RISK-BASED STRATEGIES TO SUPPORT REVALIDATION AND THE ASSESSMENT OF REQUIREMENTS TO MAINTAIN THE VALIDATED STATE OF EQUIPMENT, PROCESS AND FACILITIES USED FOR COMMERCIAL AND CLINICAL MANUFACTURING
Authors

Amgen
Mike Bradley
Tarah Clements

AstraZeneca
Alan Johnson
Kim Wenrich
Ned Wyman

Biogen
Jeremy Bollinger
James Ethridge
Jennifer Mitchell
Adam Tessneer

Genentech Roche
Andy Brewer
Neti Hansen

Lilly
Tim Cirbo

Pfizer
Michael Parks
Kathleen Bellorado

BioPhorum
Elaine Speirs
Justin John
Louisa Mitchell
About BioPhorum

BioPhorum’s mission is to create environments where the global biopharmaceutical and device industry can collaborate and accelerate its rate of progress, for the benefit of all.

Since its inception in 2004, BioPhorum has become the open and trusted environment where senior leaders of the biopharmaceutical industry come together to openly share and discuss the emerging trends and challenges facing their industry.

Growing from an end-user group in 2008, BioPhorum now comprises over 135 manufacturers and suppliers deploying their top 6,000 leaders and subject matter experts to work in nine focused Phorums, articulating the industry’s technology roadmap, defining the supply partner practices of the future, and developing and adopting best practices in drug substance, fill finish, process development and manufacturing IT. In each of these Phorums, BioPhorum facilitators bring leaders together to create future visions, mobilize teams of experts on the opportunities, create partnerships that enable change and provide the quickest route to implementation, so that the industry shares, learns and builds the best solutions together.
1.0

Introduction

The pharmaceutical and biopharmaceutical industries are asked to deliver medicines at faster speeds and lower costs, while continuing to improve compliance to ensure the safety, quality and efficacy of the drugs. There is a continuous demand on organizations to change and adapt to this paradigm. This involves a review of historical practices and implementation of more efficient practices that provide for at least the equivalent compliance to ensure companies understand the process associated with the strategy and the risk to the patient.

Typically, validation of equipment and facilities is performed when facilities are built or when new equipment is purchased and installed. Schedules include time to perform initial validation activities before they are put online and into service. The challenge is how to demonstrate that these equipment and facilities continue to remain in a validated state, compliant and suitable for use, when the new equipment and facilities are in a state of continuous use and/or when changes are made. What data and testing are required to support the validated state? Revalidation is required to remain compliant with regulations and, in some cases, revalidation is necessary because there is no other way to continuously monitor each system to ensure it remains in a validated state. This paper describes risk-based alternative strategies for defending the suitability of equipment and facilities requiring revalidation. These robust and risk-assessed approaches include real-time review, routine monitoring and in-/at-line alarms and measurements to help identify what data and testing are critical to assure the continued validated state of the equipment.
2.0

Scope

This paper provides an overview of a risk-based approach to revalidation and an assessment of what is required to maintain the validated state of equipment and facilities. It provides ideas around key areas. The approaches listed here are not inclusive of all revalidation needs, but the same concepts can be extrapolated to other equipment, process, cleaning and systems:

- New product introduction—equipment, process and cleaning (3.1)
- Defense of hold times (3.2)
- Remapping of controlled temperature chambers (3.3)
- Changes to sterilizing processes and equipment (3.4)
- Challenge of periodic review (3.5)

3.0

Revalidation and risk

Validation of equipment and systems is a regulatory requirement in the pharmaceutical industry. It is required because the industry must demonstrate that medicines are safe, effective, and of suitable quality each and every time they are made. Confirmation of ongoing conformance to operating parameters, alarm functions, cleanability, etc. and also including when changes are made, is called ‘maintaining the validated state’ and is a requirement for revalidation or a continuous monitoring control strategy.

