Qualification is an important quality assurance tool in the pharmaceutical industry. It is used to prove the reliability of technical systems. Since qualification is associated with a lot of effort, paperwork, time and costs, it is the focal point of efficiency discussions. That is also why the industry, authorities and associations regularly examine this topic, and attempt to reduce the effort to the necessary minimum without running the risk of quality impairments.

Trends in System Qualification

New approaches in the pharmaceutical industry

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Background

Qualification means documented evidence that a technical system has been properly designed and installed according to the requirements, and that it functions exactly as originally specified by the user. Qualification is part of validation, which includes evidence not only regarding the technology but also the processes and procedures. Both elements, qualification of the technology and validation of processes and procedures, are mandatory according to the rules of Good Manufacturing Practices (GMP) and an established part of official inspections, especially in the pharmaceutical industry.

The first directive for validation in practice (including qualification) was published in 1983 by the FIP (Fédération International de Pharmaceutique) [1], with initial concrete implementation information and recommendations. More than 30 years have passed since then, with further development of the topic and an increasing level of detail. A look at the time line (Figure 1) quickly reveals how not only the topic itself but also the corresponding rules, regulations and directives have developed almost exponentially.

While regulatory changes were introduced about every three to four years initially, this has increased to three or four amendments and the associated directives, rules and regulations that have been appearing about annually since the year 2000. Keeping up with this frequency is difficult, especially since the publication of new directives is also associated with new requirements for how this subject is handled.

Not only the abundance of rules and regulations related to the topic of “qualification” is a challenge, but also the amount of paper produced in the course of the qualification process (audit and test plans and reports). No wonder that ways to manage, or even better to reduce, this flood of paper were explored early on. While initial approaches focused on the topic of “reduction through selection”, meaning the qualification of select, critical technical systems only (specific selection with the help of risk assessment for example), a trend in favour of “reduction through selection plus integration” is increasingly seen today. This means one not only wants to reduce the effort and amount of paper through the specific selection of critical technical systems but, on the technical and engineering side,

take previously conducted audits and tests into account in qualification (integration) and thereby eliminate duplicate work.

The discussion that follows illuminates qualification "yesterday – today – tomorrow" and attempts to describe what the future of modern qualification may hold as well as the resulting technology challenges, in particular for suppliers.

Qualification "yesterday"

The elements of installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ) that are commonly known today were differentiated early on within the scope of qualification. IQ verifies and documents correct specification and installation, OQ the correct function, and PQ the capability of the corresponding technical system. Planned and written documentation and proof has always been a fundamental requirement here.

A validation master plan (VMP) was also required on the documentation side early on, outlining the overall project and listing the required specific actions including the necessary resources. Protocols were and still are expected today for the individual actions (IQ, OQ, PQ), describing the intended approaches, details and, in particular, the acceptance criteria. The protocols including all corresponding checklists and audit source documents have to be reviewed by the validation team – a team of interdisciplinary technical experts – and formally approved for implementation with a signature by the quality unit of the system owner. A similar procedure is carried out after implementation for the qualification results and resulting report. Its content is also reviewed by the validation team, ultimately followed by formal approval by the quality unit.

Very detailed and system-specific checklists were often developed for the implementation itself, with specification and function criteria including defined acceptance criteria based on the technical documentation being recorded as the basis for the audit. In many cases the details were transferred from the system itself or from the technical documentation into the checklists, in order to subsequently confirm inversely that these details are actually found on site and in the technical documentation. Systems developed in the USA in particular exhibited this paper-generating symptomatology.

A project encompassing only 10 technical components for example would result in a total of 30 documents for the elements IQ, OQ and PQ alone, with all corresponding checklists and attachments, not including master documents. Most projects encompass considerably more than 10 components.

Qualification "today"

At the end of the 90s and with the beginning of the 21st century, the industry became more self-critical and recognised that the stolid formalistic approach produces lots of paper and generates high costs, but does not lead to commensurate quality improvements. Quite to the contrary, the amount of paper and strict formalism often prevented truly critical problems from being identified.

