TRENDS IN ANALYTICAL INSTRUMENT QUALIFICATION

Like many industries, the pharmaceutical industry is highly regulated. It has to be: regulation saves lives. The Food and Drug Administration (FDA) is a global force in this arena through its field-based inspections and guidelines, and its approaches are frequently adopted by other regulatory bodies. Despite largely originating in the pharmaceutical industry, the principles and value-added activities of analytical instrument qualification are universally applicable. Here we use some historical scene setting to explain the trends and advantages of such an approach.

PERSPECTIVES ON QUALIFICATION

In May 1987, the FDA first introduced the terms installation qualification and process performance qualification as part of general guidelines on process validation for pharmaceutical manufacturing. These terms were based on natural progression: equipment must be installed correctly before it can be operated, and processes must be tested to assure their suitability for purpose.

Over time, the FDA proposals developed into the more familiar terms installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). The design qualification (DQ) was also an essential part of this approach. Historically, the DQ and any additional qualification documentation required by company policy were considered the responsibility of the user. This would include the user requirements specification (URS), validation master plan (VMP) and validation summary report (VSR). Therefore, qualification supply companies and original equipment manufacturers (OEMs) concentrated on the IQ/OQ/PQ. This validation approach was increasingly applied to qualification of analytical instrumentation for laboratory use; however the FDA's process validation guidance document was open to interpretation. This revealed differences in approaches to qualification between manufacturers of analytical instruments as well as differences in qualification policy within analytical laboratories. Typically, such differences are smaller at the IQ stage, but they can be significant for the OQ and PQ.

GAMP GUIDELINES

In the absence of more authoritative information, the pharmaceutical industry applied good automated manufacturing practice (GAMP) guidelines to analytical instrument qualification (AIQ). GAMP 4 classed equipment according to five software categories:

- Category 1 - operating system
- Category 2 - firmware
- Category 3 - commercial off the shelf (COTS) non configurable
- Category 4 - configurable COTS
- Category 5 - custom software

These have been reduced to four categories in GAMP 5 by expansion of Category 1 and removal of Category 2. Equipment is categorised according to its overall level of complexity and not just the software, leaving room for ambiguity. An on-line GAMP forum has developed and produced its own good process guide (GPG) on validation of laboratory computerised systems.

The application of GAMP guidelines provided a useful addition to AIQ. A software-driven approach was introduced, which focused on documentation rather than outcomes and/or instrument applications.

However, this qualification method often required a large amount of paperwork; leading to the delayed introduction of new equipment and a poor appreciation of the AIQ's benefits. One difficulty was the lack of internal validation expertise in many laboratories. The relatively poor understanding of AIQ led to uncertainty over the requirements of laboratory equipment qualification. At the same time, it became apparent that developing resources for internal validation support would detract from the core function of providing an analytical service to a laboratory's customer base.

USP <1058> ANALYTICAL INSTRUMENT QUALIFICATION

In March 2003, the American Association of Pharmaceutical Scientists (AAPS) held a milestone conference. The aim was to ease the increasing burden of AIQ and simplify qualification processes by redefining the IQ, OQ, and PQ terms.

The resulting white paper was adopted by the United States Pharmacopeia (USP) as a starting point for the USP general chapter on AIQ (<1058>), effective from August 1st 2008. It applies a risk-based approach to classification. USP <1058> presents three categories of instrumentation: Groups A, B, and C. Typical examples of equipment in each of these categories are:

- Group A - stirrer
- Group B - pH meter
- Group C - high performance liquid chromatography (HPLC) system

This appears to greatly simplify qualification of basic laboratory equipment, as conformance with specification for equipment in Group A is essentially achieved by visual inspection of the instrument. If a standalone stirrer performs its function, no further qualification is required. However, when considered as part of a dissolution system, it can no longer be classified within Group A. This demonstrates that the equipment performance must also be understood within its application context and as part of the qualification. Even a simple device (such as a stirrer) may be claimed as Group C if part of a more complex device.

AIQ TODAY

Laboratory processes are increasingly evaluated during a regulatory audit through a systems-based approach. *Figure 1* illustrates the pyramidal interdependency fundamental to quality management system operations within a laboratory. Each layer adds to the overall quality, with AIQ as the foundation. Attempting to rely only on "system suitability" or

Figure 1. The pyramidal interdependency fundamental to quality management system operations within a laboratory

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analytical method validation is no longer an acceptable defence strategy. Laboratory equipment must be suitable for its use (e.g. qualified) and analytical instrument qualification helps justify the continued use of equipment.

When qualification was first applied to laboratory instrumentation, IQ, OQ and PQ were potentially considered 'one-off' activities. This is no longer the case. Equipment must be qualified "to provide documented evidence that it is suitable for its intended use". This definition must be applied to re-qualification after routine servicing, breakdown or repair, upgrading, and moving or relocating.

Although AIQ principles have been applied to analytical instruments for more than 10 years, people still find AIQ confusing. The USP and the GPG have added to this confusion by taking different directions and using different terminology. The USP and AAPS use 'qualification' for laboratory instrumentation (the definition used throughout this article), whereas GAMP 4 and GPG continue to use 'validation'. GAMP 5 now uses the term 'verification'. An organisation must define its qualification policy associated with AIQ and justify its approaches to equipment classification. The role of the DQ for AIQ is often an area of uncertainty. A responsive, flexible qualification service provider can work with laboratories to resolve such uncertainties and ensure that truly compliant risk-based approaches, such as guidelines from the International Conference on Harmonisation (ICH), are adopted. *Figure 2* compares the complexity and risks associated with the different approaches of USP, GAMP, GPG and ICH.