To make a pharmaceutical product, numerous equipment and systems are required, including those that are direct product contact (fermenters, bioreactors, filtration systems, columns, tanks, etc.) and those that are indirect product contact (autoclaves, buffer tanks, CIP systems, cold rooms, etc.). All of these equipment and systems are validated when first introduced to the facility and process. All equipment and systems have multiple operating parameters that are important to the manufacture, storage, handling and testing of a pharmaceutical product. It would amount to thousands of tests performed on an annual or biannual basis if all of them had to be retested. The reality is that it is impossible to retest all of the parameters that were initially tested during validation. But which should be tested to ensure the ongoing validated state? One area of focus should be those that can be defined as critical and high risk if they fail. Another area of focus is on how frequently those critical parameters should be checked.
Parameters and process controls that are critical to the safety, quality and efficacy of the products must be properly controlled each and every time the equipment/system is used. These may include:

- Control(s) around critical process parameters (CPPs) such as concentration and uniformity
- Controls around sterilization temperatures (uniformity)
- Controls around cleaning to ensure products, detergents and residues are controlled between batches in a multi-product facility
- Stability of the product during the process and storage
- Impact of changes to the process, equipment and systems.

It is important to separate parameters into those that are critical to safety, quality and efficacy, and those that are important to the process. Collaboration between those that understand the equipment and those that understand the process is essential. Understanding what elements are critical to the safety, efficacy, purity and traceability of the product and separating these from the important parameters relative to how the equipment operates makes it possible to manage a compliant revalidation program or to set up a continuous monitoring program that is manageable in this highly automated industry.

This paper presents some alternative options using science and risk-based methods to defend maintenance of the validated state either routinely or following changes. These best practices are currently being used (and successfully defended) by various companies in the industry.

3.1 New product introduction (NPI)—equipment, process and cleaning

It is clear that some level of testing (or validation in commercial facilities) is required when new products are introduced, whether into a commercial or clinical facility, and/or a facility that is used for both clinical and commercial manufacturing. Multiple equipment and systems can be impacted by just bringing in a single new product. However, science and risk-based considerations should and can be used to define the testing required in these situations. The strategy for any NPI can be defined in a validation plan, by change control, by protocol or by procedure. The primary purpose of the evaluation is to describe the impact that the new process has on existing equipment and systems to ensure that they are suitable for each process (the existing/current process and the new process) and to be able to defend that the new product and the existing product will be safe, effective, pure and have a traceable history.

An evaluation would address:

- What ’elements’ of the new product/process are CPPs or critical quality attributes (CQAs) and what is the impact of those on existing equipment and systems?
- What potential impact might the changes have on current products/processes and what ’evidence’ will be required to defend that they were not impacted?
- A justification for what is required, and also what is not required, and how the information will be tested and documented (confirmatory protocols, standard operational qualification (OQ) or performance qualification (PQ) protocols, etc.)
- Finally, is there a system in place to make sure that when switching between these products the CPP is routinely updated and applicable changeover activities occur?

As an example, if temperature control of the new product is a CPP, and it is different from the current product’s CPP, the question to ask is whether the equipment is validated to control temperature within the new range? If not, what testing needs to be done and for how many runs? What needs to be done with regard to revalidation or retesting on an ongoing basis? By using a risk-based approach you could discern, for example, that since the equipment demonstrated control three times during the validation of the current range, only one confirmatory run at the new range is required. Do the alarm limits really
need to be tested and verified again? From a risk-based approach, probably not, as the original value confirmed that functionality of the alarm works and, no matter what the numerical alarm value is, it will continue to work in the same way. Obviously, calibration of the sensor at the new range would need to be assessed to cover the operating range or done and documented under the calibration program. Finally, justification could be made that calibration is the only verification required on an ongoing basis when switching products. All the justifications should be documented, and testing should be done under protocol or test plan, while calibration can fall under the routine calibration procedure and program.