Accordingly the philosophy of the industry but also public authorities has changed considerably today. For one thing, an additional element – the design qualification (DQ) – was added to the activities, since it was recognised that most mistakes are made early in the planning stage and therefore have to be excluded there. For another, the element of risk assessment was introduced as the most important GMP tool, among other things for the purpose of selecting which technical components are critical and actually require qualification, and which ones are relatively non-critical so that formal qualification is not required. Furthermore, one has realised that always representing all audit points in detailed checklists is not a compelling requirement nor necessarily helpful. Instead it makes sense to use technical documentation (such as pipework and instrumentation flowcharts, design drawings, electrical diagrams and BOMs) directly as the audit basis, and to also integrate previously completed factory acceptance tests (FAT) and site acceptance tests (SAT)) in the qualification process.

All of these measures notwithstanding, the qualification procedure is still not considered optimal and productive today. While the basic understanding of the design qualification is clear, the procedure is not. Every company performs the DQ differently.

While some compare the requirements of the operator (user requirement specification) to the implementation recommendations of the manufacturer (functional and detailed design specifications) in great detail and systematically point by point, others merely view the DQ as a review of working drawings or also simply as the preparation of a user requirement specification. Conducting the risk assessment to identify critical technical systems that are relevant for qualification is often highly formalistic and carried out more as an end in itself that for the purpose of truly reducing effort. Uniform practices have not been established for the qualification plans either. While some have boldly reduced the scope to the essential minimum already, others continue to follow the checklist principle. Finally, there is the integration of FAT and SAT results.

Here one has quickly reached the conclusion that this of course can only work if good engineering practices (GEP) have been implemented with corresponding,
properly conducted and documented tests. Unfortunately this in particular continues to rarely be the case.

The ISPE (International Society for Pharmaceutical Engineering) clearly describes this problem in its white paper [2] from March of 2005. An especially established “Qualification Task Team” openly states that, from the perspective of the experts, there is currently no truly efficient and actually effective qualification system. The systems and procedures remain too formalistic, elaborate and expensive, and do not focus adequately on patient safety. An urgent need to develop an adequate, modern qualification concept is identified.

Figure 1: Regulatory development of qualification

Qualification “tomorrow”

The ISPE Qualification Task Team developed a 10-point programme, with requirements that are to be implemented through the further development of standards and norms. A risk-based approach, the integration of manufacturer tests (FAT and SAT), and pragmatic and practical qualification documents continue to represent core points. However, the requirements of the ISPE go even further and, for example, see the possibility of drastically reducing qualification for standard equipment, possibly replacing this with a supplier qualification. In general the IQ and OQ activities in particular are to be considerably reduced, with much greater reliance on the manufacturer tests. This is viewed as the primary task of engineering and not of a pharmaceutical quality unit. The focus of the user should be clearly on the PQ, the performance qualification of the technical system.

ASTM E2500 [3] published by the ASTM in 2007 is a standard pursuing precisely this objective. It deals with building, process and ancillary systems as well as process monitoring, control and automation systems, generally grouped under the term “manufacturing systems”. A comparable standard, ASTM E2537 [4], was published in February of 2008 on the topic of “Manufacturing”. Both standards use the umbrella term “verification” that encompasses both the “usual” technical standard tests and the formal qualification and validation activities.

The ASTM E2500 standard emphasises the previously described topics “risk-based approach” and “use of manufacturer documentation/tests” as key elements. However, it also calls for a “science-based approach” and mentions “critical aspects” of

