Equipment qualification for demonstrating the fitness for purpose of analytical instrumentation†

The Analyst
Quality Issues

C. Burgess,* Dianna G. Jones and R. D. McDowall

B.J.M. Limited, Rose Cottage, Walker Hall, Winston, Darlington, County Durham, UK DL12 3PN

Received 19th June 1998, Accepted 16th July 1998

Equipment qualification is the way to ensure that analytical equipment is fit for purpose. Qualification consists of four basic elements. Design qualification or DQ (Specification of what exactly the analytical scientist requires the equipment to do). Installation qualification or IQ (Does the instrument work to the manufacturer's specification?). Operational qualification or OQ (Does the instrument work the way the analytical scientist wants it to?) and performance qualification or PQ (Does it continue to operate within the parameters monitored?). The background and approach discussed in this paper has been developed primarily within the pharmaceutical industry.

Qualification of analytical instruments cannot be achieved through method validation. Equipment qualification provides the foundation to develop, validate and run analytical methods within the operating range measured. If a method is developed using parameters out of this range, then the analytical instrument needs to be re-qualified before method validation can proceed.

Seven case studies of qualifying equipment, such as high-performance liquid chromatographs, environmental storage equipment, centrifuges and pH meters illustrate the importance of a structured and logical approach to the subject.

The key element that is missing in the majority of laboratories' approach to equipment qualification is that design qualification is often lacking. Hence, unsuitable and inappropriate equipment is purchased which can be difficult to qualify for its intended purpose.

Introduction

Analytical scientists place great faith in the readings and outputs from their instruments. When unexpected or out-of-specification results occur, the initial suspicion often falls on the sample, the preparation technique or the analytical standard employed. Rarely does the analytical scientist immediately question the equipment. Indeed, the whole underpinning of method validation assumes that the analytical equipment which is used to acquire the experimental data is operating correctly and reliably. We will return to what is meant by correctly and reliably a little later.

Some industries, which operate in a highly regulated environment, such as the pharmaceutical industry, have placed great emphasis on method validation in, for example, HPLC.[1,2] However, until recently, there has been little direct requirement for assuring that the analytical instruments are working properly.

The American Food and Drug Administration specifically requires that[3] 'Laboratory controls shall include:……..the calibration of instruments, apparatus, gauges and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges and recording devices not meeting established specifications shall not be used.'

The major regulatory guidelines for Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) are similarly vague. 'Fitness for purpose' is the phrase that is commonly used, but what does this mean in practice? Only the Pharmacopoeias[4,5] and the Australian Regulatory Authority[6] have been sufficiently worried by instrumental factors to give written requirements for instrument performance. Whilst these guidelines are not consistent at least they are attempting to ensure consistent calibration practices between laboratories.

In contrast, the ISO Guide 25 approach[7] heavily focuses on good analytical practices and adequate calibration of instruments with nationally or internationally traceable standards wherever possible.

However, there has been a resurgence of interest in the underlying data quality by regulatory authorities, particularly the FDA (Food and Drug Administration) in the USA, following a major legal ruling[8] in 1993. This case has changed the regulatory focus and put the laboratory firmly in the spotlight in terms of the assurance of the quality of the data it produces. The details of the Barr case need not concern us, although it is useful to review the key features because of the impact they had on FDA thinking in particular and regulatory perspectives in general.

The Barr ruling

The most important point about the Barr ruling is that it was the first time that the GMP regulations and their interpretation by the FDA had been subjected to a comprehensive judicial review. The written decision covered 79 pages. As Judge Wolin decided in favour of the FDA, this greatly strengthened their enforcement activities as well as other regulatory aspects. The FDA investigated Barr Laboratories over a period of 4 years, having noted deficiencies in their manufacturing process validation. FDA had issued Warning Letters to the company which were effectively ignored. However, as a result of this investigation it emerged that effectively the company was 'testing into compliance'. Pharmaceutical companies are required to register the acceptable limits for release of product into the market

† The opinions expressed in the following article are entirely those of the authors and do not necessarily represent the views of either The Royal Society of Chemistry or the Editor of *The Analyst.*

place. In some instances, out-of-specification results obtained in the laboratory had been averaged with in-specification results and in others out-of-specification results were rejected or ignored when batch release was undertaken.

One quotation from the FDA document will serve to illustrate the agency's concern; 'During the enforcement litigation, Barr prepared reports on investigations into out-of-specification results on certain batches of some of its products. These investigations reflect Barr's persistent efforts to avoid attributing out-of-specification results to process-related problems rather than identifying the causes of the out-of-specification results and correcting them to prevent their recurrence. Repeated similar out-of-specification results implicating the manufacturing process were attributed alternatively to operator error, equipment error or laboratory error.'

One of the consequences of the case has been the thrusting of basic laboratory procedures and practices into the spotlight. It is now an FDA requirement to investigate formally all out-of-specification results. Therefore, validation of methods and, for the first time, the qualification of analytical instrumentation, are being heavily scrutinised.

Such was the concern that FDA Guidance on QC Laboratory Certification[9] was developed by former FDA Mid-Atlantic Region NDA/ANDA Technical Operations Group Manager Henry Avallone to help explain the concept of laboratory certification to field office personnel. He identified eight main areas to be addressed for laboratory certification: management systems; operating procedures; personnel training; data accountability; method validation; equipment; facilities; certification documentation.