Performing a risk assessment is the most effective way to get from the NPI to the final determination that the equipment and systems are continuing to operate in a validated state. Where applicable, the risk assessment should:

- Map out the ‘changes’ required to the equipment, systems and processes to introduce the new product
- Define the potential impact(s) each of these changes could have on the ‘quality’ of both the proposed new product and the existing products
- Define the evidence (testing, calibration, etc.) that supports the current products and determine whether this evidence can also be applied to the new products
- Define the new evidence that will be required
- Review the assessment of contamination (and/or viral) control strategy—adventitious agent contamination and closed/open-system design of the facility
- Review the assessment of material control strategy—cell bank, raw materials and in-process safety testing
- Review the assessment of analytical control strategy—analytical method validation and detection of product
- Review the assessment of equipment control strategy—design, validation, carryover preventions, and cleaning (e.g. worst-case soil analysis and cleanability testing)
- Review the assessment of process control strategy—multi-product/concurrent manufacturing procedure with line clearance
- Review the assessment of facility control strategy—cleanroom design, viral design, and biosafety level design
- Review the assessment of new product cleanability at lab scale using the current cleaning program to determine if it is worst case or cleaned more easily than current products.

Additional considerations that may need to be assessed when introducing a new biological product are shown in Figure 1. There may be similar considerations for other types of products. It is important that the assessment also includes consideration of the impacts on the processes that maintain/monitor the processes after validation (the quality systems, testing, maintenance, calibration programs, etc.). Having, and enforcing, robust standards can significantly minimize the revalidation effort, especially when products are being transferred between sites within an organization. Standards are required for:

- Equipment, automation and facility design, requirements, specifications and testing
- Process automation and data systems, requirements, development/testing lifecycles, software maintenance, alarm and data strategies, lifecycle testing, etc.
- Quality systems (change controls, validation, calibration, maintenance, disposition/batch release)
- Process operations to minimize change when transferring from facility to facility
- Materials and supplier management
- Cleaning approach and design (chemicals, testing, defense, path strategies, post-cleaning controls and timers)
- Control strategies (viral, microbial, manufacturing, batch controls).

These strategies need to be assessed from the perspective of the product, the equipment, and also the health and safety of the manufacturing environment for the staff (e.g. hazards of cytotoxic materials, volatile solvents, sampling hazards, etc.).

The key is to define what is changing, the potential impact of the changes and what needs to be demonstrated to ensure the ongoing validated state of the equipment. Time spent ‘thinking’ and using science and risk-based thinking can significantly reduce the burden of revalidation.
3.2 Hold times

Process hold times are used to define a maximum time limit that processes/steps can be held, or must be completed within, to avoid negative impact to the microbial quality and/or chemical quality of the product. Once the maximum allowable time has been determined it is established as a manufacturing control (e.g. expiry timers, batch record step limits, etc.) to maintain the validated state of the product/process. If established times are exceeded, the impact on quality and chemistry must be assessed.

When a manufacturing facility is at maximum capacity, finding time for at-scale testing for hold times is challenging. This often results in hold times driven by schedule limitations rather than quality limitations, which can significantly impact the flexibility and ongoing scheduling of manufacturing. In terms of risk, the purpose of assessing hold times is to define a time limit within which the products is not impacted. The following points should be considered:

- The potential quality impact of the change
- Existing evidence that will continue to be valid following the change
- Additional evidence that may be required to ensure and justify the continued safety, quality and efficacy of the products.
Using a science and risk-based approach, hold times can be applied to any process step—but are most commonly required for steps where either the hold time is critical to the process (e.g., storage), where the hold time is critical to the microbial control of the product (e.g., pre-filtration media hold times, sterile hold times, etc.), or where the hold time is critical to the chemical quality/stability of the product (e.g., viral inactivation at low pH in biologics). Steps where holds occur—but where these holds are not critical to the safety, efficacy, purity and/or traceability of the medicines—do not need to be defined as critical and do not need critical hold time controls. In many instances, product stability is studied at small scale and for groups of products, and hold times less than 24 hours can easily be defined as not critical based on the fact that 24 hours or less can be defined as routine or continuous processing times. In addition, performing a cumulative hold time run can be done to include one batch where all maximum hold times are run, providing an overall worst-case scenario.

Hold time strategies for which times are critical and those for which times are not, are typically defined and documented. A strategy would normally include a combination of small-scale laboratory studies (used to define chemical stability) and perhaps ‘at-scale’ runs (used to define microbial stability).

