Trends in Analytical Instrument Qualification

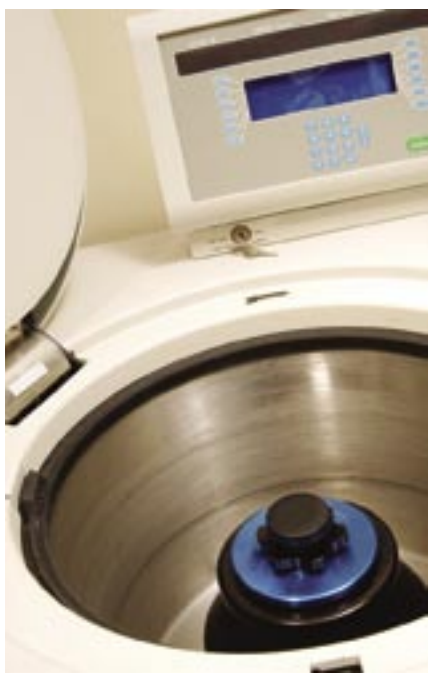
by Paul Smith

Companies are increasingly using outsourced multivendor qualification services for analytical instrumentation (1). This trend and the advantages of such an approach over other available options can be explained by some historical scene setting, along with descriptions of some of the main qualification approaches available.

Like many other industries, the pharmaceutical industry is highly regulated. It has to be: Tight regulation protects lives. The Food and Drug Administration (FDA) is a global force in this tight regulation through the actions of field-based inspections and through the regulatory guidelines it issues. Typically, approaches introduced by the FDA are adopted by other regulatory bodies and other industries. Therefore, although analytical instrument qualification largely originated in the pharmaceutical industry, the principles and value-added activity are universally applicable to other industries.

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 it put forward for pharmaceutical manufacturing (2). Those terms were based on natural progression: Equipment must be installed correctly first before it can be operated, and processes must be tested to provide "documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics" (2).



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Over time, those FDA proposals were developed into the more familiar terms *installation qualification* (IQ), *operational qualification* (OQ), and *performance qualification* (PQ). The original validation approach has been increasingly applied to qualification of analytical instrumentation for laboratory use. FDA's process-validation guidance document was open to interpretation — and those interpretations became more diverse as principles were applied to qualifying analytical instruments. 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.

In absence of more authoritative information, the pharmaceutical industry applied good automated manufacturing practice (GAMP) guidelines to *analytical instrument qualification* (AIQ). Application of GAMP guidelines (3) provided a useful addition to AIQ. However, it also introduced a software-driven approach focused on documentation rather than on outcomes and/or instrument applications. The documentation- and software-driven approach has tended to dominate AIQ. It was common, for example, to find qualification of a new laboratory pH meter, possibly the same model as one in use, requiring over 30 pages of qualification documentation — a process that, for a pH meter, essentially involves routine calibration using traceable reference buffers and that is usually well documented in any company SOP on the subject.

Delays in introducing new equipment, even when IQ/OQ/PQ

was purchased with it, could result in a poor appreciation of the benefits of AIQ and the perception that it formed a bottleneck. One of the difficulties was that laboratories often lacked internal validation expertise. Their relatively poor understanding of AIQ led to "mystique" and uncertainty over exactly what was required to qualify laboratory equipment. This isn't surprising, because the core function of an analytical laboratory is to provide an analytical service to its customer base. Developing resources for *internal* validation support would seem to detract from that core function.

