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The year 2006 marked the 30th anniversary of the formal introduction of process validation concepts and requirements by the US Food and Drug Administration. Despite more than 30 years of common usage, only recently have the theory and practice of validation become fully developed and widely understood, although many misconceptions remain.

Origins of validation

The concept and practice of pharmaceutical validation first became law in June 1963 with the publication of good manufacturing practice (GMP) regulations. Before that, there was no requirement to validate production processes. Product quality was presumably ensured by collecting and analyzing drug samples. Despite the law, there remained little inspectional focus on process validation. This changed, however, when a nationwide epidemic of septicemia occurred that was caused by contaminated intravenous fluids (large-volume parenterals, LVPs). Between July 1970 and April 1971 in many hospitals in the United States, there were outbreaks of nosocomial (hospital acquired) septicemia caused by *Enterobacter cloacae* or *E. agglomerans*. All of these hospitals used infusion products made by one manufacturer, and all affected patients had onset of septicemia while receiving the company’s infusion products.

Septicemia was epidemiologically and microbiologically traced to intrinsic contamination of the company’s screw-cap closure for infusion bottles, which were sealed with a newly introduced elastomer liner. Investigations in the laboratory and in the manufacturing plant into the mechanism of contamination of these products revealed the following:

- Epidemic strains were present in numerous areas throughout the manufacturing plants
- Viable microorganisms gained access to the interior of screw-cap closures after the autoclave step of production
- Cooling closures actively drew moisture through the thread interstices into the inner-most depths of the closure
- Transfer of contaminants from closures to fluid was easily effected by simple manipulations duplicating normal in-hospital use (1).

Nine deaths were initially attributed to this outbreak. Further analysis estimated that between 2000 and 8000 cases had actually occurred. Not all cases ended with the death of a patient. Nonetheless, nearly 10% of the case patients in the studied hospitals died while bacteremic or shortly thereafter (2).

On closer examination, FDA, the Centers for Disease Control and Prevention (CDC), and company officials discovered several manufacturing problems. Although component bioburden (bottles, caps, etc.) was acceptable pre- and poststerilization, product cooling and additional downstream processing were identified as the sources of contamination. Sterilizer cooling water was considered a possible source of contaminants. Water for bottle cooling was obtained from a municipal source, and chlorine content was frequently below that required for...
In late 1971, FDA began an intensive review and evaluation of LVP production because of justified concerns that not all manufacturers could ensure the level of microbiological quality required for LVP drug products. This review was first limited to specific, individual manufacturing or container-closure problems. In 1973, the review expanded to include extensive sampling of LVP products, comprehensive facility inspections, and detailed discussions between the industry and FDA (3).

In March 1973, another outbreak of LVP-attributed septicemia occurred, this time associated with a different manufacturer and a different product (5% dextrose in lactated ringers or D5LR). A hospital in Milwaukee reported three cases of septicemia that developed within three hours from the start of infusion. Hospital officials suspected that each 1-L bottle of D5LR used was intrinsically contaminated. One patient died as a consequence of their intravenous therapy, and another fell critically ill. Later, CDC learned of two additional cases of septicemia caused by contaminated D5LR, one at another Wisconsin hospital and one in Ohio. The manufacturer recalled more than six lots of contaminated product. The recalled infusion was prepared by a newly modified process which included exposure of the bottles to increased pressure during the autoclave cycle (4).

Concerned with the ongoing problems in the LVP industry, FDA issued a draft proposal in February 1974 that defined requirements and specifications for LVP manufacturing and processing. This was followed with the publication of a draft section to the Code of Federal Regulations, Part 212, “Current Good Manufacturing Practice in the Manufacture, Processing, Packing, or Holding of Large Volume Parenterals for Human Use,” on June 1, 1976. This was the first time FDA had issued well-defined process standards for drug products, and although these standards had been discussed with industry in advance, many manufacturers objected to the limitations now being placed on LVP manufacturing and the obstacles to innovation (3). Consequently, the draft LVP regulations and proposed regulations for small-volume parenterales were withdrawn by the agency, although many of the concepts, particularly validation, were voluntarily applied by industry nonetheless.

So began the start and evolution of validation practices and technologies to the seemingly complex set of rules and guidelines used by industry today. Publications of the late 1970s and early 1980s, particularly those of the Parenteral Drug Association (PDA), introduced the concept of qualification and validation to the industry at large. Companies began to qualify and validate their sterilization processes initially, and then applied these same validation principles to other systems. With FDA’s 1987 Guideline on General Principles of Process Validation, the validation of equipment, systems and processes became widespread and mandatory as manufacturers of all drug types were alerted to FDA’s expectations for process validation (5).

One example of this validation process is the qualification and validation of heating, ventilating, and air conditioning (HVAC), which is universal in the industry. The importance of HVAC to product quality and safety cannot be minimized. This important concept was not lost on FDA, which should be evident for anyone who reads these dated but insightful regulations.

