Qualification 4.0 – Unused Opportunities

How an efficient, time-optimized qualification could work – Part 1[*)]

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In 1987, the U.S. Food and Drug Administration (FDA) laid the foundation for validation, including equipment qualification, with its "Principles of Process Validation" [1]. The latter is limited to "Installation Qualification" (IQ). Over the years, the Pharmaceutical Inspection Convention (now extended to form the Pharmaceutical Inspection Co-operation Scheme (PIC/S)) added the elements "Operational Qualification" (OQ), "Performance Qualification" (PQ) and later "Design Qualification" (DQ). 30 years have passed since then. 30 years the industry has been struggling with the topic and the associated mountains of paper. A white paper [2] on the sense or nonsense of the procedure, which has been published in the meantime by ISPE, has resulted in a standard paper of the American Society for Testing and Materials (ASTM) [3], which would like to use Good Engineering Practice (GEP) to simplify the procedure, but only receives moderate attention. In the meantime, the elements of risk assessment, the user requirement specifications (URS) and a traceability matrix have been added. In the age of Industry 4.0 the pharmaceutical industry is stuck. Qualification has developed into a project blocker, an uncontrolled time and cost factor. The following article shows the fundamental problems of qualification in today's world. It illuminates the causes and makes suggestions on how qualification could be implemented much more efficiently.

Importance and Development of Qualification

The introduction of qualification in the 1980s was based on the basic idea that quality cannot be tested into a product, that quality must rather be ensured by securing that all components involved in the production of a pharmaceutical product are in order and efficient. In addition to trained personnel, good and traceable documentation, raw materials in accordance with specifications, elaborated procedures and much more, there was also the demand for properly installed and functioning technical equipment. The systematic verification of correct installation and function by means of prepared checklists should guarantee this. The integration of the Quality Unit, which formally approves the corresponding test plans beforehand and finally evaluates deviations and reports, should underline the importance of this procedure.

The elements of installation and operational qualification were further supplemented, firstly with Performance Qualification, then

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As a member of various working committees, he was involved in the development of GMP regulations and harmonizing of guidelines and continues to act as a consultant for challenging GMP projects and as a 3rd party auditor. Since 2013 Ralf Gengenbach is president of the "Verein Interessengemeinschaft Pharmabau VIP 3000 e. V.". He is active in expert committees, gives lectures, is a speaker and author of numerous publications.

The book "GMP – Qualification and Validation of Active Pharmaceutical Ingredient Systems" is considered a standard work in the industry.

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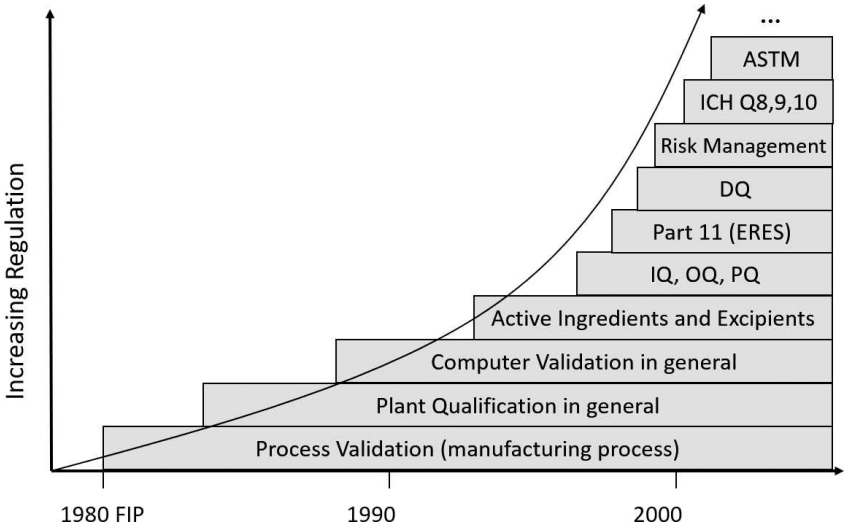
with Design Qualification. The latter in particular was due to the fact that it was recognized that quality is determined at an early stage, namely in the design phase. In the case of an incorrectly selected design, the Installation Qualification can only confirm that the (incorrect) design was built as (incorrectly) planned. However, the error itself cannot be corrected.