This list will be very familiar to those operating in an ISO Guide 25 (NAMAS or equivalent national agency) accredited laboratory. Indeed, the majority of these items were not new to the pharmaceutical industry. What was new was an explicit statement of requirements for the qualification of laboratory equipment. 'The qualification of laboratory equipment and the maintenance of such equipment, along with the adequacy of standards, reagents and test solutions are of concern in the certification of a laboratory. For the microbiological laboratory, organism viability, media growth promotion, incubators, autoclaves, hoods and automated equipment used for organism identification all require qualification and calibration. Therefore, it would seem that in order to certify a laboratory, equipment should be listed, along with documentation that it is adequate and operating effectively for its intended purpose. It is also good laboratory practice to have a quality assurance program that will assure that reference standards, buffer solutions, titrating solutions, reagents and other apparatus are adequate and maintained properly. For some equipment, such as HPLCs and test systems that they may be a part of, a holistic approach rather than a qualification of each component part, such as a pump, may be used. This method has been found acceptable as written by Furman *et al*'.[10]

Modular and holistic qualification

Furman *et al.*, discussing the validation of computerised liquid chromatographic systems, present the concept of modular and holistic qualification. Modular validation is the qualification of the individual components of a system, such as the pump, autosampler, column heater and detector of an HPLC. The authors make the point that whilst 'calibration of each module may be useful for troubleshooting purposes, such tests alone cannot guarantee the accuracy and precision of analytical results'.

Therefore the authors introduced the concept of holistic validation, where the whole chromatographic system was also qualified to evaluate the performance of the system.

The reader may question why such an approach is needed. One pragmatic reason is that in our experience it is necessary! We cite an HPLC system that was qualified by us and the individual modules were just within acceptable limits. However, when a holistic test for the whole system was carried out, the system failed to meet the 'suitability for use' criteria.

The concept of holistic qualification is important as some laboratories operate with a policy of modular equipment purchase. Here they select components with the best or optimum performance from any manufacturer. Furthermore, to ensure optimum throughput, some of these laboratories may swap components when they malfunction. Thus, over time, the composition of a system may change. Therefore, to assure themselves and any regulatory bodies that the system continues to function correctly, holistic qualification is vital.

Some laboratory equipment requires maintenance and preventative maintenance (PM) programs should include such equipment. For example, HPLC units, spectrometers and autoclaves all require routine preventative maintenance. Regulations require that equipment include maintenance logs or documentation. Therefore, laboratory certification should provide for a review of the preventative maintenance program.

Management usually only sees the topmost layer of these processes and is probably unaware of the 'iceberg' that underlies them. This aspect is shown pictorially in Fig. 1, whereby only the tip of the iceberg is generally visible.

What the Barr Ruling has done is to shift regulatory attention downwards into the data level which hitherto it had not overly concerned itself with.

Approaches to integrity of analytical results

The 'bottom up' approach is the one usually favoured by the analytical specialists. Like 'Lego', the quality of the end result is built in from the foundations up. In testing terms this is illustrated in the diagram below (Fig. 2). These 'Lego' bricks are equivalent to the individual modules in any measurement system. Each brick is qualified as suitable for use before the next layer is built. In this way, integrity is assured all the way to the topmost layer. If firm foundations are not built, the information generated will not stand scrutiny. By following this approach quality is built in from the lowest level.

The role of the instrument in providing the integrity of data is fundamental to the end result. If you cannot place your faith in the reliability of the basic analytical signal within predetermined limits then the information generated will be worse than useless. The reliability of the data quality should be linked to performance standards for both modules and systems, as well as having a regular maintenance programme.

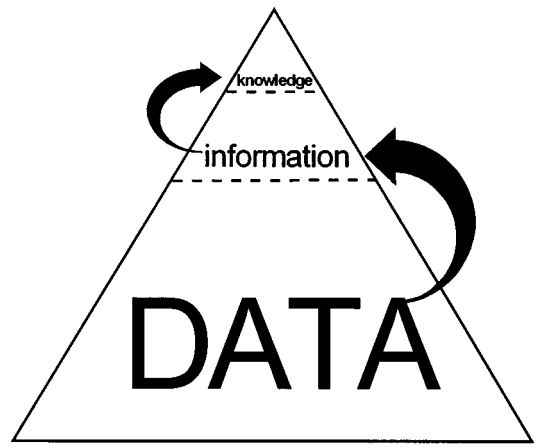

Fig. 1 Data, information and knowledge triangle.

Definitions for equipment qualification

The Regulators, not surprisingly, have tended to look at the 'iceberg' from the other direction, *i.e.*, top down, and adopted an approach which has become known as the 4Q's model, **DQ, IQ, OQ** and **PQ** which are: **D**esign **Q**ualification; **I**nstallation **Q**ualification; **O**perational **Q**ualification; and **P**erformance **Q**ualification.