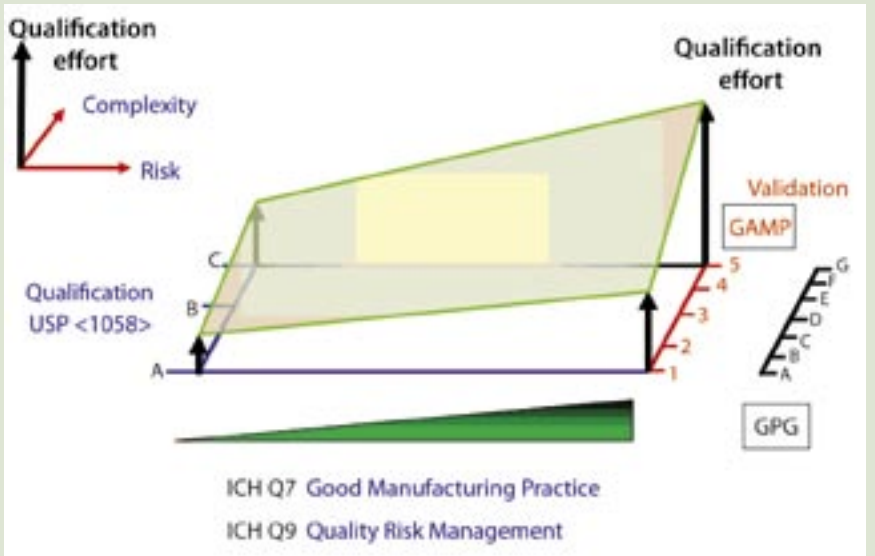
In March 2003, the American Association of Pharmaceutical Scientists (AAPS) held a key milestone workshop entitled *A Scientific Approach to Analytical Instrument Validation* in Arlington, VA. Representatives included quality assurance specialists, consultants, validation experts, regulators, and instrument manufacturers. The AAPS white paper produced after the conference has become an important qualification guidance document (**4**). Part of the driving force for the conference was to ease the increasing burden of AIQ and simplify qualification processes by redefining IQ, OQ, and PQ terms in a refreshingly clear way.

USP <1058> Analytical Instrument Qualification: The success of the AAPS approach resulted in the United States Pharmacopeia (USP) adopting the AAPS paper as a starting point for the new draft general chapter on AIQ (<1058>) (**5**). It applies a risk-based approach to classification of equipment. The current draft presents three categories of instrumentation: Groups A, B, and C. Typical examples of equipment in each of these proposed categories are

- Group A — stirrer
- Group B — pH meter
- Group C — HPLC system.

This would appear to greatly simplify qualification of basic laboratory equipment. Equipment in Group A is essentially that for which conformance with specification is achieved by visual inspection of the instrument while it performs its function; no further qualification is required. However, when a stirrer is considered as part of a dissolution system, for which careful control of paddle geometry, axial alignment, and rotation speed are all critical to control the dissolution process, that stirrer then can no longer be classified within Group A. This therefore provides a very good example of an important point: The equipment performance must also be understood in the context of its use in an application and as part of the qualification. Even a simple device (such as a stirrer) may be claimed as group C if it is part of a more complex device. Conformance of equipment in Group B to user requirements is achieved by conformance with equipment SOPs. Typically, this means that the equipment is calibrated (and operated) according to the SOP. Equipment in Group C requires a full qualification process (IQ/OQ/PQ).

Figure 1: The different approaches of the USP, GAMP, GPG, and application of ICH risk-based considerations



GAMP Classifications: Returning to GAMP, equipment is classified according to five software categories:

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

Typically, equipment is categorized according its overall level of complexity and not just the software, which leaves room for ambiguity over equipment classification. An on-line GAMP forum has developed and produced its own good-process guide (GPG) on validation of laboratory computerized systems (**6**). It includes seven classes of equipment qualification (compared with the three classes of the draft USP).

ICH Guidances: In principle, risk-based approaches are imbedded within the USP general chapter <1058> on AIQ and GAMP 4, to varying amounts. However, when the International Conference on Harmonisation (ICH) guidance Q7A (**7**) and Q9 (**8**) principles are applied more directly to AIQ, a more complex situation arises. The level of qualification applied is generally dependent on the complexity of the equipment (which is a risk-based approach). It could also depend on the type of work that equipment is used to perform. For example, in principle, less qualification could be performed on equipment dedicated to test raw materials rather than to test drug product or drug substance or when used in other pharmaceutical environments. Figure 1 diagrams the different approaches of the USP, GAMP, GPG, and ICH risk-based applications.