A further development was that there was a desire to move away from the purely formal filling out of checklists and to concentrate more on the critical aspects. The topic of risk assessment was introduced. In addition, the identification and designation of quality-critical attributes (Critical to Quality Attributes (CQA)) and quality-critical process parameters (Critical Process Parameters (CPP)), which should be given special consideration during qualification, was introduced. Process understanding and technical knowledge became the focus of attention as an essential – and quite reasonable – requirement of the authorities in order to achieve the originally pursued goal with the qualification.

Over the years, the topic of qualification has been extended from the production of finished pharmaceuticals to the production of the associated starting materials. Furthermore, process automation and IT systems of all kinds were successively integrated with the GAMP Guidelines [4] and the Part 11 requirements.[1)] Figure 1 illustrates the rapidly increasing regulatory development in this area.

Figure 1



Regulatory development of qualification (source of all figures: the author/gempex GmbH).

Qualification is Questioned and Redefined

After the qualification had manifested itself at many companies in mountains of paper, endless formalism, time delays in projects and enormous additional costs without offering any significant recognizable advantages, the criticism became louder and louder. In 2005, the International Society for Pharmaceutical Engineering (ISPE) published an extremely critical statement on this topic in a white paper [2]. It speaks of inefficient, ineffective systems. Further it says, the focus on patient safety was missing and the overall approach would be too complex, too formalistic and too expensive. The statement *"The current process is document intensive and does little to add value and provide assurance that the product manufactured is of the highest quality"*[2)] summarizes the problem impressively in one sentence. A 10-point program (Fig. 2) is drawn up and it is suggested that procedures should be aligned with it and laid down in generally recognized standards. In addition to the guidelines published by the ISPE itself, reference was made to standards like the one of the American Society for Testing and Materials (ASTM),[3)] which were to comment on this topic.

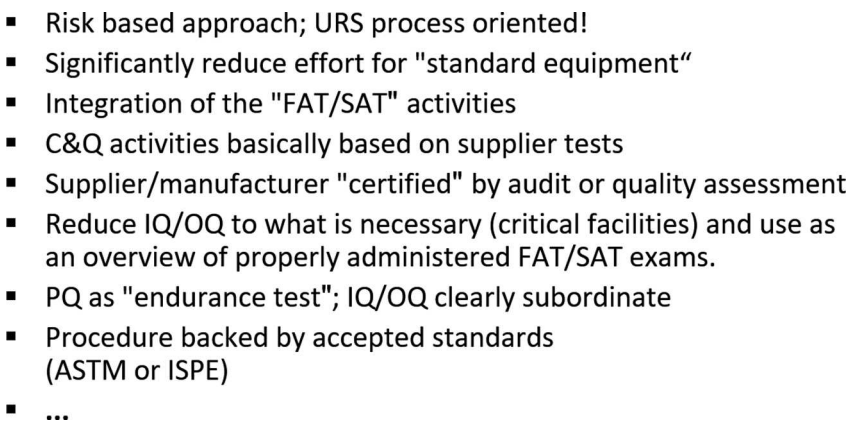
In 2007, ASTM launched a corresponding guide for pharmaceutical and biopharmaceutical plants. The document ASTM E 2500 [5] deals with the specification, design and verification (qualification) of equipment including control and automation systems. In addition to the already known topics of a risk and science-based approach, the elaboration of CQA and CPP as well as a "Quality by Design" (QbD) oriented approach, the "Subject Matter Expert" (SME) and the increased

[1)] Requirements for computerized systems that are used in a GxP-regulated environment and are used for electronic records with electronic signature if necessary. Specified beside others in the USA 21 CFR 11 or in the EU-GMP-Guidelines Annex 11.

[2)] *"The current approach is complex in terms of documentation and does little to add value and ensure that products would be produced to the highest quality"*, extract from ISPE White Paper, Mar 2005.