The Pharmaceutical Analytical Science Group (PASG),[11] have produced a position paper on equipment qualification. Here they proposed the following definitions of the 4Qs. Design Qualification: defining the quality parameters that are required of the equipment and manufacturer; Installation Qualification: assurance that the intended equipment is received as designed and specified; Operational Qualification: confirmation that the equipment functions as specified and operates correctly; Performance Qualification: confirmation that the equipment consistently continues to perform as required.

These definitions are consistent with those recently published by the Eurachem-UK Instrumentation Working Group,[12] Pharmaceutical Inspection Convention (PIC) and our own contained in this paper.

There is, however, one difficulty with this nomenclature. A modified form of the 4Qs model is used for validation of computerised systems. Here the same terms are used as equipment qualification; unfortunately they have a different meaning.[13]

User Requirements Specification (URS) is equivalent to the design qualification. Installation Qualification: documented verification that all key aspects of hardware installation adhere to appropriate codes and approved design intentions and recommendations of the manufacturer have been suitably considered. (In practice, this means ensuring that the system is installed as specified and sufficient documented evidence exists to demonstrate the fact.) Operational Qualification: documented verification that the equipment or system operated as intended throughout required or anticipated operating ranges. (In practice this means works as specified and sufficient documented evidence exists to demonstrate it.) Performance Qualification: documented verification that the system performs as intended throughout all anticipated operating ranges. (In practice ensuring the system in normal operating environment produces an acceptable quality product and sufficient documented evidence exists to demonstrate this.)

Thus, in computerised system validation there is an additional stage before the system can be released for operational use and there is no on-going assessment of system performance such as required in equipment qualification.

These differences in terminology can be very confusing for those analytical scientists involved in both equipment qualification and computerised system validation. It also asks the question why different groups can develop the same terminology with different meanings?

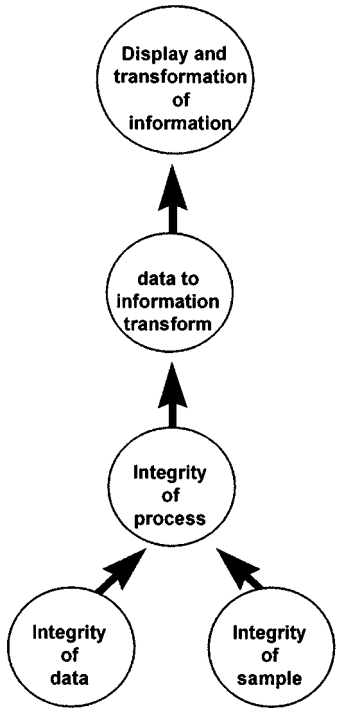

Fig. 2 The 'bottom up' approach to data integrity.

Interpretation for equipment qualification

Our interpretation of these 4Qs, from a laboratory user's perspective, is shown below and is framed as a series of questions. These questions need to be addressed before progressing to the next stage in the process. Failure to address the question adequately or at all will result in unresolved problems being carried to the next stages. The smiling face indicates the outcome of successfully answering the question. More details of our 4Qs model have been published previously.[14,15]

- ❑ **Design Qualification**
  - ● What do you want the instrument/system to do?
  - ☺ Setting 'suitability for use' criteria to meet business needs
- ❑ **Installation Qualification**
  - ● Does the instrument/system work the way the manufacturer says it should?
  - ☺ *Compliance with Specification*
- ❑ **Operational Qualification**
  - ● Does the instrument work for your specific applications?
  - ☺ *Operability in your environment*
- ❑ **Performance Qualification**
  - ● Does the instrument continue to work in the manner intended?
  - ☺ Ongoing Compliance

These principles enshrine the heart of good analytical instrumentation practices. There can be no doubt that a properly implemented 4Qs discipline will enable the most cost beneficial analytical systems to be installed and operated as fit for their intended purpose until equipment retirement.

A convergence of ideas

We have discussed the changes and approaches which have been developed within the pharmaceutical industry over the last five years or so. However, much in the way of harmonisation of procedures and practices in analytical chemistry has been going on outside these activities. Many of these initiatives are now coming to fruition. CITAC have produced an International Guide to Quality in Analytical Chemistry[16] which attempts to harmonise the following areas: ISO Guide 25, ISO 9001 and 9002 and GLP. In addition, a recent Eurachem-UK Instrumentation Working Group has published 'Guidance on Best Practice for the Equipment Qualification of Analytical Instruments'.[17]

The Instrumental Criteria Sub Committee of the Analytical Methods Committee of the Royal Society of Chemistry has been active for many years in producing Guidelines for the Evaluation of Analytical Instrumentation. Since 1984, they have produced reports on atomic absorption (currently being revised), ICP, X-ray spectrometers, GLC, ICP-MS and HPLC.[18,19] These are excellent source documents to facilitate the equipment qualification process.

These and other similar initiatives highlight the need for proper and adequate qualification and calibration of analytical instrumentation.

Equipment calibration, qualification and method validation

It is important to recognise the difference between equipment qualification and method validation. In some analytical scientists' minds these are the same and therefore by validating a method, the equipment is considered qualified. This is wrong. It should be realised that equipment qualification assesses the performance of modules and/or the system over the complete operating range of the instrument that the laboratory anticipates using. For instance, a UV detector for an HPLC could have an operating range of 190–650 nm when delivered from the manufacturer, but a laboratory may only use the instrument between, say, 210–280 nm. Therefore, the qualification would cover this smaller overall operating range. Individual methods, usually requiring a single wavelength, would be validated separately after the qualification, but based upon the knowledge that the detector worked to documented and scientifically argued acceptance criteria. If a new method was developed that utilised a wavelength outside the qualified operating range, the detector would require requalification, ideally before any further method development and certainly before method validation could continue.