After the potential impacts are defined, the next step is to think of alternative ways to gather evidence to defend the change. Figure 2 provides an overview of two simple alternative processes for defending hold times.

<table>
<thead>
<tr>
<th>Hold time</th>
<th>Alternative approach</th>
<th>Change considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Media/library preparation time</td>
<td>Alternative (preferred)</td>
<td>Revalidation testing is never required but hold time needs to be evaluated when:</td>
</tr>
<tr>
<td>Overview</td>
<td>Use a calculation to determine the maximum allowable hold time possible until a certain microbial level is reached. Calculation is based on factors important to microbial growth:</td>
<td>• There is a change to the microbial load (material specs, material amount, new materials)</td>
</tr>
<tr>
<td>Allowable time from start of material addition to end of solution filtration. Applicable to any ‘growth-supporting’ media or buffer solution used to support the process.</td>
<td>• Temperature</td>
<td>• There is a change to growth conditions (temperature)</td>
</tr>
<tr>
<td>Quality threat</td>
<td>• Microbial doubling rate (time)</td>
<td>• There is a change to solution character (ability to support/promote growth)</td>
</tr>
<tr>
<td>Rich organic non-sterile mix ideal for microbial growth. With excessive growth can get exotoxins, endotoxins and degraded material function.</td>
<td>• Starting microbial load</td>
<td>• The process consistently takes longer to complete in the time allowed.</td>
</tr>
<tr>
<td>Classic approach</td>
<td>• Adaption (lag) time.</td>
<td></td>
</tr>
<tr>
<td>At-scale testing (3X) and measure bioburden.</td>
<td>Advantages:</td>
<td></td>
</tr>
<tr>
<td>Define hold time as the shortest of the three times that still meets the microbial criteria.</td>
<td>• Represents ‘worst case’ based on material specifications (starting load)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Can adjust the outcome (e.g., specs, temperature)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No testing needed—can easily apply to any change.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Challenge:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Defending the science of the calculation (organism selected, lag time, etc.)</td>
<td></td>
</tr>
</tbody>
</table>

| B Sterile hold (static)—prior to process | Alternative (preferred) | Revalidation testing after change is not needed. All that is required is to demonstrate that the changed/modified systems and vessels are still able to pass the pressure hold integrity test. Factors that would impact this: |
| Overview | Loss of sterility is really about the vessel integrity. Integrit is demonstrated by measuring pressure decay (leakage) over time (pressure hold test). By correlating leakage rates in vessels that passed at-scale sterile hold testing, to the pressure hold alarm equivalent to these leakage rates, the actual tested sterile hold times can be applied to any vessel with a pressure decay alarm equal to, or more rigorous than, the leakage rate in the vessel that retained sterility. | • Changes to the post-sterilization conditions—eliminate over pressurization |
| Fermenters/bioreactors must ensure a sterile environment for the culture process. Sterilization in place (SIP) is used to establish a sterile boundary, and once established the boundary is normally pressurized (leak out if a leak occurs). How long we have confidence that this boundary is retained is the sterile hold time. | Advantages: | • Changes to the allowable leakage rates (allow a greater pressure loss during the hold test) |
| Quality threat | • Minimal at-scale testing and alarm can apply to any subsequent system meeting the alarm criteria | • Trend monitoring shows a pattern of increase in pressure decay—beware that temperature change can create a false positive or negative. |
| Viable organisms in the boundary will contaminate the culture. Loss of batch or uncharacterized metabolites in the process—quality issue. | • After change it is only necessary to demonstrate modified vessel still meets the pressure hold criteria. | As each process culture is effectively a sterile hold test—it is recommended that after a time period the original report defending the ‘static sterile hold’ approach is revised to include evidence that the actual processes retained sterility. |
| Classic approach | **Challenge:** | |
| 3X testing. Hold after SIP, flush surfaces with sterile water and demonstrate sterility. | Correlating leakage rate to the alarm and writing a report. Technical articles can be used for support. | |
| Define hold time as the shortest of the three times that passed. Can also use sterile media. | | |
3.3 Controlled temperature chambers

Depending on their processes, manufacturing facilities may have hundreds of controlled temperature environments. These may be single units or freezer farms and may consist of the following:

- Controlled warehouse environments
- Refrigerated and frozen cold storage environments
- Standalone refrigerators and freezers for QC samples and reagents
- Stability chambers
- Incubators for cell growth and media warming, etc.
- Cryogenic storage for cell lines.

