A White Paper on
Risk-Based Qualification for the 21st Century

Forward

The pharmaceutical industry is experiencing change at an incredible pace. Recent and significant product recalls, coupled with extreme pressure to reduce costs to the consumer while maintaining product quality, have brought great scrutiny to the industry. Once "economic proof" suppliers, manufacturers are now forced to compete on a quality and cost basis like never before. An area within our industry that is ripe for change is the facility and equipment qualification process. The current process is document intensive and does little to add value and provide assurance that the product manufactured is of the highest quality. The current process also does not follow a clear path of patient risk mitigation and clear product and process understanding. At the same time the present practices in most companies are very cost ineffective. There is a potential benefit in streamlining these practices by establishing industry standards and mechanisms, which ensure the quality and feasibility of a facility or equipment project from the initial user requirements to the final performance qualification.

This whitepaper defines the principles upon which such practices should be based. It gives the directions for how ISPE, in cooperation with industry and regulators, aims to establish a risk-based approach to qualification. This is in accordance with the risk-based thinking that both industry and regulators are striving to attain.

A Qualification Task Team, convened at the request of ISPE's International Leadership Forum in response to challenges from FDA, has drafted the attached White Paper on "Risk-Based Qualification for the 21st Century." The task team has received input from over three-dozen representatives of industry, equipment vendors, validation consultants, and regulators. Several white papers on this subject have been drafted and reviewed by staffs within pharmaceutical companies from August 2004 through January 2005. The attached white paper represents the evolution of ideas from the previous white papers, which culminated in an intensive workshop on the subject that was held at ISPE's Tampa Conference in February 2005.

Both the FDA and industry recognize that for most companies, qualification (IQ/OQ/PQ) has become an expensive, time-consuming process that adds little value in terms of ensuring equipment is fit for use in pharmaceutical manufacturing. This task team was challenged to recommend far-reaching changes to how qualification is structured and executed, in order to improve the industry's ability to deliver manufacturing facilities that meet product and process quality requirements in a timely and cost-effective manner.

This whitepaper proposes that the equipment and facility commissioning and qualification activities should follow a risk-based approach based on the concept of risk mitigation for patients. For simple standard manufacturing equipment that are extensively used in the industry, the required effort should be far less than for complex custom-built equipment. For very quality-competent suppliers, the C&Q activities need not overlap much with the supplier's good engineering practices, to include supplier's own inspections and testing.

Furthermore, the user's C&Q activities should depend on documented quality activities, including testing conducted by the supplier or integrator of an equipment or facility. This reliance could be justified based on an independent vendor or equipment certification scheme, or it could be supported by a risk assessment/ quality audit assessment by the customer in a manner similar to GAMP practices.

This guidance should be in the form of internationally accepted standards through ASTM, possibly supplemented by ISPE technical documents. Such standards and guidance need to strip away the non-value added aspects that currently plague qualification practices, and focus instead on demonstrating, through PQ, that user requirements have been met. As a proposal to accomplish this, the team identified a number of principles upon which improvement can be based. It is the team's belief that if both industry and regulators can reach agreement in these areas, and provide clear guidance that all will adhere to, significant cost and time savings can be achieved, while at the same time improving the quality of systems and equipment for the manufacture of pharmaceutical products.

Statement of the Current Situation

In March, 2001, ISPE published Volume 5 of the Pharmaceutical Engineering Guides for New and Renovated Facilities, "Commissioning and Qualification." This guide was developed by an international team from pharmaceutical manufacturers and suppliers, and was subject to FDA review and endorsement. Many organizations within the industry have implemented some or all of the principles found within the Commissioning and Qualification Baseline Guide. Implementation has ranged from simple use of system impact assessments to eliminate qualification of indirect and no-impact systems, to full use of all guide principles, including component impact assessments focused on only those aspects that can affect product quality, and maximizing use of documented good engineering practices. In such cases, IQ/OQ protocols have been reduced to a few pages, identifying the 10% or so of components and functions necessary to meet user requirements and support quality manufacturing, referencing GEP documentation to avoid repeated inspections and testing.