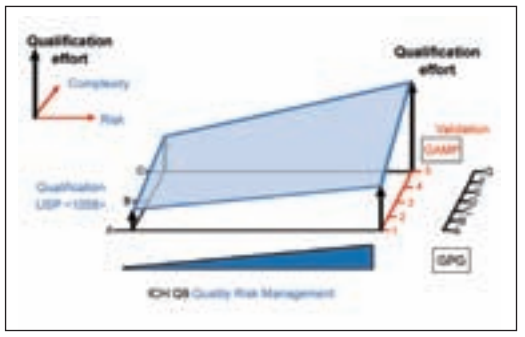

Figure 2. The complexity and risks associated with the different approaches of USP, GAMP, GPG and ICH.

CHOICES AVAILABLE FOR EQUIPMENT REQUALIFICATION

When selecting their approach to AIQ, laboratories are faced with a choice of three options:

- do it yourself (DIY)
- original equipment manufacturer (OEM)
- multivendor approach

DO IT YOURSELF (DIY):

With the DIY approach, equipment re-qualification is performed by in-house resources. This requires people with appropriate expertise to reduce the potential compliance risk of inadequate IQ/OQ/PQ documentation and associated regulatory inspection failure. However, this dependence on a small number of individuals can be risky should they decide to export their specialist knowledge to another organisation. The dynamics in this situation can rapidly shift from total control to barely maintaining operational compliance. An additional constraint can be the limited flexibility of resources against an expected work profile.

ORIGINAL EQUIPMENT MANUFACTURER (OEM)

The advantage of using the original equipment manufacturer (OEM) is that having designed and manufactured the equipment, it will have a thorough knowledge of the instrumentation. However, each OEM has its own documentation format, style, content, and structure, which are related to policy documentation on how to produce IQ/OQ/PQ protocols. Interpretation of what should be included in IQ/OQ/PQ qualification documents therefore varies between manufacturers. There should be no problems if a laboratory contains equipment from only one source – but most laboratories contain equipment from several manufacturers. This results in a fragmented approach to qualification that laboratory management must defend in an audit. Presenting and defending different approaches to equipment qualification during regulatory audits is a skilful, technical, and burdensome task. The high level of capability, expertise, and communication skill required may off-set many of the advantages associated with an OEM-based approach.

MULTIVENDOR

With a multivendor qualification approach, a single organisation provides a qualification service for all its laboratory equipment. This facilitates a harmonised and consistent approach to IQ/OQ/PQ across all equipment in the laboratory. For some analytical instrument platforms there are a number of multivendor organisations to choose from. However using more than one multivendor service provider to qualify all laboratory equipment undermines the benefits of this approach. Choosing a service provider with a broad multivendor capability is therefore an important consideration.

Areas that need to be carefully considered when applying a multivendor approach include:

- capability
- total contract costs
- asset management
- integrated protocols

Competition between service providers can generate a price-comparison driven market. Not all multivendor qualification services appear to be the same price because they are not all providing the same level of service. A customer must clearly understand what is included in the IQ, OQ, and PQ documentation so that it can make a true comparison when competitive tendering is used.

A global multivendor service provider can draw on a large pool of resources. This allows it to overcome the primary difficulties of the DIY approach: maintaining resource flexibility and managing complex qualification projects within tight deadlines. An additional benefit of a consistent, harmonised approach to AIQ and documentation makes regulatory compliance simpler to understand, manage, defend, and adhere to.

Therefore, multivendor approaches can offer considerable cost avoidance advantages as well as increased instrument up-time. More importantly, data originally part of multiple OEM management systems can now be located in central multivendor asset-management systems - where the true costs of ownership, performance trending, and knowledge-driven asset management can be seen.

Decisions about when to 'retire' poorly performing equipment and reliability information are all available, along with metrics relating performance to service level agreement (SLA).

A hyphenated technique, such as liquid chromatography–mass spectrometry (LC–MS), is an example of critical equipment that is best supported by a multivendor qualification approach. With high-specification systems, components of an LC–MS system are commonly from different suppliers (see *Figure 3*). If each vendor performs its own OEM-based qualification (which the customer will have to coordinate), then the components will be represented by different documentation and qualification approaches. More importantly, the LC–MS will not be qualified as a whole system. This approach is unsatisfactory from a regulatory perspective and complicates fault diagnosis. When a multivendor approach is used, documentation is harmonised into a single integrated qualification protocol, which supports simpler fault diagnosis and delivers true cost savings.

Figure 3. With high-specification systems, components of an LC–MS system are commonly from different suppliers

CONSULTATIVE RELATIONSHIPS

Many OEMs now claim multivendor capabilities - for HPLC and gas chromatography (GC) in particular. When looking for a laboratory services partner, the following are important considerations:

- proven track record of multivendor capabilities
- global investment in multivendor equipment and training facilities
- documented training which is available for inspection
- robust and secure supply-chain and parts procurement
- customised documentation and protocols
- scalable services ranging from small multivendor engagements to bespoke, complete service offerings (including large-project management, door-to-door relocation, and deployment of specialised resources to a site)

Analytical instrument qualification has matured significantly from the original process validation guidelines introduced 20 years ago. The multivendor services that are now available offer significant advantages over more traditional DIY and OEM-based approaches. The traditional model of outsourcing laboratory services is giving way to true consultative partnerships in which flexibility of services and related documentation align and integrate with a customer's own policy and quality management system.

> ***"The relatively poor understanding of AIQ led to uncertainty over the requirements of laboratory equipment qualification."***