In practice, laboratories typically apply a consistent qualification standard unless they are segregated

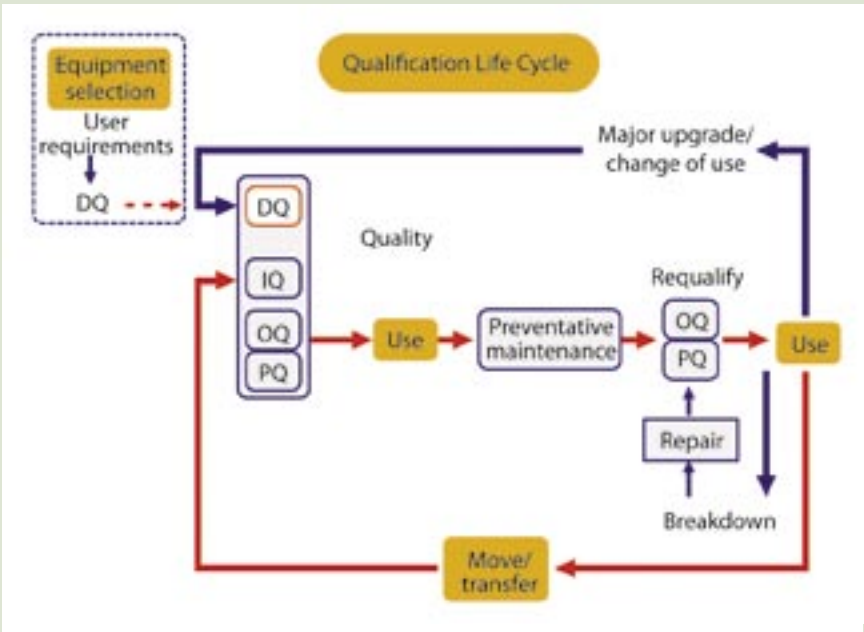
and dedicated to performing specific analytical functions. Significant variations in qualification approaches between laboratories are common within the same company.

AIQ: Although AIQ principles have been applied to analytical instruments for more than 10 years, people still find AIQ confusing. The different directions the USP and the GPG have taken add to this confusion. Even the terminology is different: The USP and AAPS use *qualification* for laboratory instrumentation (the definition used throughout this article), whereas GAMP and GPG continue to use *validation* for laboratory instrumentation. *Validation* is applied to analytical method validation, software validation, and manufacturing process validation. The key decision an organization must make is to define its qualification policy associated with AIQ and include justification for approaches to equipment classification. Increasingly, this is an area that multivendor service providers can support by applying cross-industry best-practice expertise.

Figure 2: Fundamental interdependencies of a quality management system operating within a laboratory

Systems-Based Approaches: Increasingly, laboratory results are evaluated during a regulatory audit through a systems-based approach rather than by the historical hierarchical approach of selecting a representative example and reviewing all aspects of the sampling, analysis, and manufacturing (including AIQ and training records). Systems-based audits require systems-based thinking, and laboratory management must be able to robustly defend the question, "How do you know your analytical results are valid?" Although critical, qualification of analytical equipment is only part of the interdependent quality system used to provide a robust defense. Figure 2 illustrates the pyramidal interdependency that is fundamental to quality management system operations within a laboratory. Each layer adds to the overall quality, with AIQ as the foundation. Attempting to rely on "system suitability" or analytical method validation is no longer an acceptable defense strategy: Laboratory equipment must be suitable for its use (e.g., *qualified*).

Figure 3: A typical 4Q qualification lifecycle



Choices Available for Equipment Requalification

When deciding an approach to AIQ, laboratories are typically faced with a choice of three options:

- Do it yourself (DIY)
- Original equipment manufacturer (OEM)
- Multivendor approach.