The main risk is that storage outside the required conditions can directly impact quality, and this is made worse by the very long times (months) that the product or critical material may potentially be exposed to these conditions. Chambers are typically validated to demonstrate that the environments used for the storage of materials and/or product can be controlled and maintained within the required ranges for the materials and products to be stored and to provide evidence that the monitoring probe(s) used provide a reliable measure of this environment. Periodic remapping is used to provide assurance of the validated state of the equipment which ensures that the chambers are still able to provide the required environment even after a defined period has passed.

Given the large number of units and the criticality of this equipment, small changes can make a significant difference to the overall workload for routine revalidation. The use of a science and risk-based strategy for testing and retesting the validated state of these types of controlled temperature environments is very important.

The risk assessment needs to focus on the following:

- How critical are the materials stored in the chamber?
- How sensitive to temperature change are the materials/products?
- How long might the materials be stored—product warehouse (months) vs sample refrigerator (a few hours)?
- How detectable are the quality impacts of wrong conditions (e.g. poor cell growth performance/culture morphology in an incubator)?
- How ‘detectable’ are excursions from the conditions (e.g. temperature)? Note: this is associated with the alarm settings. An alarm that does not activate until the temperature has been out of range for four hours might not be appropriate for critically sensitive reagents, etc.

These risks should be factored in when assessing the impact of changes and the risk to product quality, and in defining testing and frequencies for maintaining the validated state of equipment. Remapping is still the major revalidation activity that is performed to confirm the validated state of the equipment. Locations of hot and cold spots, and frequency of remapping are the primary areas that need to be assessed and justified.

This is where data can help support the justification. If there is data to support that a freezer maintains a controlled environment for months and years then this can be used to support defining the frequency of remapping. Revalidation data can also be used to determine if freezers have drifted after a year’s time—that data can be used to define a new frequency. If recalibration data supports stability of the unit, it can be justification for either pushing out revalidation or recalibration frequency. If hot/cold spot temperatures do not change by more than 1 to 2 degrees during remapping (this can be defined based on the criticality of what is being stored), there may not be a need to move or relocate the temperature-monitoring probe. In place of full validation mapping, the data can be extracted from the recording system and evaluated over a specified period for trends or failure points to determine the unit’s overall performance within its validated range. Adverse trends or events trigger an investigation. If none are identified, then the data can be filed for future use.
Also based on the criticality of what is being stored, consideration should be given to the mechanical aspects of cold rooms similar to utilities. These systems work to provide air at the required conditions (temperature, flow and perhaps humidity). As these outputs are measured directly, there may not be a need to validate mechanical aspects. A comparison is a chilled water system that provides cooling to a reactor. Typically, the temperature of the reactor is measured directly and so it may not be necessary to validate changes to the chilled water system. Impacts will always be detectable and although there may be business concerns, revalidation concerns can be addressed.

Depending on the continuous monitoring system/monitoring programs/plans, an automated system can be used with validation mapping inputs to identify temperature shifts at the point of use. The system could send automatic notifications for immediate evaluation and serve as a real-time monitoring system for critical temperature controlled units (TCUs).

The science and risk-based approach will look at all aspects and determine the overall strategy based on criticality and not every controlled temperature unit or group of units will have the same revalidation requirements. If continuous real-time monitoring is not possible then revalidation requirements may be put into a category based on criticality (high, medium and low), each with a different testing strategy and frequency.

3.4 Sterilization processes and equipment

Most companies have to define strategies for validation and revalidation of equipment sterilization.

