the system's capacity. The last thing you want is to spend $2 million for a spray dryer and find out that the nitrogen system and piping is too small to satisfy the dryer's consumption.

Drainage. Drainage is the most difficult utility to retrofit, and not all drains are created equal. Some are designed to transfer liquids directly to normal waste streams, some treat the effluent before sending it to city waste, and others capture the effluent so it can be taken away and processed. Ensure that the room in which new equipment is to be installed has the proper drain system with floor connections next to the intended equipment location. If the room does not have drains or has the wrong type of drain, be prepared to spend big dollars and allow for significant downtime to trench new drains. Note that, depending on the city or state, a permit will likely be required for the new drainage.

Explosion proofing. Pharmaceutical production equipment and cleanrooms, including those than employ solvent handling and processing, such as spray drying, are categorized in terms of their explosion potential. In North America, hazardous location electrical codes and standards use a "class, division" system as the basis for classifying hazardous locations. Locations are divided into three classes based on the type of hazard and the explosive characteristics of the material and two divisions based on the occurrence of risk of fire or explosion the material presents.

You can mitigate the potential for explosions in cleanrooms by ensuring that electrical outlets, lighting, and sources of heat and spark are separated from the surrounding environment to protect them from dust, moisture, vapors, or other contaminants. This isolation can also protect the surrounding environment from outgassing, heat, arcing, air pressure leakage, electromagnetic interference, and other conditions that could negatively affect process integrity and personal safety.

In cases where cleanrooms can pose an explosion risk based on the materials that will be processed, it's prudent to seek the advice of a qualified industrial electrician or other expert to assess the controls currently in place and determine whether additional protection is needed. This is particularly important for manufacturing processes that don't use physical containment or isolators to transfer flammable materials and solvents from one piece of equipment to the next and rely solely on the cleanroom infrastructure for protection. Some types of production equipment, including specialized computers, are certified to meet the requirements of the specific hazardous location class and division to provide an extra level of protection for the process, facility, and personnel.

GMP networks and servers. When connecting new equipment to GMP networks and servers, you must define the critical quality attributes (CQA) of the product being manufactured and ensure that CQA data is automatically sent from the equipment to servers, is backed up per schedule, and is periodically tested for retrieval of data and metadata to ensure that the data is attributable, legible, contemporaneous, original, and accurate (ALCOA). This requirement is often overlooked when installing new equipment.

Formal change control for new equipment, and even equipment that is moved from one location to another, must include an ALCOA assessment when connecting to GMP networks. This is particularly important when installing additional network data cabling to accommodate newly purchased equipment. The network architecture must be able to identify the equipment connected to specific data port IDs located in cleanrooms and map the equipment's data to secure and compliant server locations.

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FDA warning letters for computer networks cite the failure of validation documentation to include complete updated design documentation, and complete wiring/network diagrams to identify all computers and devices connected to a system. Given that networks change frequently, maintaining accurate diagrams that reflect the network's current configuration requires revision control (formal change control). Additionally, the World Health Organization (WHO) guidance on validation of computer systems states that GxP computer systems and network validation should include the system physical and logical architecture and map out the relevant workflows and data flows.

Photo 1: Ensure that the room in which new equipment is to be installed has the proper drain system with floor connections next to the intended equipment location or be prepared to spend big dollars and allow for significant downtime to trench new drains.

3. Assessing the new equipment's impact on utility validations

Once you've determined the existing utility capacity and compared it to the new equipment requirements, assess whether installing the new equipment will affect previously executed utility validations. If the installation and functionality of new equipment requires adding new utility points of use (POU) to connect the equipment to the utility, you will need to update the drawings, schematics, and materials of construction detailed in the utility's installation qualification (IQ) and assign new piping and instrumentation diagram numbers to the POU. Tied to this change, the operational qualification (OQ) will likely require revision to test the functionality of the new POU and, for gas systems, a pressure-hold challenge will be required.

Performance qualification. The performance qualification (PQ) tests the ability of the utility to perform consistently over long periods of time within tolerances deemed acceptable by the manufacturing process as a whole and should include challenging the utility while under a load comparable to that expected during routine production. This is the most important element to test when connecting new equipment to an existing utility because it confirms whether the utility will be able to keep up with demand while all POU are in operation serving equipment.