However, much improvement remains to be realized. As this paper is being written, a number of major pharmaceutical manufacturing capital projects, either planned or in progress, are struggling with issues such as:

- The ISPE guide is not a regulatory document nor even regulatory guidance – fear that field inspectors won't respect guide principles.
- Projection of OQ protocols running thousands of pages per unit operation.
- Unwillingness (due to fear of regulatory action and entrenched practices) to narrow focus of IQ/OQ/PQ to just that which can affect product quality.
- Designs are not perfect – writing IQ against the detailed design (as per the V-model) leads to unnecessary and excessive deviations. Project teams are processing hundreds of such deviations, few or none of which results in field changes, but instead are simply a paper exercise.
- Pre-mature implementation of regulatory change control.
- How to qualify PAT systems.

The current situation needs to be improved in several major ways:

1. The C&Q Guide provided the impact assessment process to reduce systems subject to qualification (i.e., avoid the qualification "bullet"). The entire way in which we perform qualification needs to be revised so that it no longer represents a bullet to be avoided.
2. Guidance or standards are needed that not only define a minimum standard, but also state what is excessive.
3. Guidance or standards are needed that are recognized as official, e.g., that carry the same weight as an FDA or ICH guidance document.
4. The FDA and international community have shifted to a risk-based approach to compliance. This represents opportunity for further evolution of C&Q practices.

Shifting the Qualification Paradigm

A risk-based approach to qualification means that we must first understand our processes, and be able to identify and assess the risks to product quality inherent in a particular manufacturing process. We must then ensure that adequate risk-control mechanisms have been incorporated into the design; these risk-control mechanisms should be the focus of our qualification efforts. Items that pose little or no risk to product quality should not receive regulatory attention; the assumption of some risk is inevitable.

The current qualification paradigm is based on a comprehensive verification of installation and operation against detailed functional requirements and detailed design specifications. This needs to shift to a focus on just those aspects that can directly affect product quality. Those aspects need to be determined using principles of risk management as espoused by FDA and international regulators. The project team and vendors, exercising good engineering practices and judgment, should confirm that the installation and operation is acceptable from an engineering perspective; IQ/OQ should audit the GEP/ commissioning work to confirm that those quality-impacting aspects have been achieved. The PQ is the true test of acceptability as defined by a process-based user requirements specification. More focus should be applied to design qualification, to ensure Quality by Design objectives have been met.

Process Analytical Technology systems can be very sophisticated – these systems often use a custom process model and control scheme based on detailed process understanding. If we were to apply today's "brute force" or "shotgun" method of qualification, excessive time and money will be required to validate these systems, which will discourage their implementation. New, innovative approaches to testing these systems, which include consideration of new knowledge gained during such testing, must be defined and deployed to the industry.

Principles for 21st Century Qualification

A group of over 20 representatives, primarily senior managers from industry, plus consultants and regulators, met in Tampa on 14 February 2005 to complete work on a set of guiding principles for this effort. The group agreed on 10 principles of good Commissioning and Qualification Practices:

1. Focus on that which affects product quality. Qualifying equipment to put approved protocols on the shelf is not the end goal; qualifying processes should be the primary focus. To achieve this, definition and control of a process-based User Requirement Specification is an important function with quality impact. The primary quality and regulatory focus should be to ensure critical process parameters, critical functions, and critical design features that could affect product

quality are defined and controlled.

2. Requirements. User requirements, based on the process (and not on equipment or systems), are the key to acceptability. The PQ is generally where user requirements are confirmed as being satisfied. Hence, IQ/OQ are subordinate in importance to the PQ.

3. Risk assessments, process development and experimental design are used to identify critical features, functions, and critical process parameters. These become the basis for qualification (IQ/OQ/PQ). Having a solid process understanding will foster regulatory expectations for Quality by Design.

4. Only critical process parameters will be used as the basis on which to define the formal "qualification information." This should also include any physical design features or control functions that could impact the ability to clean, sterilize, sanitize, or properly manufacture the product, to the extent these activities impact product quality and safety.

5. All activities must contribute value to the start-up and delivery of manufacturing capacity. We won't do anything just for the sake of regulatory compliance. Activities that are simply a paperwork exercise, resulting in no impact to installation, operation, or performance of systems, should be reduced or eliminated. Engineering judgment should be used to determine how to inspect or test specific features and functions of equipment and systems.