Equipment qualification to ensure efficient method transfer

If there is one compelling reason for equipment qualification, it lies within the need to transfer methods between laboratories. Why are so many of our collaborative trials a failure? The answer lies in the fact that the key analytical variables have not been identified and controlled through specification and/or procedural practice. These may lie within the method but more often are due to the operating parameters of the equipment or system.

The need to standardise on a specific manufacturer's column (and sometimes individual production batch) is well known and will not be elaborated further here. However, the same principle holds for equipment: if temperature is a key factor, how can it be specified if there is no assurance that instrument A's temperature readout is not operating within known limits? Furthermore, if a laboratory is transferring a method involving an HPLC gradient separation and there is no specification even to the level of the pump, there may be many problems in the technology transfer. Examples are high pressure *versus* low pressure solvent mixing or differences in dead volume between the pump and column can affect the gradient formation and hence the separation and, overall, the method transfer. Without specification there can be no reliable control. Our methods will lack the robustness and reliability needed for fitness for their intended purpose.

Calibration is often confused with qualification. As pointed out by Parriott:[20] 'The term calibration implies that adjustments can be made to bring a system into a state of proper function. Such adjustments generally cannot be performed by chromatographers and are best left to trained service engineers who work for, or support, the instrument manufacturers'.

Calibration is therefore inextricably linked to equipment qualification and preventative maintenance. Whenever calibration involves adjustments of the type described above, it is important to document the activity and, where appropriate, requalify the instrument concerned.

Qualification in practice

In this section we would like to discuss some of our experiences in equipment qualification. Overall, a laboratory that starts retrospective equipment qualification should expect a modular failure rate between 40 and 60% against reasonable predetermined criteria. This may seem to be very high. However, it is good considering the majority of equipment has usually been purchased with no design qualification. Therefore attempting to qualify equipment for tasks for which it was not designed can be seen as an exercise in futility.

Avallone,[21] in giving FDA guidance on laboratory certification, stated the following expectation: 'The qualification of laboratory equipment and the maintenance of such equipment along with the accuracy of standards, reagents and test solutions are of concern in the certification of a laboratory'.

Design qualification

Overall, the major problem in equipment qualification is that design qualification is totally absent in many laboratories. This means that money, in many organisations, is wasted in purchasing inappropriate instrumentation. However, the lack of DQ has ramifications throughout the whole of the 4Qs approach. Without a specification which acts as a guide, laboratory management should not be overly surprised if equipment does not work as expected or anticipated.

This area is where a structured approach to equipment specification and purchase will repay with interest the work involved in defining exactly what is required for each item of equipment. However, once in control, with the direction in selection and purchasing compared against a written specification, the remainder of the 4Qs model becomes relatively straightforward.

The best approach to design qualification is summarised as writing down what you want the equipment to do. This can cover several areas, dependent on the scope and complexity of the equipment or system to be purchased. Typical areas to consider are as follows.

1. Technical requirements. Detail the operating specification of the system or instrument. Consider both the upper and lower ranges of each operating parameter as this provides an input to the operational qualification tests. Think carefully; do you want the instrument for a single task that will not change or do you want it to do several tasks of varying complexity? The first is relatively easy to specify; the second is more difficult. You need to think about possible operational changes, the scope of activities and the required parameter ranges of the equipment.

2. Environmental considerations. Where is the instrument going to be placed and are there any considerations that the manufacturer should know about? Examples are: in-process equipment should be very robust for non-analytical staff to operate, some systems analysing biohazard material may be located in a fume hood or Category III biohazard suite, *etc*. Both of these examples will have impacts on robustness, reliability and serviceability of the instrumentation purchased. Infrastructure factors need to be considered; for instance, a new mass spectrometer will probably require a new power supply and space for diffusion pumps to maintain the vacuum. What about the footprint required and the location of the mains services?

3. Sample presentation. How will samples be introduced to the instrument? Is there an autosampler required? If the answer is 'yes', then this will also require a technical specification under item 1.

4. Data acquisition needs. Will the system have its own data system or must it be linked to an existing data system? What constraints are placed upon the equipment?

5. Operability factors. What training is required to use the system and what are the service requirements?

6. Health and Safety issues. Are specific requirements needed regarding electrical supply, radio interference, *etc*.

7. Integration with other equipment or interface with computer applications should be specified. A typical example may be the transfer of data to a spreadsheet or integration of the system with a laboratory information management system (LIMS).

8. Cost benefit analysis. This is the overall justification of the equipment based on balancing all the costs of the system against the benefits once it is operational.

The design qualification allows the user to evaluate equipment against a specification. This allows objective criteria to be set against which different instruments can be objectively assessed. In addition, it provides the basis for the operational qualification tests to be devised and appropriate acceptance criteria set.

