White Paper Series

BAS Requirements for FDA-Regulated Environments

Challenges and Opportunities for Industries

Title 21 ***CFR*** Part 11 (of the Code of Federal Regulations) describes ***FDA (Food and Drug Administration)*** guidelines on electronic records and signatures. It defines the criteria under which they are considered "to be trustworthy, reliable, and generally equivalent to paper" (Title 21 CFR Part 11 Section 11.1 (a)). In practice, Part 11 requires pharmaceutical manufacturers, medical device manufacturers, biotech companies, and other FDA regulated industries to implement controls (such as audits, system validations, audit trails, electronic signatures, and documentation for software and systems involved in processing data) that are required to be maintained by or in compliance with FDA ***predicate rules***. (See the Glossary of Terms section for explanations of italicized terms.)

The FDA introduced Title 21 CFR Part 11 to promote usage of digital technology in the life sciences industry that would be compatible with the FDA's responsibility to protect public health. This resulted in the need for updating industry processes and procedures that address compliance of "***validated***" systems.

Companies rarely welcome new government regulation of any kind, but the FDA created incentive and opportunity for companies to improve performance and efficiency. Operational improvements from upgraded ***Building Automation Systems (BAS)*** has been especially notable since consistent temperature and humidity within manufacturing facilities is often critically important for quality control in pharmaceutical production.

The constantly monitored and controlled environment under a BAS system reduces variances in atmospheric conditions within spaces, which in turn improves product quality, reduces lost products and waste due to excursions of environmental parameters outside of allowed ranges, and improves the company's financial performance. Providing a BAS with enhanced capabilities that automate many of the former "manual" processes frees staff for additional productive uses of their time. Automatic generation of alarm conditions allows facility staff to take corrective actions before the production process is affected, reducing downtime and improving plant efficiency. As one example, **KMC Controls**, a manufacturer of BAS systems, performed **projects with life sciences companies** that allowed its clients to substantially reduce staffing costs, improve product quality, and reduce product waste.

Although Title 21 CFR Part 11 has an impact on many aspects of building equipment and operations, **this white paper discusses implementation of Building Automation Systems under these FDA regulations.**

Validated System Implementation

"Validated" systems are areas in life science (e.g., pharmaceutical, bio-tech, and medical devices) facilities in which the FDA requires clear, documented assessments of all critical systems. The rationale used to assess these types of systems and spaces and the documentation of that rationale is key to communicating, planning, and (if audited) defending a company's implementation of the validation process.

With the rapid evolution of Building Automation Systems and their application to such "validated" facilities throughout the world, **there is a common misunderstanding that the Building Automation System must be "validated." This, however, is not true.** Building Automation Systems and their implementation are only one of many tools used as part of an overall ***Quality Assurance (QA)*** process to provide a process that culminates in a "validated" system. BAS vendors provide equipment and capabilities that make such validation easier. However, each manufacturer of end life-science goods that are covered by the Title 21 CFR Part 11 requirements maintains the end responsibility of implementing the process and procedures that will result in a "validated" environment.

Determining which portions of a BAS system require ***commissioning*** **and qualification vs. commissioning only** is not demanding. However, management must document this process of decision making, procedures generation, and eventual implementation of the procedures so that any future audit questions may be answered effectively by the facility's staff. Three factors affect whether or how much of a system requires qualification:

- **Interpretation of FDA regulations applicability to the company's operations.** How the FDA code applies for a particular facility should be outlined in the company's master validation plan. Plans should discuss the application of FDA regulations to all relevant research processes and procedures, product manufacturing, product stability, warehousing, distribution, and other related areas. (For additional information on interpretation/application of FDA regulations, see the *ISPE Baseline Pharmaceutical Engineering Guide, Volume 5: Commissioning and Qualification* in the For More Information section.)

- **The company's own policies concerning critical functions.** When determining which critical systems (such as safety, security, information systems, and quality assurance) require qualification or other higher level testing in addition to commissioning, the company's own corporate policies must also be considered during the planning phase. Policies concerning security, information technology, maintenance procedures, and quality assurance typically play the greatest role in BAS validation.