[3)] ASTM – Founded in 1898 as the American Society for Testing and Materials, today as ASTM International a central standardization body in the USA.

■ **Figure 2**



Excerpt from the 10-point program, ISPE White Paper, 2005.

involvement of suppliers are now also brought into consideration, rounded off by a desired continuous process improvement. In a diagram, the thoroughly logical process is shown as follows:

- Provision of all existing data and information concerning product, process, regulatory and company-specific requirements
- Derived from this the creation of a user requirement specification (URS)
- Elaboration of the technical specification and design in consideration of the QbD approaches and with the involvement of SMEs
- Verification of proper implementation by the SME, taking into account the supplier documents
- Integration of the Quality Unit only at the end with formal acceptance and release on the basis of deviation reports
- Start of operations with continuous improvement and periodic quality reviews

The whole process should be accompanied by risk assessments at various levels, design reviews and technical change management. Good Engineering Practice (GEP) is taken for granted.

Simplified, the recommendations of the ASTM standard were also translated as “Back to the Roots” – reasonable and reliable engineering work and involvement of the Quality Department only where it is necessary – at the end.

The Madness Takes no End – Reasons for Inefficient Qualification

Despite these certainly very logical and plausible approaches and suggestions, little or nothing has changed to this day – even 17 years after the publication of the white paper.

In the age of Industry 4.0, paper still dominates the qualification scene, formalisms cause budgets to burst, personnel resources to dwindle, and target dates to move into the infinite distance. Not to mention the missing benefits.

This may sound exaggerated, but unfortunately in many cases it is still reality. The question is, what is the reason for it?

■ GEP or how engineering technology is reinvented

It is a well-known phenomenon that in cases where a new discipline is just establishing itself in the scientific/technical environment, certain basic principles are rediscovered, invented, developed. Thus, when biotechnology began to establish itself, one could observe when studying the relevant literature that the basics of mathematics, physics, thermodynamics and others were taken up, interpreted and explained in a new way, although everything was widely known and described.

A similar phenomenon is observed in the qualification in interaction with Engineering Technology. In the beginning, it was the simple Installation Qualification (IQ) and Operational Qualification (OQ) checklists, but today this has expanded significantly to include the User Requirements Specification (URS) and Functional-/Detailed Design Specifications (FDS, DDS), Factory Acceptance Test (FAT) and Site Acceptance Test (SAT)[4] documents, test plans and much more. Documents that increasingly blur the line between Engineering Technology and qualification. Although terms such as URS, FDS, DDS, FAT and SAT have existed for a long time, they are used today in connection with GMP and qualification as if they had been invented here. Meanwhile they also found entrance beside others into the EU-GMP-Annex 15.

In principle, this would not be a tragedy if it were not for the interaction with the Quality Unit and the need for GMP/qualification-relevant documents to be subject to a certain formalism, the obligation to use certain signatures and then to change control. If a FAT or other technical document is checked by the Quality Unit, the question arises as to how competent a Quality Unit can even assess such a document and, on the other hand, it considerably inflates the formalism and thus the effort involved. In principle, the more activities and documents that belong to engineering technology are pushed into qualifi-

[4] FAT and SAT are the technical acceptance tests carried out by the manufacturer or supplier, which are first carried out in the factory and then after installation at the later site.

cation, the more complex and time-consuming the qualification process becomes. This does not mean that the Quality Unit is left out when clarifying the scope and content of such documents. However, final coordination, adaptation and approval are the responsibility of the SMEs.

Tip: A clear assignment of documents and activities to GEP and GMP should be ensured. Only the really relevant and qualification-specific documents should be included in the formal qualification concept and others left as much as possible on the engineering side.

■ The validation team – everyone talks and everyone decides

It is a basic characteristic of GMP and in particular of qualification that work is done across departmental boundaries. No activity requires the participation of so many disciplines as qualification. Whether it is the future operator, the Quality Unit, research and development, Quality Control, Process Engineers, Measurement and Control Technicians, IT, planners and suppliers – sooner or later all of them will be needed within the framework of the qualification with their specialist input.