Burgess and McDowall[22] illustrated the problems that the lack of a design specification could cause by using an analogy of travelling from London to New York. Consider the DQ as a specification for a trip from London to New York. You have a number of options to consider. Do you want to travel by air or sea? Do you want to travel by a scheduled carrier or do it yourself? The fastest way to New York is by Concorde; this is very fast but it is very expensive. How would you justify the expenditure? At a quarter of the cost but with half the speed is a subsonic jet. However, if you do not specify the carrier and the travel agent just books the lowest price, you could get a carrier that has a very poor safety record. If you travel by sea, the cruise liner takes 30 times longer but the comfort factor is greater with a higher level of privacy and a good safety factor. It is essential to carry out DQ if 'fitness for intended purpose' is to be assured.

General approach to qualification

Calibrated testing equipment and traceable standards

It is important to realise that, when qualifying equipment, the accuracy and precision of the test methods employed need to be better, or at least as good, than the analytical methods which will use the equipment later.

Wherever practicable, all the equipment used in the qualification of the analytical instrumentation should be calibrated by a NAMAS (or equivalent nationally) accredited laboratory. Furthermore, traceable or certified reference materials (CRM) and standards are used wherever possible. The reason for this is to ensure that the results of the qualification are beyond reproach. Independently prepared calibrated instruments and certified materials mean that the qualification is fully independent and not reliant on vendor material.

Qualification guidance

Process validation,[23] published in 1987, gives a good overview of qualification activities; however, the document does not differentiate between IQ and OQ. 'Qualification studies establish confidence that the process equipment and ancillary systems are capable of consistently operating within established limits and tolerances. After process equipment is designed or selected, it should be evaluated and tested to verify that it is capable of operating satisfactorily within the operating limits required by the process. This phase of validation includes: examination of equipment design; determination of calibration, maintenance and adjustment requirements; and identifying critical equipment features that could affect the process and product. Information obtained from these studies should be used to establish written procedures covering equipment calibration, maintenance, monitoring and control.'

In assessing the suitability of a given piece of equipment, it is usually insufficient to rely solely upon the representations of the equipment supplier, or upon experience in producing some other product.

Sound theoretical and practical engineering principles and considerations are a first step in the assessment. It is important that equipment qualification simulates actual production conditions, including those which are 'worst case' situations. Tests and challenges should be repeated a sufficient number of times to assure reliable and meaningful results.

All acceptance criteria must be met during the test or challenge. If any test or challenge shows that the equipment does not perform within its specifications, an evaluation should be performed to identify the cause of the failure. Corrections should be made and additional test runs performed, as needed, to verify that the equipment performs within specifications. The observed variability of the equipment between and within runs can be used as a basis for determining the total number of trials selected for the subsequent performance qualification studies of the process.

Prospective installation qualification

The vendor is usually best placed for this activity, but the laboratory should evaluate all material critically. Experience shows that there is a wide range in the quality of vendor IQ material. However there is a strong regulatory view that it forms a vital function within equipment validation and qualification:[24] 'Laboratories can reduce the amount of effort and expense of qualification of laboratory instruments for GMP/GLP functions if they rely on vendor supplied data and information to support their applications' and 'Laboratories should view with suspicion vendors who are not willing or able to supply written documentation to support qualification and validation of laboratory instruments'.

Prospective operational qualification

There is a very broad range in the quality of vendors' OQ material. Ask yourself this question: how can a vendor design a generic OQ which matches your operational needs?

For the simplest systems or instruments this may be reasonably possible. Experience tells us that it is not always the case, however. As complexity and user configurability of instruments and systems grows so the usefulness of the vendor generic OQ diminishes. Often there is a good reason for needing independent qualification.

The key to deciding if vendor material is useful to your laboratory is to assess the tests carried out against the design specification. If the vendor's material matches all your key parameters, then the vendor's material should be suitable for your use. However, in our experience, this is rarely the case as

laboratories often operate in ways that are not covered by the vendor's generic documentation.

Roles and responsibilities in equipment qualification

The balance of roles and responsibilities is a function of the skill and resource base of the laboratory concerned. The journey from DQ to PQ will differ according to circumstance. However, it is always the end user who is ultimately responsible for the qualification.

Fig. 3 illustrates one example of overlaps in roles that could be involved in equipment qualification. The original equipment manufacturer (OEM) and/or the vendor is responsible for designing the equipment. Through the writing of the design qualification, the user is able to assess their needs against the instruments available. The vendor or OEM then installs the instrument. The end user is responsible for carrying out operational qualification and performance qualification. An independent compliance agent may be considered where technology transfer is needed to acquire qualification skills or to carry out the actual operational qualification work.

Case histories of retrospective IQ and OQ

These actual case histories of qualification examples are from many varied laboratories where usually there was no policy for or structured approach to equipment qualification.

Case History 1: HPLC Column Block Heaters

Observations. Column block heaters are rarely qualified in our experience as they do not attain the set temperatures. The reason is that the thermal transfer is poor. One such instrument was set at 60 °C and a NAMAS calibrated temperature probe inserted into the heating block; there was no column connected to the heating block. Within 4 min the readout on the controller unit stated that the temperature of the block was 60.0 °C. Unfortunately, the NAMAS probe said the temperature was 24 °C. The probe was left inserted in the column heater for a further 3 h and the maximum temperature reached at the end was 55 °C.