- **Potential environmental impact (risk) to the company's products and employees.** Potential impact affects product quality and employee safety. How do space environmental conditions such as temperature, humidity, and air flow/pressure affect product consistency and quality? How does a BAS component or system help protect employees from exposure to hazardous substances or other risk factors? Determining potential "impact" in different areas will be explored more in the next section.

Note that **none** of these factors are determined by the type, model, or vendor of a specific BAS system. **All** of the above items are determined by the product, process, and end manufacturer of the products and goods manufactured within the facility.

Detailed planning of the BAS system design, implementation, and system testing are crucial elements of ensuring the validated systems will perform as intended. Also, a BAS system's inherent capabilities to trend, record, and maintain operational data is crucial to the long-term validation process of the facility.

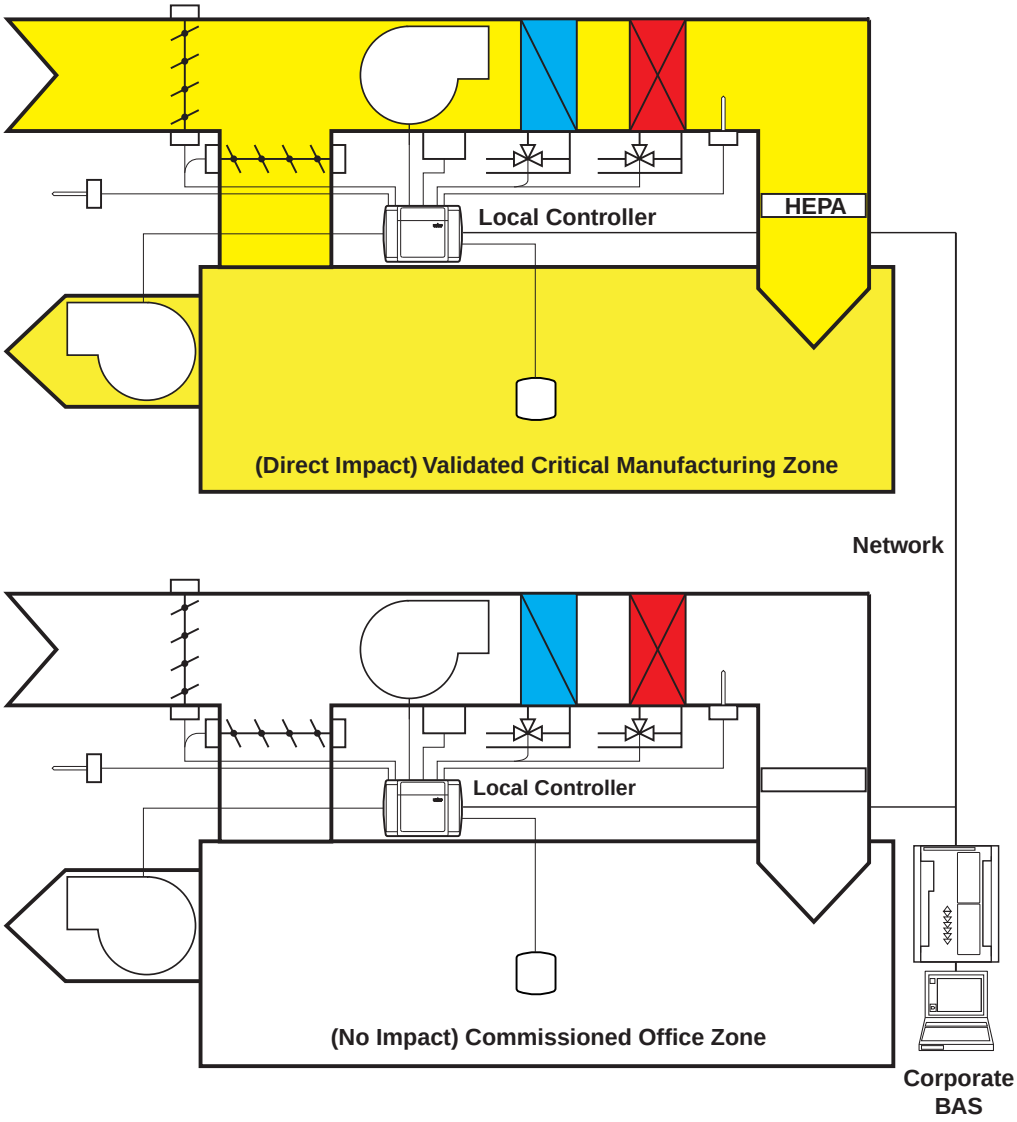
In this regard, achieving "validation" of a system that meets the Title 21 CFR Part 11 requirements is similar to achieving the criteria necessary for a modern ***LEED® (Leadership in Energy Efficiency and Design)*** certification for a commercial building. In both cases, understanding of the requirements to achieve the end result is necessary. In both cases, the use of specialized consulting professionals to carry out the planning and execution of the project is highly recommended and almost a necessity to ensure the desired end result. In both cases, prior proper planning of the overall process will prevent poor execution, cost overruns, and delays in the final approval of the project. The "up front" cost of such planning may be substantial, but it results in a clear understanding by all interested parties of the expected deliverables, how they will be delivered, and minimizes any conflicts and rework as the project is actually executed.