The coordination of activities across the multitude of disciplines and the demand for information and data is already difficult enough. But even more difficult seems to be the coordination and final release of documents. One meeting chases the next. Countless resources are tied up. Documents are edited in an overlapping and contradictory manner and laboriously merged into one version. Previously conducted reconciliations and approvals are repeatedly cancelled because one department does not found it's interests and concerns sufficiently taken into account. At the same time, there is not enough time for meetings to discuss everything that needs to be discussed, to explain necessities and certain decision paths and decisions to even the last person involved. This is only a small part of the problems that arise especially in larger qualification projects.

The early and clear orientation of an appropriate project organization and the definition of necessary tools and instruments are essential and last but not least essential factors for success in qualification. The following recommendations can be helpful in this respect:

- Use of modern tools for editing or commenting on documents on a central platform, which only allows one access at one time on one specific document and thus collects all edits in this document (e.g., Microsoft SharePoint®); avoidance of document circulation via e-mail. Simultaneous editing by different persons on different copies does not bring any time advantage.
- Specification of fixed time limits for reviews and revisions; when the time limit is reached, the document should generally be considered as reviewed and revised.
- Inclusion in the team of at least one administrative person who is exclusively responsible for document management and primarily for the signature collection process. This investment pays off several times over for large projects.
- Documents should only be discussed in meetings if there are last open points worthy of discussion. Meetings should be timed the way that several documents can be worked through in a concentrated manner (at least half-day meetings).
- Only those persons who are needed in connection with the clarification of open points should participate in the meetings. The fewer participants, the better. There is no need to give explanations to all disciplines on all points. There is no need for each participant to attend for the entire duration of the meeting if he or she is not needed.
- For larger projects: Use of a validation coordinator (project manager), whose main responsibility is to ensure that the above-mentioned and generally established rules of the game are followed.
- Definition of clear responsibilities: The role of the disciplines is to make their technical contribution. Decisions are made at the level of the future operator and the Quality Unit.

There would certainly be a whole range of other recommendations concerning the organization and management of such projects. However, the recommendations listed above refer to those points in the qualification process that have proved to be the biggest problems and brakes in the past.

Tip: A main focus should be on early project organization. Qualification projects are highly complex and multidisciplinary. It should generally be proceeded on the principle "Everyone is allowed to express his opinion, but only one person decides".

■ The problem with the User Requirement Specifications (URS)

The URS (and here especially the German "Lastenheft") is one of those documents that originated in Engineering Technology and only found its way into the GMP environment much later, specifically in qualification. In the German VDI Guideline 2519 of Dec 2001, the "Lastenheft" is defined as a "*compilation of all requirements of the contract giver with regard to the scope of delivery and services. The requirements from the user's point of view, including all boundary conditions, must be described in the specifica-*

tions. These should be quantifiable and testable. In the Requirement Specification it is defined, WHAT and WHAT FOR is to be solved."

Following this definition, the German "Lastenheft" is a document that is created from the contract giver's point of view, whereas the contract giver must not necessarily be the later user/operator. The English definition "User Requirement Specification", on the other hand, tends to refer to a document that is expressively be created by the user – i.e. the subsequent operator. Sure, the client and the user can of course be the same person.

This difference may seem like a sophistry at first, but it is basically a cause for a number of major problems in the qualification process. Why?

The specifications – or better the URS – is today the starting point and a key document for all qualifications. It defines the requirements – especially the GMP requirements – for the project or the respective technical system. It is now common practice to carry out the first stage of the risk assessment on the basis of this URS and to derive the qualification measures from it. A so-called traceability matrix helps to link all actions from the URS via the risk assessment to the qualification and to ensure complete processing.