When a column was connected through the heating block and mobile phase was pumped, there was a temperature gradient (-2 to –4 °C) observed from the top to the bottom of the column. The mobile phase was actually helping to heat the bottom of the block by more efficient thermal transfer.

Conclusion. The major problem is that Design Qualification is urgently needed. Forced air ovens or controlled temperature baths are better for controlling the temperature of HPLC columns as they can maintain temperatures within ±0.5 °C. However, whatever type of heating system is chosen, selection of the unit must be linked to a practical acceptance test of fitness for purpose.

Case History 2: HPLC Binary Gradient Pump

Observation. A five year old HPLC pump had been installed and was maintained regularly by the manufacturer. The binary gradient forming capability was found to be inaccurate by more than 5%. An investigation found that the wrong software EPROM was installed and an incorrect cam of the mixing pump had been input during manufacture.

Conclusion. The advice from the Process Validation guidelines not to rely solely on the vendor's information is in this case true. Independent qualification after purchase would have found the problem and enabled it to be rectified. Problems with method transfer may have occurred in trying to establish methods between laboratories.

There are also issues surrounding the maintenance of equipment. This equipment was regularly serviced and yet no one spotted it until we carried out our independent tests. What does this say about the quality of the vendor's service activity? What does it say about the specification of the service contract?

Case History 3: A/D Converters of Chromatography Data Systems

Here is an example where 32 channels of a networked chromatography data system were challenged with ten replicate gaussian peaks generated by a traceable signal generator.

In Fig. 4, the results of challenging each of the 32 channels on a data system with 10 gaussian peaks with the same maximum amplitude (0.815 V) are shown. The source for this was a calibrated signal generator.[25]

The resulting peak heights calculated by the data system have been averaged and these figures have been plotted with their standard deviations to give an indication of the precision of the data. The measured μvolt peak heights are in the range of 812 000 to 816 000 compared with the input voltage of 815 000 μV. For the most part the majority of the A/D units are very accurate and precise. But, as you can also see from Fig. 4, there is one exception where the measured voltage is 825 000 μV.

Is this difference (higher by approximately 1.2%) significant? Does it matter? This is obviously an area for further investiga-

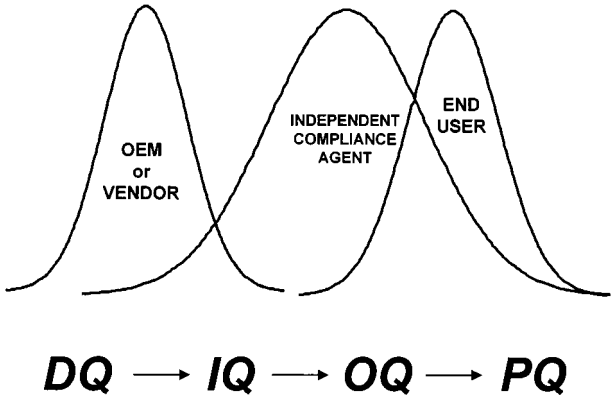

Fig. 3 An example of the overlaps in roles.

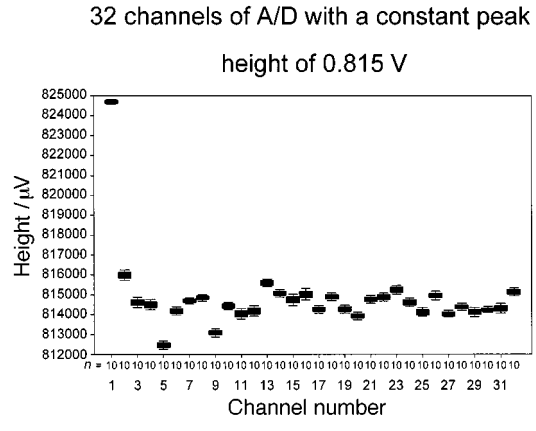

Fig. 4 Observed peak heights from a calibrated input voltage.

tion. For instance: what is the uncertainty in the calibration of the voltage source? What is the specification for the accuracy of the A/D unit? Is this a unit that has degraded over time or has it always performed with this apparent bias (hence the importance of performance qualification)?

In contrast, if you look at the means of the peak area measurements for all of the A/D units the overall mean is very good and there does not appear to be any problem. The unit only appears to be an outlier when measuring peak height as the relative standard deviation is greater for height than area. This argues strongly for the use of peak area rather than peak height for quantifying chromatography peaks (see Table 1).[26]

Case History 4: Controlled Environment Storage

Observations. This was a domestic refrigerator purchased and used for storage of laboratory standards, samples and reagents. No design qualification had been undertaken. The unit had been in routine operation for some time. The refrigerator was qualified over five days by placing calibrated data loggers at the top and bottom of the unit. The acceptance criteria for the mean temperatures were set using the requirements stated in the United States Pharmacopoeia XXIII, 1995, of the range 2–8 °C. When the data were analysed the temperature in the top of the unit was over the upper limit of 8 °C. In contrast, the temperature in the bottom of the fridge was usually under the 2 °C lower limit and often as low as −5 °C. Over the five day monitoring period there were 84 accesses to the fridge!