**HVAC system qualification and validation**

The procedures for HVAC validation are now commonly understood. HVAC system validation is always based on design. Engineers and owners design systems, and validation specialists interpret these designs and reduce this information in the form of protocols. Quality assurance professionals and regulatory authorities review the designs at various stages of development to ensure compliance with GMP regulations and appropriate industry standards (7).

The standard sequence for HVAC system validation is installation (IQ), operational (OQ), and performance qualification (PQ). To ensure regulatory compliance, design review begins when drawings and specifications are approximately 35% complete, but always before long lead-time equipment is ordered from vendors (7). Rarely are serious errors or omissions noted during review of HVAC designs, because design criteria are understood by reputable engineers and engineering companies designing these systems.

In nearly all pharmaceutical facilities, multiple air handlers exist, each designed to support a specific zone within the building. Each zone is exhausted by one or more exhaust fans interlocked with the air-handling unit (AHU), and depending on design, return fans also. IQ and OQ protocol boundaries should be set that encompass one AHU and the interlocked return and exhaust fans only. HVAC zones do not operate in isolation but are influenced and controlled by conditions in adjacent zones. This is an important consideration when confirming room pressurizations and air-flow directions during OQ.

Information for validation purposes must be carefully selected from approved HVAC design documents. Drawing sets and specifications literally contain thousands of field-verifiable design elements. The validation process must provide a
high degree of assurance, not absolute assurance, so that the HVAC system was installed and performs according to design. Validation testing is not and cannot be exhaustive. Equipment inspections, test durations, sampling frequency, etc., must be carefully chosen to provide the high degree of assurance stated previously, while avoiding over testing. If proposed testing and inspections are not meaningful, or if the cost/benefit or cost/risk ratios are high, the testing or inspection should be reconsidered. If there is no regulatory requirement and if testing appears meaningless or costly, the test or verification should be omitted.

Installation qualification. Airflow drawings (AFDs) are the most useful of all HVAC design documents, and certainly fundamental to IQ. AFDs provide the system layout in schematic detail, and each drawing is often limited to a single AHU and associated ductwork, instrumentation, dampers and exhaust fans. AFDs are not drawn to scale, and systems cannot be built entirely using AFDs. This is the purpose of duct drawings. AFDs are basic in that they identify system-critical components that must be inspected during IQ. Critical items are those where a tag number is usually assigned: these include AHU, exhaust fan, humidifier, air monitoring device, reheat coil, and so forth.

An IQ protocol must be prepared for documenting the results of system inspection. Protocols should be designed to record data into tables in protocols, with one table reserved for each major component (AHU, exhaust fan, etc.). A tableular protocol format ensures the appropriate comparison between design (specified condition) and system installation (actual condition) is performed. The validation engineer or specialist should inspect system components while construction and installation are in progress for the following reasons:

- Access to system components is easier and missed verifications are minimized. Staging and ladders are usually in place, and ceilings and interstitial spaces remain open for entry. Insulation and other coverings that obscure instruments and dampers have not been applied.
- Deviations often occur because drawings are misinterpreted during protocol preparation, but construction errors do occasionally happen. It is far easier and much less costly to identify and correct a deviation while construction is in progress. Significant additional project cost and schedule delays are inevitable when rework is performed after the system is complete. (8).

Operational qualification. HVAC system OQ begins after system IQ is completed. Outstanding items from IQ may remain open, but provided these are limited in number and do not affect system operation, OQ may proceed. It is important to resolve IQ punchlist items and deviations promptly and to explain the circumstances of each in the IQ Summary Report.

It is advisable to perform HVAC OQ concurrent with system commissioning. Recent changes in the pharmaceutical industry have placed added emphasis on commissioning to reduce validation costs and to accelerate project schedules. More owners and facility managers are using independent commissioning agents to commission HVAC and similar mechanical systems. It is the responsibility of the validation team to interface early with the commissioning agent to benefit from the synergy between commissioning and qualification. Because commissioning is a noncompliant activity, the standards for documentation and control are less formalized. Commissioning affords the opportunity to debug and troubleshoot the system while avoiding some of the deviation reporting commonplace in validation. When properly commissioned, HVAC systems are turned over to the owner free of common operational defects that complicate OQ and PQ.
Airflow diagrams play an important part in HVAC system OQ because airflow directions, air volumes, and room pressurizations are commonly indicated on these drawings. AFDs often contain operational sequences in their margins. These sequences become the basis for system functional testing as well as an important part of the functional requirement specifications for the corresponding building management system.