Microbial inactivation using moist heat, gases, chemicals, dry heat or radiation fundamentally follows first-order reaction kinetics. The logarithmic rate that organisms are inactivated during the cycle is constant. While conditions are constant, the number of viable organisms remaining is based on the lethality of the cycle conditions (temperature and time). A system is considered to be sterile when the probability of a viable survivor, given the cycle conditions and time, is less than or equal to $1 \times 10^{-6}$. Factors that are relevant to sterilization cycles include:

- Starting microbial load
- Resistance of the organism or spores to the proposed cycle (how quickly they are inactivated—the ‘D’ value)
- Cycle parameters (temperature and time).

Factors that may reduce cycle effectiveness:

- For moist heat cycles, this might be air/non-condensable gases, condensate accumulation, restricted steam flows (loading, physical restrictions, protective packaging), surface residues/finis, etc.
- Dryness requirement (visual check-few drops, no pooling, weight before and after SIP, etc.)
- Post-cycle controls and the integrity of the sterilized system/container after the cycle (hold time, storage conditions).
For an equipment item to be sterile, there are clear requirements that must be met. Failure of product sterility is a critical risk to patients. However SIP is often used loosely and most processes are really just ‘microbial control steps’. A risk-based approach is important and can save a significant amount of effort in both the initial validation and the post-validation maintenance of changes. Risk-based concepts should be used to:

- Define the requirements for the cycle: true 'SIP-sterile' (Tier 1) for sterile operations or 'SIP-bioburden reduction' (Tier 2) for microbial control:
  - What stage of the process is the sterilization?
  - What impacts would an undetected failure have on patients?
- Define the strategy for the initial validation using matrix, bracketing and/or most challenging loads/paths:
  - Autoclave loads
  - SIP cycles and paths
- Evaluate testing requirements such as the use of thermocouples (TCs) and biological indicator (BIs) for Tier 1 vs SIP for Tier 2. BIs may not be needed for revalidation of Tier 2. Fewer TCs or in-line TCs only can be considered for revalidation of Tier 2. Finally for Tier 2, testing frequency could be reduced to every two to three years or after impactful change
- Assess loads and move all common SIP-sterile items into the same loads
- Assess the impact of changes (e.g. impact on the factors listed above) associated with a validated cycle. Will the change potentially result in accumulation of condensate, or the ability to detect air, or impact the exposure to steam, etc.?

- Define requirements for how the continued performance of the process will be demonstrated over time:
  - Is periodic revalidation required or could performance be defended based on other cycle controls (trap temperatures, cycle profiles, etc.)? How effectively is the routine, monitored system able to represent the validated system?
  - How detectable would an abnormal cycle be if it occurred (e.g. is there continuous monitoring of cycle conditions, etc.)?
  - How robust is the cycle? Are the cycles overkill (excessive) or are they tailored to the process? The ‘overkill’ strategy allows the site to risk assess the control system as lower criticality, especially if routine monitoring has a high level of detection.

Remember that it is all about product safety, quality and efficacy relative to the product. If a cycle is defined as SIP-sterile, it requires strict testing and revalidation requirements. Time spent evaluating and defining the real requirements for each specific part and where it is used in the process will simplify the overall process for the cycle. SIP-bioburden reduction would have to be validated the first time it is used but may not need subsequent revalidation or could be revalidated every five years. By defining SIP-sterile loads, and looking at the cycle and operating parameters of the autoclave, cycles that are overkill cycles with the same cycle parameters could be set up on a rotation of those loads and one load every year as opposed to having to do all of them every year.

This concept also applies to filtration used for microbial control and/or sterility (vent filters, gas filters, liquid filters, ultrafiltration, etc.). A risk-based approach can be used to define potential threats to patients and how these threats will be mitigated and/or detected. This allows clear risk-based quality strategies to be defined, for example:

- Pre- and/or post-filtration integrity testing (or no testing!)
- Replacement frequency
- Controls for steaming (number of allowable cycles, etc.)
- Preparation/flush strategies and requirements, etc.
3.5 Periodic review

Periodic review is another type of risk review and is an element in the overall strategy for ensuring and defending the quality of products given to patients. The purpose of a periodic review is that systems, processes and facility/equipment remain in a validated state of control and are suitable for use over time. There are many factors that are impacted by time/use, including:

- Wear/damage to mechanical parts
- Change in function and performance for elastomers and seals
- Degradation/corrosion of surfaces parts
- Preventative maintenance strategies
- Proactive or predictive maintenance strategies.