6. Risk-based asset delivery. Different types of equipment and systems (custom, off-the-shelf, simple, complex, etc.) require different levels of attention to ensure quality. An approach to defining how much "good engineering practice" should be applied to a given item, based on risk of problems, should be applied rather than "cook book" lists of activities and documents. The GAMP categories use this approach for automation systems; similar approaches for equipment and systems should be defined and described.

7. Value-added documents. Documents serve a useful purpose of controlling activities, they ensure completeness, and they serve as a record of what occurred. Only data which serves a useful purpose should be collected. Acceptability of documents should be based on technical merit; documents should not be "dressed up" to meet some imagined regulatory expectation. The operations and maintenance groups should determine the acceptability of turnover packages, for it is they who will ultimately use them for on-going operations and maintenance.

8. Use of supplier documentation. Supplier's standard inspection and test documentation may be used and no other documents be produced that duplicate this information, provided that documentation clearly shows the items of interest have been verified or tested in an appropriate manner. This is subject to the

supplier being of adequate quality.

9. Test planning. Defined tests should only be carried out once (at an agreed location and by agreed parties, i.e. either by the supplier or by the manufacturing company, with accountabilities agreed upfront), unless there is a clear justification for undertaking further tests at a later stage of commissioning. Commissioning should be a comprehensive activity, with IQ/OQ as an audit that commissioning verified the quality-impacting items. PQ may involve additional testing. Some tests may occur at different stages of development/ implementation and therefore appear to be repeats.

10. Fostering innovation. Any program must remain flexible enough to apply sound and qualified scientific and engineering judgment based on the situation at hand. We must not be too prescriptive as to stifle innovation.

Action Plan

ISPE's Qualification Task Team has studied this subject for the past six months. We believe the above principles are sound. Some of them are already contained in the current Baseline Commissioning and Qualification Guide. However, it is our assessment that additional development of the Guide is needed to further streamline how industry performs these tasks. It is time to update the Guide and move further down the path to rationalize qualification practices in our industry.

It is our assessment that consensus based standards would benefit the industry, by providing a clear set of expectations (as well as what is not expected) that both industry and regulators would adhere to. It is our understanding that consensus standards such as from ASTM are required by Executive Order to be used by US federal agencies. The development of these standards would, by their nature, ensure input and consensus from all interested parties. We believe that concise standards, backed up by an updated, complimentary Baseline Guide, would be valuable tools for industry and could cause a major improvement in how we deliver GMP manufacturing capacity.

The Qualification Task Team also identified a number of concerns and pitfalls that we expect to encounter as we first debate the specifics of change, and then attempt to implement such change throughout the industry:

1. Where does responsibility and accountability lie when equipment later proves faulty?
2. What is an appropriate level of oversight to ensure vendors and project teams are doing what they are supposed to do?
3. How will we deploy consensus standards to regulators world-wide, and what sort of transition acceptance phase will be needed?

4. The focus on user requirements is good, but more clarification on what user requirements are is needed.
5. A process is needed to deal with legacy systems. How should be take advantage of knowledge of existing products and processes?
6. How is "engineering judgment" gauged or applied? It is a sound concept but further definition will be needed.
7. We will need to define required documentation. We should look to how other world-class industries achieve quality in their manufacturing facilities – what do they find adds value/ is necessary?
8. We mustn't be too prescriptive such that we stifle innovation and creativity.
9. We mustn't let standards be a barrier to entry of new vendors with novel technology or a better mousetrap.
10. Significant organizational change will be necessary, and this may be the biggest barrier to success. The QA organization will need to refocus away from the details of individual installation and operational test cases and protocols, and instead focus on critical features and risks to product quality, based on process understanding and risk assessments and confirmed by a comprehensive PQ.

ISPE's Qualification Task Team requests endorsement from ILF as to the general basis for this initiative, endorsement for the 10 guiding principles, and endorsement regarding the recommended path forward – creation of qualification standards and concurrent updating of the Commissioning and Qualification Baseline Guide.

Respectfully submitted, Qualification Task Team Steering Committee

Brian Lange, Merck & Co., Inc.
Bruce Davis, Astra Zeneca
Paul D'Eramo, Johnson & Johnson
Tim Howard, Eli Lilly and Company
Gert Moelgaard, NNE A/S
Robert Chew, Commissioning Agents, Inc.

ILF Sponsors

Ron Branning, Genentech
Ulrich Rudow, Johnson & Johnson