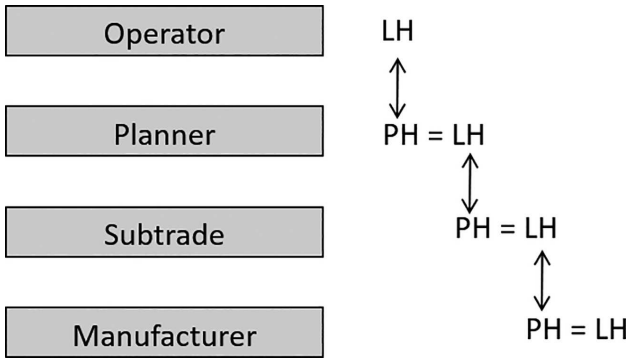
URS is also important in connection with technical change management. Even during an ongoing construction project, it is expected that significant changes – especially regarding GMP requirements – will be discussed, evaluated and documented. When a change exists, this is determined, among other things, by the specifications in the URS.

But what if the URS is a highly technical and very detailed document of a "contract giver" who, for example, is involved in the project as a planner? If the level of detail goes as far as pipe hangers, steel constructions and screw covers? That is exactly when the problems arise, because all these details must then be considered in the risk assessment, because for every smallest change it must be decided what is and what is not to track by the technical change management. A too detailed technical URS pushes technical, not necessarily qualification relevant points into the qualification and makes the handling of the URS a real challenge.

A construction project is a highly complex matter, and in reality, there are not only requirement specifications for different systems, but also at different planning levels. Figure 3 illustrates this.

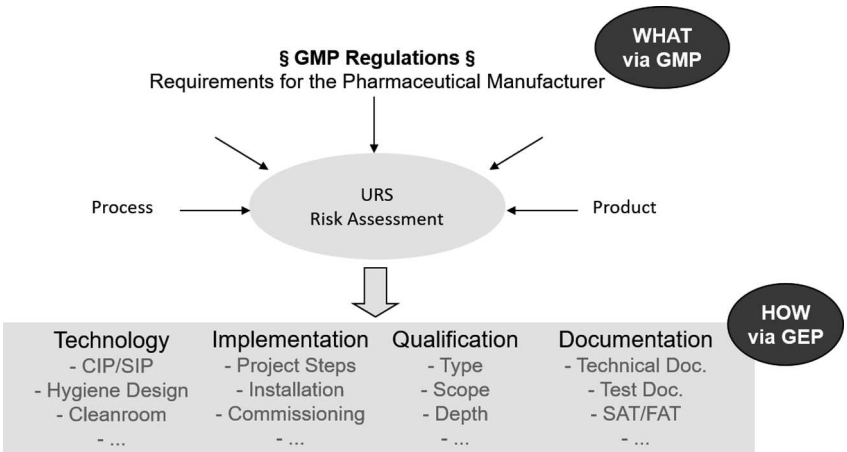
In order to be able to handle the qualification in a reasonable way and to really concentrate the measures on the quality-critical requirements, it is absolutely necessary to distinguish clearly and in a unique way between a "User Requirement Specification" (URS on the highest level) and a technical specification (detailed level). A URS should focus exclusively on the user – the future operator of the system. Which products he wants to produce, for which markets, considering which regulations. What are special challenges – good cleanability, multi-

■ **Figure 3**



Requirement and functional specifications in the planning process.

■ **Figure 4**



Derivation of technical specifications from the URS.

product plant, critical products. Which control and monitoring parameters play a role, which quality attributes are important. It is then the task of the engineers to derive the technical specification from these user requirements. The technical specification should also be the specification for the next planning and/or execution level. Figure 4 illustrates this process.

In this context, the inclusion of the term URS in the EU-GMP-Annex 15 must also be seen as unfortunate. On the one hand, it is said to reflect the specifications of a piece of equipment in it, on the other hand, the URS is identified as a lifecycle document to be maintained. Both are unfortunate and reflect the problem in the pharmaceutical industry that engineering technology, as known from chemical plant construction, does not exist there. Machines and apparatus are purchased from the supplier ready for operation, which had previously made detailed technical specifications virtually superfluous. The URS are therefore often seen as a replacement for an in-house technical specification, which explains the permanent maintenance and update, but also makes the qualification process considerably more difficult.

Tip: In the qualification concept should clearly and unambiguously be defined what is a user specification and what is a technical specification and what at which level by whom is created. The User Requirement Specifications (URS) should only include requirements from the user's perspective while technical details should be left to the engineers.

The second part of this article with the literature will be published in the next issue of this journal.

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