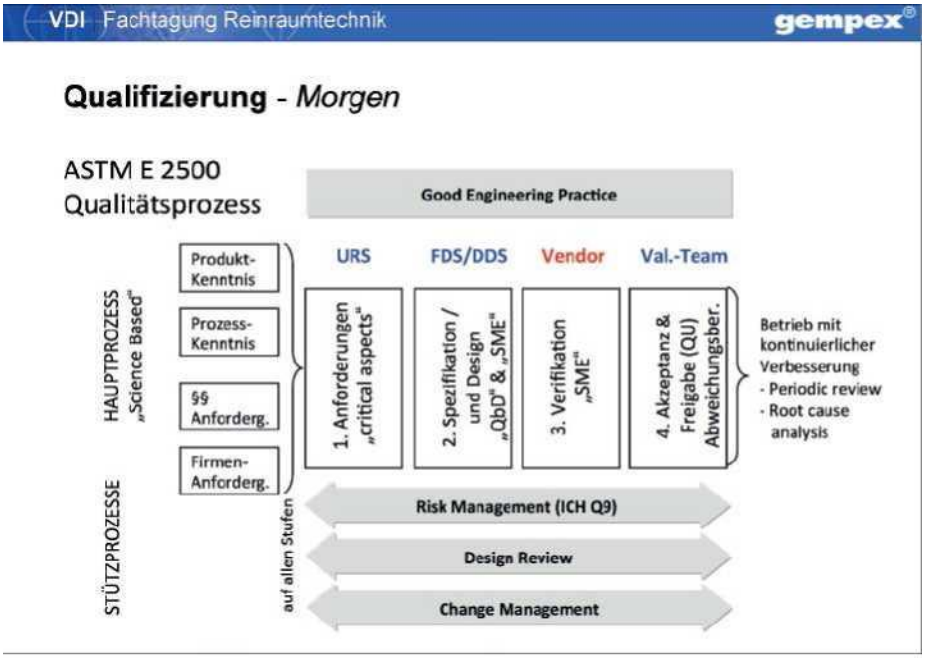

Figure 2: Qualification process according to ASTM E2500

the manufacturer systems, the “subject matter expert” and continuous process improvement. A flowchart, which is reproduced in simplified form in Figure 2, forms the centrepiece of the normative guideline.

This “idealised” procedure is based on the main and support processes. The general requirements and critical aspects are defined for the main processes based on product and process knowledge and under consideration of regulatory and internal company requirements, and described in a user requirement specification (URS).

Technical experts also develop the functional design specification (FDS) and detail design specification (DDS), already taking all relevant quality requirements into account at this stage (QbD = quality by design). The realisation phase is followed by the familiar test and qualification phase, now summarised here under the term “verification” and placed under the care of the “subject matter expert”, meaning the technical expert (manufacturer or supplier). Only then does the quality unit come into play,

formally accepting the verification results at the very end and approving the technical system, including a report on deviations where applicable. This procedure is accompanied by risk assessment, design review activities and change management that apply to all steps as supporting processes and also presume good engineering practices.

Qualification "the day after tomorrow"

At first glance this normative proposal appears quite similar to the current, already established procedures. The actual intent and planned process improvements however only become apparent with repeated reading and concentration on the details.

Clearly one of the focal points is the identification of "critical aspects" that were purposely not reduced to "quality critical aspects" here. Rather, the objective is to determine all essential and critical characteristics and elements of the technical system from the outset under the aspect of good engineering practices, and to consider these points in design and implementation, which requires the manufacturer to have a corresponding quality awareness and quality system.

Another focal point of this concept is the assignment of the "verification activities" to the technical experts, the people who know the technical system best. Their job is to put it through its paces in the end and confirm its suitability. In principle this approach is already being practised at a low level today. Often the manufacturer or supplier carries out the truly critical and relevant tests, which are subsequently repeated in qualification to meet the formal system requirements. In case of a procedure according to ASTM E2500 this would then be merely "official".

Finally the concept also makes it clear that risk assessment is not a one-time thing but a continuous process, taking place across multiple project stages and supported by a continuous design review, naturally always based on the assumption of good engineering practices.

Thus the future concept could take the form of finding suitable and qualified suppliers who are intimately familiar with quality and qualification, and therefore fully cover all IQ and OQ elements from the outset, working according to ASTM E2500 or a comparable standard. Simply downloading the corresponding certificate would be the final remaining formal act. The PQ as a hard performance test would still have to be carried out by the manufacturer, but is also surely within their area of expertise.

The challenge

The statements made by the ISPE in the white paper clearly address a real and widely recognised problem.
What's more, the future concepts described in the cited ASTM standards seem reasonable and by all means realistic. Considering that the discussion of these problems already goes back eight years and no signs of an implementation are discernible - at least here in Europe - the actual roots of the problems must go deeper. A review of actual practices shows that they continue to be found in the not truly existent "good engineering practices", which would fully integrate a topic such as qualification. They lie in the lack of guidelines for manufacturers, describing how they should carry out a qualification or also just a formal verification according to the requirements. And they are found in the ongoing conservative thinking of the pharmaceutical industry and public authorities who, at this point and perhaps with good reason, are not willing to give up an important part of quality assurance and transferring it to the manufacturers.

After 30 years of qualification and at least eight years of optimisation efforts, it therefore continues to be a great challenge to gain control of this issue to an extent that the concept can be described as efficient, effective and economical.

Bibliography available from the author on request.

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