The impact of the quality system processes over the period also needs to be assessed, for example:

- Post-validation changes that have been made to the systems, equipment, processes
- Corrective maintenance work
- Corrective actions from quality events, etc.
- Number of exceptions and performance issues associated with the system.

Periodic review does not equal a comprehensive review of the original validation or revalidation. Periodic review should be a high-level risk-based assessment of the potential impact that time/use and quality system processes may have had on the performance of a system/process.

- Have required preventive maintenance and calibration been performed?
- Have significant changes been made to the system, equipment, process and/or data management?
- Have there been performance issues or a significant number of quality events associated with the system?
- For computerized systems—have there been software updates/maintenance and issues/tickets, data backup, user maintenance, etc.?

A risk-based approach should be used to define the overall quality strategy for periodic review for all GxP systems and processes at a site, based on threat level to patients. This strategy will assess the criticality of the system to product quality, the ability to detect a performance degradation (e.g. continuous monitoring of water systems) and regulatory requirements (that cannot be risked away!). The risk-based approach can also define whether the review can be of real-time information and data (such as for automated systems) or process information based on the release data of batches made over a period of time. Risk assessment can also define what information is not required, such as not looking at change controls if your program ensures that after a change the equipment is placed back in the validated state.

A tiered approach to the periodic review can be helpful. The tiers can be linked to the amount and type of information needed, the testing required, as well as the frequency of the periodic review such as annual, every other year or every three years. An example of how the tiers may be defined:

- Tier 1—The system/equipment is not considered a direct impact on product processing or is used for direct product processing but is not complex (such as a tank). System has been operating well and is being maintained and calibrated, perhaps a few exceptions/few simple changes but nothing of concern to patient safety or efficacy. The review can be documented and closed. This could apply to 80 to 90% of equipment and systems, and by using electronic quality-based records will make documentation quick and clear.

- Tier 2—The system/equipment is considered a direct impact on product processing or is used for direct product processing but is not complex and/or calibrated (such as a high temperature controller). The high-level review finds multiple changes and/or more issues have occurred during the period. These equipment and systems should be evaluated based on an assessment of appropriate testing, calibration, etc. that can be performed to ensure the maintenance of the validated state.

- Tier 3—The system/equipment is considered a direct impact on product processing, is used for direct product processing, impacts sterility and is complex equipment (such as a UF, column, autoclave). The review team finds multiple significant issues or discrepancies have occurred during the period. These equipment and systems should be evaluated based on an assessment of appropriate testing, but specific revalidation testing would need to be done to ensure the maintenance of the validated state. In addition, any failure in the quality system(s) should also be investigated and corrected to prevent future occurrences.
4.0 Conclusions

The importance of the concept of delivering medicines at faster speeds and at lower costs, while continuing to deliver and improve compliance to ensure the safety and efficacy of the drugs cannot be overstressed. Revalidation and/or demonstration of an appropriate state of control over time is required in order to maintain GxP processes and systems. The choices are either do everything and test everything, do everything and test less, or think about the risks early and define appropriate policies and strategies that ensure that the appropriate testing is completed based on risk, and that the quality, compliance and supply reliability of the products provided to patients is defensible.

Organizations understand their facilities, equipment, processes and systems from a holistic perspective and can determine what works best for revalidation. The revalidation best practices described in this paper are a collection of concepts and processes that have been used successfully across the industry. There may not be a one-size-fits-all approach to revalidation, but many of these practices can streamline and focus revalidation requirements on those that offer most value and are not just testing and documentation for no positive gain. By taking the time to define the controls up front for equipment, relying on data and using scientific understanding, an organization can set itself up with a simple, compliant and valuable revalidation strategy.