For example, consider a CDMO that is adding a large commercial-scale spray dryer to its current collection of three small-scale spray dryers. The CDMO plans to use all of the spray dryers simultaneously to manufacture sponsor products and requires the use of pharmaceutical-grade nitrogen. The ability of the nitrogen system to keep up with demand is essential, as the quality of sponsor products and timelines for deliverables is paramount to the CDMO's success. Repeating part or all of the nitrogen's PQ while operating all spray dryers simultaneously provides documented evidence that the nitrogen system will meet the requirements of all connected equipment.

4. Equipment installation and calibration/validation

When calibrating equipment, it is important that the calibration match or exceed the intended operational range of the equipment that will be used during actual production activities. Too often, equipment is operated at rpm, flow rates, compression forces, or other settings outside the calibrated range of the equipment. This is a common audit observation made in sponsor and regulatory inspections of production facilities.

Requirements for validating equipment should be detailed in a validation master plan (VMP) that outlines the quality requirements for the types of equipment already in-house. The VMP defines the systems, equipment, methods, and facilities that are in the scope of the plan; compliance requirements for validation, including how the validated state will be maintained; required validation deliverables; and the validation risk-mitigation strategy.

Equipment-specific validation protocols must follow the requirements of the VMP whether written in-house or provided by the equipment manufacturer or installation company. Regulatory agencies commonly observe deviations from the VMP requirements on audits, because companies too often approve the equipment manufacturer's validation protocols without carefully comparing them to the VMP.

Equipment change control should reference the requirements for calibration and validation detailed in the VMP. The challenge arises when a company purchases a state-of-the-art piece of equipment that is not within the scope of the VMP. In this case, the most compliant and thorough course of action is to review the equipment manufacturer's validation package and identify IQ, OQ, and PQ gaps for the equipment's intended use. The equipment change control should reference both the manufacturer's validation package and the gap validations that you will perform.

Note that in all cases, the equipment owner as well as validation and quality personnel must approve the manufacturer's validation protocols and your internal gap validation protocols prior to execution. You should also update the VMP to include the validation requirements for the new equipment and document these deliverables in the equipment change control.

A common mistake companies make is to forget to complete a written statement, approved by all parties, including quality personnel, that the equipment is released for GMP use.

5. Review/approval of turnover packages, executed validation data/reports and release of equipment for GMP use

Some companies often treat this stage in the change control process as a rubber-stamp activity, but it is an extremely critical phase, where you can identify and remedy issues, gaps, deviations, and deficiencies with input from personnel in quality, engineering, validation, and the department owning the equipment. The endgame is not just to sign off and archive validations and their change control documentation, but also to prepare for inspection by regulatory authorities. As such, companies should not rush this stage of the process or simply rubber stamp the process as approved.

A common mistake companies make is to forget to complete a written statement, approved by all parties, including quality personnel, that the equipment is released for GMP use. Although all of the associated val-

idation and calibration documentation may be approved, inspectors from regulatory agencies around the world look for this designation that the equipment is suitable and released for GMP activities.

6. Evaluation of the effectiveness of the equipment change control

An effectiveness check is a valuable way to identify where equipment commissioning gaps and problems may exist and also for formulating a plan to prevent the same issues from occurring during future activities. In practice, companies rarely perform this evaluation, as the staff members involved in the change control are generally quickly redirected to the next new piece of equipment to commission. As a result, companies tend to repeat the same failures over and over unless a robust change control effectiveness check is built into the equipment commissioning process as a required step.

Takeaway

New production equipment can be exciting to the end user. It is often seen as a stainless-steel marvel that provides technical capabilities and increased processing speed that was not previously available. However, such equipment is often far from plug-and-play. In many cases, the equipment will impact the electrical, gas, water, drainage, heating, and cooling utilities servicing a wide array of equipment in the GMP setting.

The six stages of equipment change control discussed in this article provide a detailed roadmap for evaluating a facility's current capabilities and comparing them to the requirements of new equipment. Careful evaluation, planning, and direct input from engineering, validation, and quality departments, can help you avoid the common pitfalls associated with installing new equipment. *T&C*

References

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