These choices have a great impact on instrument requalification and the triggers that drive its requirements. Historically, when qualification was first applied to laboratory instrumentation, the requirement to requalify was not considered, and IQ/OQ/PQ were potentially considered "one-off" activities. However, this is no longer the case. The very reason why it is essential to qualify equipment — "to provide documented evidence that it is suitable for its intended use" — is that it must be applied to requalification after routine servicing, breakdown or repair, upgrading, and moving or relocating.

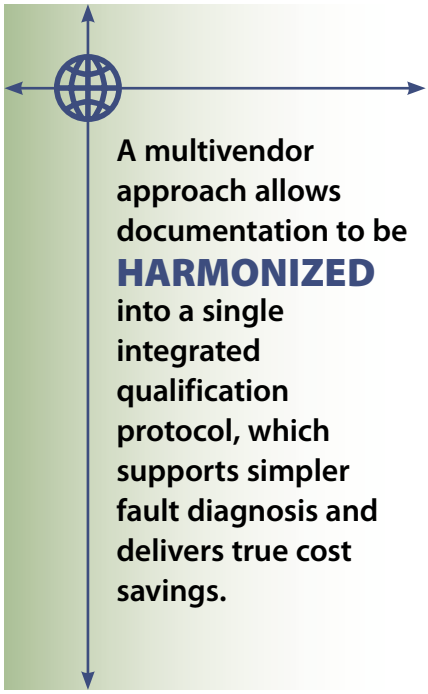
Figure 3 illustrates that for the 4Q model. When equipment is repaired after a breakdown, laboratory management has to review analytical results generated using the equipment since the time of the previous calibration or qualification to determine the impact of the breakdown on reported results. Typically, point-of-use tests such as "system suitability" (Figure 2) are critical to that review. The next step is to identify the cause of a failure and take preventative actions to prevent recurrence of the problem and close out the corrective and preventative actions (CAPA) (**9**). Finally, before the instrument can be returned to use, the impact of its failure on qualification status must be understood and the appropriate requalification work performed.

The extent of the OQ/PQ requalification required depends on the nature of the breakdown or repair, the quality of the documentation, the integrated quality management

system, and the rigor in which the change-control process has been developed and applied. Developing a quality management system that applies Six Sigma principles to qualification and validation significantly simplifies the process (**1**). Additionally, investing time in defining and developing a change control and requalification matrix can significantly reduce the requalification workload with minimal risk.

Do It Yourself (DIY): With the DIY approach, by which equipment requalification is performed by in-house resources, a number of areas need to be carefully thought through, including expertise, risk, and flexibility. Efficient laboratory operation, particularly for requalification of critical equipment, appears to be well suited by the DIY approach. Control over when the work is performed is potentially a matter of internal prioritization. With this approach also comes the need for people with the appropriate expertise to reduce the potential compliance risk of poor IQ/OQ/PQ documentation and execution — and a poor regulatory inspection. One of the additional inherent risks associated with this approach is the critical dependence on the expertise of a small number of individuals that may decide to export their hard-earned expertise to another organization. This can rapidly change the dynamics of a situation from full control and workload prioritization to core fire fighting — to keep the laboratory operationally compliant. An additional constraint on the use of internal resource is the limited flexibility of the finite pool of resource against an expected work profile, with the need to manage peaks and troughs.

Original Equipment Manufacturer (OEM): The advantage of using the original equipment manufacturer (OEM) is that it has designed and manufactured the equipment and therefore understands the equipment and its qualification well. Typically, most pharmaceutical organizations purchase the initial IQ/OQ/PQ along with their equipment. Installation is usually included in equipment purchase, so there are natural initial synergies to using an OEM qualification when equipment is first purchased.



A major factor in choosing to use an OEM-based qualification approach is the complexity of that qualification.In principle, the OEM understands its equipment better than anyone else. This is most true for cutting-edge analytical instrumentation and very specific high-end equipment. However, the majority of routine analytical instruments and technologies are well established, well understood, and to use a well-known phrase "not rocket science." For HPLC equipment for example, the majority of breakdowns continue to be associated with replacement of the lamp or with pump seals and check valves.