Determining "Impact" and "Boundaries"

ISPE Baseline Pharmaceutical Engineering Guide, Volume 5: Commissioning and Qualification outlines a process to identify environmental conditions that have "direct impact," "indirect impact," or "no impact" on the product. The process evaluates the "basis of design" conditions of the facility and control components against the products made within the space defined by the "system."

A "direct impact" system must be able to detect or prevent a product quality issue. "Direct impact" systems require commissioning and supplementary qualification. "Indirect" and "no impact" systems are commissioned using ***Good Engineering Practices***. In addition to the impact on product quality, the potential impact of systems on employee health and safety must also be considered.

Direct impact "validated" systems affect product quality and consistency. Such systems need a ***Quality Assurance (QA)*** department and key technical experts for approval and sign off in each step of the development and operational process. All actions performed by operators of these systems must be documented, organized, and maintained throughout the life cycle of the facility and must be performed by operators with specific training.



The commissioning and qualification plan must clearly define the system "boundaries." A "system boundary" will be defined generally as a logical system that contains all components necessary to produce the ultimate "deliverable" of the space. In a production facility, this typically means the goods produced within the given manufacturing space. In a research facility, this might include areas for development of compounds, housing of animals used in testing, and similar areas. A company should produce overall guidelines for such spaces to follow as part of the master validation plan. These guidelines are then further broken down into specific "systems" that are tailored for specific uses.

In general, such "systems" require the application of an environmental control system consisting of HVAC systems, controls, sensors, and other related equipment specific to the controlled space for maintaining the quality and consistency of the products or research conducted within the space.

For HVAC systems, an airflow diagram of the subject space would include air distribution systems for fresh outside air, exhaust air, and return/recirculated air. From the logical associated equipment, determine the smallest boundary that encompasses the equipment, production process involved, and maintenance thereof. The goal is to make a reasonable decision that all such equipment is logically included within the boundary (but **only** the critical equipment).

The selected boundary is based on the presence or absence of critical components. In the illustration shown, the HVAC system has a direct impact on the "Critical Manufacturing Zone" conditions and qualification will be required. In the example shown, space temperature, humidity, and room differential pressure sensors that control room pressurization are all considered "critical" components since they measure environmental factors that affect the quality and consistency of the product delivered from this space. At the same time, the associated air handling unit system (AHU), fans, and ductwork for outside air, exhaust air, and return air are also included in the boundary of the system. Since the deliverables in the space must be produced within specified parameters of temperature, humidity, and cleanliness for quality reasons, the local digital controller and modules associated with the mechanical equipment are also included.