As a noncompliant activity, commissioning does not include all typical HVAC system OQ tests and verifications. Nonetheless, HVAC OQ protocols must contain the following testing and documentation requirements at a minimum:

- Standard operating procedures for system operation and maintenance are available (at least in draft form)
- System instrumentation is calibrated (may be performed in combination with building management system IQ and OQ)
- System air-balance report is reviewed. Actual room-air change rates are largely responsible for room cleanliness found in HVAC air-balance reports. Because room-air change rates are largely responsible for room cleanliness when HEPA filters are installed, air-change rates must meet specification
- Room-to-room directional airflow must be verified. AFDs commonly include arrows that show airflow direction between rooms. HVAC zone diagrams may include pressurization symbols (+, −, or 0) that designate pressurization. Air moves in the direction of lower pressure. There may or may not be an absolute pressure specification (i.e., 0.05-in. water column), depending on the facility. Airflow direction can be verified, for example, by examining installed differential-pressure gauges, by opening doors slightly and passing a smoke stick or equivalent at the door opening, or by measuring differential pressure under (across) the door. Where an absolute pressure differential is specified, this must be verified using calibrated instrumentation.
- Optional testing includes a 3–30 day burn-in period, where the system is observed for any signs of improper or incorrect operation. Temperature, humidity, and pressurization are passively monitored using the building management system. Because OQ is only a snapshot in time in the lifecycle of an HVAC system, this testing may prove beneficial for facilities and products where unexpected system failures cannot be tolerated.

**Performance qualification.** HVAC system PQ begins only after OQ has been completed successfully. Because airborne viable and nonviable particulate levels, room bioburden, and temperature/relative humidity control rely on a system operating as designed, the transition to PQ must occur only after OQ is complete and all deviations are resolved. Like IQ and OQ, the test procedures for HVAC system PQ are now well defined. Standard PQ acceptance criteria are published by organizations such as the European Commission (EC), International Organization for Standardization (ISO), and FDA.

Currently, the definitive standard for multinational companies is the EC Guide to Good Manufacturing Practice, Revision to Annex 1, Manufacture of Sterile Medicinal Products for Humans and Veterinary Use. The proposed LVP regulations required that air microbial quality be monitored in both critical and noncritical areas, al-
though this was not accepted practice at the time. Allowable microbial levels or the types of organisms permitted were not specified because little historical data were available to FDA. In time, however, voluntary standards and guidance documents appeared that manufacturers agreed to comply with. Both the United States Pharmacopeia and EC Guide to Good Manufacturing Practice provide recommended microbial standards that many manufacturers observe, although these standards are not legally enforceable. With proper HVAC design and construction, room finish selections, disinfection procedures, and personnel gowning, there are few difficulties attaining and then maintaining these standards.

For all particulate-controlled areas in most types of facilities, both nonviable and viable airborne particulate monitoring must be performed. PQ testing also must include the enumeration of surface bioburden using RODAC plates or swabs, preferably before and always after room sanitization and cleaning. Nonviable airborne particulates are measured using calibrated laser-type particle counters while rooms are operating under both static and dynamic conditions (i.e., with personnel present performing all expected operations and activities). Dynamic conditions present a genuine challenge to an HVAC system to maintain air quality, and the test results obtained provide insight into the contaminant products will likely be exposed to. Three days of monitoring under each set of conditions are usually adequate to detect excursions. Air and surface sampling are always conducted where critical operations are performed (e.g., at vial filling or where aseptic connections are made). Those areas where sterile materials are open to the environment, even momentarily, must be monitored during PQ. This includes stopper bowls on filling machines and where filled vials are loaded into lyophilizers.

HVAC PQ also includes testing to prove that rooms and areas are maintained within specified ranges of temperature and relative humidity. This testing may be performed using room instrumentation, provided that instruments are calibrated and the building management system is qualified. One useful test is to demonstrate equivalency between portable temperature/relative humidity instrumentation and the building management system itself. Handheld instruments are placed in the geometric center of the room to be measured. Instruments are activated and allowed to collect data for 24 hours or more. Collect data are then compared with data recorded by the building management system during the same time period. There should be a close correspondence between both the portable instrument and building management system data. If not, one should challenge the placement of the building management system instrumentation because a true indication of room temperature and relative humidity does not exist.

The IVP regulations of 1976 clearly recognized the importance of designing, operating, and validating HVAC systems as one of several means for protecting product quality. FDA understood that the production of contaminated LVPs could have been avoided if HVAC and other critical systems were properly designed and validated. These dated regulations established design criteria, materials of construction, and performance standards for many systems and equipment used by industry today. Although never formally implemented, a lasting effect remains, which currently influences the design and validation of modern facilities. The contribution of the 1976 IVP regulations to drug safety and quality is largely unknown but should be appreciated by all-critical design standards and the origins of validation were their outcome, details that are seldom recognized or understood.

References
5. FDA, Guideline On General Principles Of Process Validation (Food and Drug Administration, Rockville, MD, May 1987).
9. EC, Guide to Good Manufacturing Practice Revision to Annex 1, Manufacture of Sterile Medicinal Products (European Commission, Brussels, Belgium, May 2003).