These data can be seen in Fig. 5 and 6.

After defrosting the refrigerator, the unit was requalified. The results are shown in Fig. 7 and 8. The temperatures were within specifications with the one exception of the temperature spike in the middle, where the door was left open for 15 min. Fortunately, there was an access log to record the fact.

Table 1 A/D converter performance; peak area compared with peak height

Parameter	Peak area/μV s^{-1}	Peak height/μV
Mean	6 232 887	814 821
Minimum	6 217 089	812 269
Maximum	6 243 955	824 828
Standard deviation	5582.6	1895.6
RSD (%)	0.09	0.23

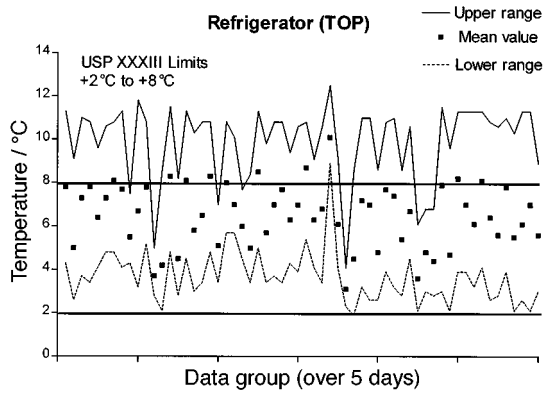

Fig. 5 Initial monitoring on the top shelf.

Conclusions. Domestic refrigerators are usually not suitable for laboratory work. Moreover, monitoring at the top and bottom of any temperature controlled environment is very important as the results show. Monitoring the temperature in the middle may have resulted in the qualification of median temperatures that may have been within the acceptance limits set.

Postscript. Once qualified, this refrigerator was moved into another laboratory. It failed to cool down at all! Therefore, it is vitally important to ensure that qualification is carried out *in situ*. Furthermore, if equipment is moved, performance qualification is essential to ensure that it continues to operate as intended.

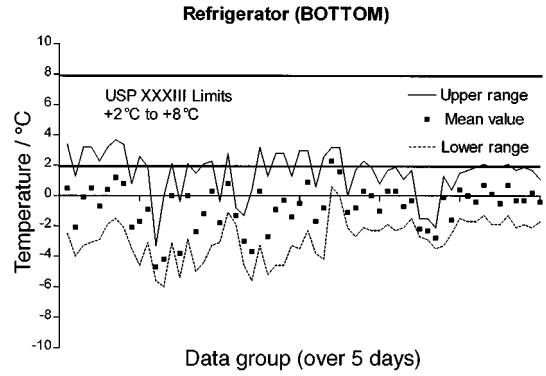

Fig. 6 Initial monitoring on the bottom shelf.

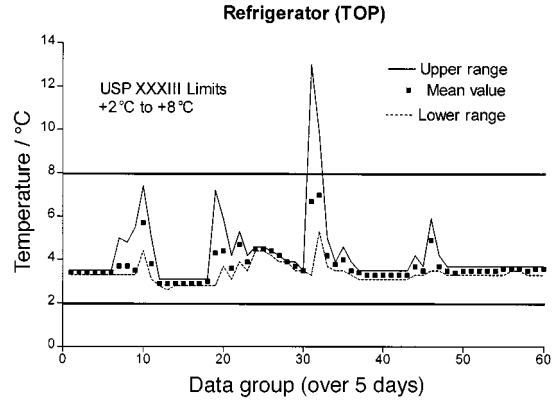

Fig. 7 Repeat monitoring on the top shelf.

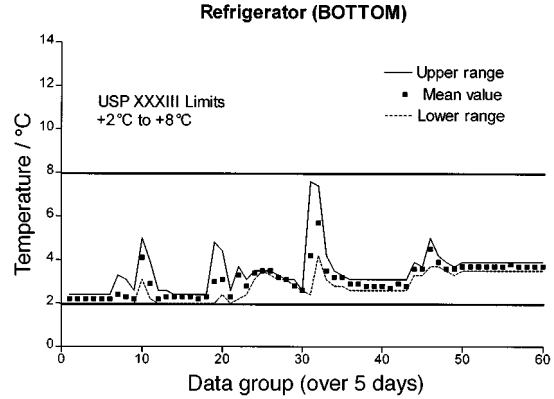

Fig. 8 Repeat monitoring on the bottom shelf.

Performance qualification

It is important to realise that once equipment qualification has been started, there is no stopping the process. Often, considerable effort and resource can be put into a first phase effort of equipment qualification; this must be maintained to ensure ongoing quality and the best return on a laboratory's investment. This is best summed up by the PIC guidelines on Qualification and Validation in Pharmaceutical Manufacture:[27] 'Qualification and validation can not be considered once-off exercise ….. An on-going programme should follow its first implementation'.

Therefore, as HPLC pump seals can wear and spectrophotometer lamps have a finite life, the analyst must be aware of the critical instrument parameters to be monitored as part on an on-going performance qualification programme for equipment. Wherever possible, the PQ activities should be brought into the routine operation of the analytical process to ensure the equipment is fit for purpose.