Since this was determined to be a "direct impact" space, the FDA regulations require the company to provide logs of the three critical environmental parameters (temperature, humidity, space pressurization) as part of the on-going validation of the environment during the production of the deliverables within the space. However, such real-time logging does not need to be maintained within the space—it only needs to be maintained for historical record-keeping purposes. Thus, the corporate BAS database server and record keeping are located outside of the boundary for this system.

Utilities serving the mechanical and control systems also need consideration and boundaries may need to be selected at this level of the facility. A logical boundary location, for example, may be the local breaker panel serving the space.

Keeping the area with the boundary as small as is feasible simplifies the validation. A component by itself would not suffice as a system, however. For example, the HEPA filter shown in our "system" is a required component needed to produce the air quality conditions for the production of the product. However, because it is the overall control of the space conditions that affect the quality and consistency of the deliverables within the space, the "system" boundary must incorporate the AHU, ductwork, controls, fans, and HEPA filtration system as shown. A system with even one "critical component" will be considered a "direct impact" system and require qualification.

If a building does have a critical zone, that doesn't mean the **entire** building needs validation. "Normal" spaces, such as offices, conference rooms, cafeterias, lobbies, and rest rooms will probably need only to be guided by general building codes and practices. "Green" building practices, however, require more stringent standards and require certification requirements of another kind (e.g., LEED certification).

For whatever plan a company implements, it must document its rationale for selecting the boundaries and document the logic and processes. This documentation protects the operation in the event of an FDA audit. The documentation should:

- Support the "system" boundaries assignments by the company.
- Provide the relevant definition of "direct", "indirect", and "no impact" systems for the company's products.
- Detail what commissioning or qualification steps applied to each.

Again note that there is no specific BAS manufacturer's model number, system type, or solution that is "validated." BAS systems, however, provide features that make the implementation of these operational processes easier to execute, maintain, and document over the life of the facility.

BAS Options for Validation

There is no one way to incorporate BAS into a validated system. The best choice depends on a number of factors, but the main possible options are:

- Provide physically separated networks for validated and non-validated areas of the facility.
- Place validated systems on dedicated BAS network controllers and subsystems that are connected to a common BAS network implemented throughout the rest of the facility. (This scheme is shown at a high level in the illustration.)
- Combine validated and non-validated systems on the same common BAS network and keep separate operator access via logical security.

In general, wherever a BAS is integrated into a validated system, future expansion or change to that system (such as retrofits or replacements) is more com-

plicated. In validated systems, procedures must be in place to properly record the time, date, reason, and person accountable for any change made to the system, as well as what changes are made. In most BAS systems, this feature may be an automatic function of the operational "audit log" program available. Keeping only the parts of the BAS system that are absolutely necessary within the system critical boundaries simplifies initial and future compliance issues.

Segregated networks require either multiple BAS operations staffs or a single staff managing multiple user interfaces for multiple networks. A benefit of these types of systems is that they separate the changes made to a non-critical versus a critical system, simplifying the documentation and maintenance of validated systems. Segregated networks and staffs may make it more difficult to operate the facility as a whole, however, since data needed to operate one system might be accessible only to another system or a failure in one side might prevent proper operation in the other.

Common networks allow a single BAS staff to manage both validated and non-validated systems, reducing staff costs, training costs, and facility equipment costs. Compared to a system with dedicated separate architectures, commonality of components will probably reduce the first cost of construction in a new or expansion construction project. With a common network, determining cause and effect and designing maintenance and operational procedures accordingly is probably easier. Modifications made to either validated and non-validated systems, however, require special attention.

With any of these options, system implementation using the BACnet "open protocol" will allow for interoperability between vendors and competitive bidding on future expansion projects. This would also reduce equipment costs and the validation burden during any future changes and retrofits.