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. This means that each OEM has a unique interpretation of what should be included in IQ/OQ/PQ qualification documents. If a laboratory contains equipment from only one manufacturer, there should be no problems. However, most laboratories contain equipment from several manufacturers. This results in a potentially fragmented approach to qualification — that the laboratory management has to defend in an audit. Typically, it will perform a gap analysis for all qualification documentation to identify areas of potential risk and sensitivity from a regulatory perspective and then develop an action plan to overcome those difficulties. This action plan must list completion time frames and assign resources so that, if presented in an audit, it retains credibility in the eyes of an external auditor, such as the FDA.

Smoothly presenting and defending different approaches to equipment qualification during regulatory audits is a skillful, technical, and burdensome task. It requires a high level of capability, expertise, and communication skill — circumventing many of the advantages of using an OEM-based approach. In some instances, the fragmented approach of using different companies for qualification of equipment has resulted in FDA warning letters (**10**).

Multivendor: With a multivendor qualification approach, a single organization can provide a qualification service for all its laboratory equipment. Areas that need to be carefully thought through when applying this approach include

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

For some analytical instrument platforms, such as HPLC and GC, there are a number of multivendor organizations to choose from. Using more than one multivendor service provider to qualify all laboratory equipment will dilute the prime advantages of this approach. Therefore, choosing a service provider with a broad multivendor capability is an important consideration.

In a commercial service or commodity market, 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

Figure 4: A multivendor LC–MS system qualification

so that it can make a true "apples-to-apples" comparison when competitive tendering is used. When an organization requests companies to bid for laboratory services competitively, a cost bias may otherwise lead it to select a service provider based on price rather than on quality of service. Asking for clarificaiton of terms used (e.g., "Can you tell me what you mean by *calibration?*") and examples of qualification documentation are essential strategies. In some instances, some service providers "balance" their profitability by offering a low price for their qualification and maintenance service, only to increase the cost and frequency of parts replacement. The total cost to a customer increases, but that additional cost may not be readily apparent.

The larger pool of resources a global multivendor service provider can draw on overcomes one of the prime difficulties of the DIY approach to maintaining resource flexibility and managing complex qualification projects with tight deadlines. Additionally, a consistent, harmonized approach to AIQ and documentation makes regulatory compliance simpler to understand, defend, and adhere to. Therefore, multivendor approaches can offer considerable cost avoidance advantages as well as increased instrument up-time (**1**).

Rationalization of OEM qualification (and service maintenance contracts) also provides hard cost savings. More important, data that were 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).

An example of critical equipment that is best supported by a multivendor qualification approach relates to hyphenated techniques such as liquid chromatography–mass spectrometry (LC–MS). With high-specification systems, components of an LC–MS system are commonly from different suppliers. So, for example, the autosampler, HPLC system, and MS may be from different manufacturers (Figure 4). If each of the three vendors performs its own OEM-based qualification (which the customer itself will have to coordinate), then the components of the system will be represented by different documentation and qualification approaches. More important, the LC–MS will not be qualified as a whole system. Each OEM will qualify only its part of the whole system. This approach is unsatisfactory from a regulatory perspective and complicates fault diagnosis. When a multivendor approach is used, documentation is harmonized into a single integrated qualification protocol, which supports simpler fault diagnosis and delivers true cost savings.

Consultative Relationships

Analytical instrument qualification has matured significantly from the original process validation guidelines introduced 20 years ago. This maturity means that multivendor services 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 the flexibility of services and related documentation align and integrate with a customer's own policy and quality management system.

Many OEMs now claim multivendor capabilities — for HPLC and GC in particular. Pharmaceutical companies seeking such partnerships need to focus on the basic infrastructure that underpins and supports this service provision:

- global investment in multivendor equipment and training facilities
- proven track record of multivendor capabilities
- training documented and available for inspection
- robust and secure supply-chain and parts procurement
- flexibility and capability to customize documentation and protocols
- scalable services that support small multivendor requirements, such as offerings of complete services for managing large projects, door-to-door relocation, and deployment of full engineers to a site.

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