For instance, chromatographers use system suitability tests to ensure chromatographic performance before starting a run. Some of the parameters used may be diagnostic for assessing the overall performance of the instrument. However, system suitability tests are method specific and therefore are not all encompassing. They may have to be backed up with other tests, such as assessing the lamp energy of the HPLC detector or other parameters.

Conclusions

The introduction of a systematic management approach encompassing retrospective and prospective equipment qualification is essential. Piecemeal approaches and differing systems across laboratories are major obstacles to a uniform regulatory compliance strategy and may present a barrier to ease of inspection. A systematic approach is also essential to minimise laboratory management costs. This is particularly vital for retrospective qualification. Additionally, prospective validation costs are not always included as part of the purchase approval process. One system encompassing retrospective and prospective equipment qualification is crucial for compliance and cost control.

Furthermore, there is a positive business benefit to be gained by such an approach as it leads to more cost-effective laboratory operations, for example: a mechanism for retrospective qualification of existing instrumentation; control of capital expenditure for new equipment against defined business needs; less equipment variety leading to lower training and documentation costs; more assurance of suitability for use; and a cohesive and consistent framework to demonstrate on-going compliance.

Acknowledgement

Dr Mats Sundgren, Analytical Chemistry, Astra Hässle, for providing the A/D converter data.

References

1 International Conference on Harmonisation Note for Guidance on Validation of Analytical Procedures: Methodology, 1995, CPMP/ICH/281/95.
2 *FDA Center for Drug Evaluation and Research, Reviewer Guidance; Validation of Chromatographic Methods, November 1994.*
3 21 CFR 211 Subpart I Laboratory Controls, § 211.160 (b) (4).
4 *United States Pharmacopoeia XXIII*, 1995, < 621 > chromatography, < 711 > dissolution testing, < 831 > refractive index, < 851 > spectrophotometry and light scattering.
5 *British Pharmacopoeia 1993*, Appendix II: Infrared spectrophotometry, Ultraviolet and Visible Spectrophotometry (*Pharm. Eur*. V.6.19 Absorption Spectrophotometry), HM Stationery Office, London, UK.
6 *Australian Code of GMP for Therapeutic Goods—Medicinal Products*; Appendix D, November 1991: Guidelines for Laboratory Instrumentation.
7 NIS 45, Edition 2, May 1996, Accreditation for Chemical Laboratories.
8 Department of Health and Human Services Food and Drug Administration [Docket No. 93N-0184], Barr Laboratories, Inc.; Refusal to Approve Certain Abbreviated Applications; Opportunity for a Hearing, vol. 58, no. 102, Friday, May 28, 1993 p. 31035, (Notice) 1/1061.
9 *The Gold Sheet*, 1994,**28**(12), 8.
10 W. B. Furman, T. P. Layloff and R. T. Tetzlaff, *J. AOAC Int.*, 1994, **77**(5), 1314.
11 M. Freeman, M. Leng, D. Morrison and R. P. Munden, *Pharm. Technol. Eur*., November, 1995.
12 P. Bedson and M. Sargent, *Accreditation and Quality Assurance*, 1996, **1**, 265.
13 *Good Automated Manufacturing Practice: Supplier Guide for Validation of Automated Systems in Pharmaceutical Manufacture*, Version 3, May 1998, ISPE.
14 C. Burgess, *Laboratory Automation and Information Management*, 1995, **31,** 35.
15 C. Burgess, in *Spectrophotometry, Luminescence and Colour; Science and Compliance*, ed. C. Burgess and D. G. Jones, Elsevier, Amsterdam, The Netherlands, 1995.
16 *CITAC Guide 1, International Guide to Quality in Analytical Chemistry, An Aid to Accreditation*, Edition 0, August 1995.
17 Eurachem—UK Instrumentation Working Group, *Guidance on Best Practice for the Equipment Qualification of Analytical Instruments: HPLC*, 5th Draft May, 1998.
18 Analytical Methods Committee, *Anal. Proc.*, 1984, **21**, 45; 1985, **22**, 128; 1986, **23**, 109; 1987, **24**, 3; 1987, **24**, 266; 1990, **27**, 324; 1991, **28**, 312; 1993, **30**, 296.
19 Analytical Methods Committee, *Analyst*, 1997, **122**, 387.
20 D. Parriott, *LC-GC***,** 1994, **12**(3) 132.
21 *The Gold Sheet*, 1994, **28**(12), 8.
22 C. Burgess and R. D. McDowall, *LC-GC Int.*, 1997, **10**(2), 87.
23 FDA Process Validation Guidelines, 1987.
24 R. F. Tetzlaff, *Proceedings of DART '94*, Advanstar Communications, Amsterdam, October, 1994.
25 M. McConnell, M. Canales and G. Lawler, *LC-GC Int.*, 1992, **5**(3), 34.
26 C. Burgess, D. G. Jones and R. D. McDowall, *LC-GC Int.*, 1997, **10**(12), 791.
27 Pharmaceutical Inspection Convention, *Principles of Qualification and Validation in Pharmaceutical Manufacture, Document PH 1/96*, Bundersverband der Pharmazeutischen Industrie (PBI), Frankfurt am Main, Germany, January 1996.

Paper 8/04670K