There is no one right answer for all situations. Factors such as financial requirements, corporate policies already in place, maintenance needs of the spaces and networks, training and capabilities of the operations staff, and qualification complexities of the facility must all be taken into consideration. Again, using an independent consultant specializing in this area is often money well-spent during the planning, implementation, and qualification phases of a project.

Glossary of Terms

BACnet® (Building Automation Control Network): An interoperable, nonproprietary, communication protocol standard (ANSI/ASHRAE Standard 135), conceived by a consortium of building managers, system users, and manufacturers under the auspices of ASHRAE (American Society of Heating, Refrigerating and Air-Conditioning Engineers).

BAS (Building Automation System): An integration of controls and devices to provide unattended and automatic operation of buildings systems. Systems may include HVAC, elevators, fire suppression, smoke control, security, lighting, and other subsystems. (See more on **http://www.kmccontrols.com/products/Understanding_Building_Automation_and_Control_Systems.aspx**.)

CFR (Code of Federal Regulations): The codification of rules published in the Federal Register by the executive departments and agencies of the federal government.

Commissioning: A process of testing, verifying, and documenting that new building equipment and systems are installed and able to operate according to the design intent. It generally does not require the rigorous ongoing documentation that validation does.

FDA (Food and Drug Administration): An agency of the United States Department of Health and Human Services responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, pharmaceutical drugs (medications), vaccines, blood transfusions, medical devices, electromagnetic radiation emitting devices, and veterinary products.

GEP (Good Engineering Practice): A term applied to engineering and technical activities that ensure that a company manufactures products of the required quality as expected (e.g., by the relevant regulatory authorities).

GAMP (Good Automated Manufacturing Practice): A technical subcommittee of the International Society for Pharmaceutical Engineering (ISPE) and a set of guidelines for manufacturers and users of automated systems in the pharmaceutical industry. (See more on **http://en.wikipedia.org/wiki/Good_Automated_Manufacturing_Practice**.)

HVAC (Heating, Ventilating, and Air Conditioning): A term generally used to describe a building's comfort system. In older buildings, heating (radiators), ventilation (windows), and air conditioning (window units) may be separate, but usually these services are integrated into a single system that conditions and distributes air throughout the zones of building.

LEED® (Leadership in Energy and Environmental Design): A U.S. Green Building Council consensus-based, voluntary certification program created to establish "green building" benchmarks and measure the environmental performance during the life cycle of a building.

Predicate rule: Any requirement set forth in the Public Health Service Act, the Federal Food, Drug and Cosmetic Act, or any FDA regulation other than Title 21 CFR Part 11.

QA (Quality Assurance): The administrative and procedural activities implemented in a quality system so that requirements and goals for a product, service, or activity will be fulfilled.

Validated/validation: In the life science industry, the documented act of demonstrating that a procedure, process, and activity will consistently lead to the expected results. It often includes the qualification of systems and equipment. (See more on **http://en.wikipedia.org/wiki/Validation_%28drug_manufacture%29**.)

More Information

BACnet International Success Stories: Neutec Pharmeceuticals, http://www.bacnetinternational.net/success/stories.php?sid=52.

FDA Title 21 CFR Part 11, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11.

Part 11, Electronic Records; Electronic Signatures — Scope and Application, http://www.fda.gov/regulatoryinformation/guidances/ucm125067.htm.

GAMP® Good Practice Guides, http://www.ispe.org/index.php/ci_id/2652/la_id/1.htm.

General Principles of Software Validation; Final Guidance for Industry and FDA Staff, http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm085281.htm.

ISPE Baseline Pharmaceutical Engineering Guide, Volume 5: Commissioning and Qualification, http://www.ispe.org/baseline-guides/commissioning-qualification.

ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning (HVAC), September 2009, http://www.ispe.org/ispe-good-practice-guides/hvac.

About KMC Controls

For more than 40 years, KMC designed and manufactured control system hardware and software for flexible building automation. KMC remains the only privately held U.S. manufacturer to offer a complete line of components and digital automation systems. Learn more at www.kmccontrols.com or follow KMC on your favorite social media: