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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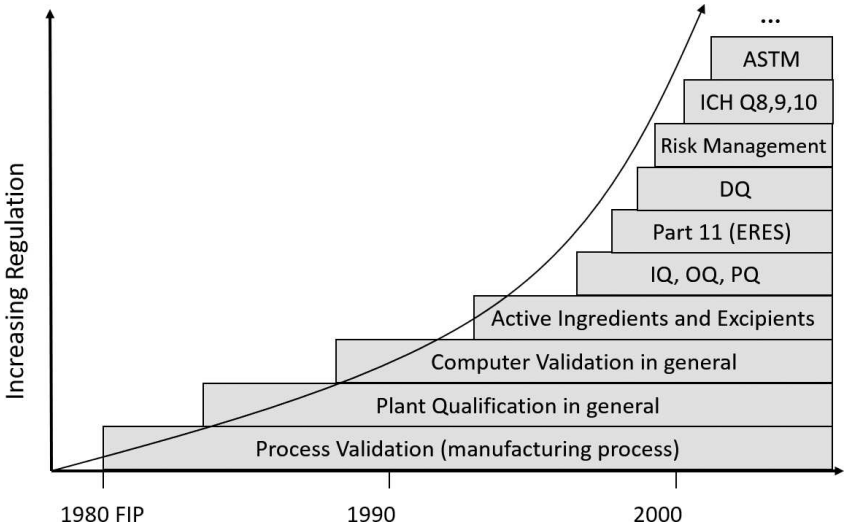
with Design Qualification. The latter in particular was due to the fact that it was recognized that quality is determined at an early stage, namely in the design phase. In the case of an incorrectly selected design, the Installation Qualification can only confirm that the (incorrect) design was built 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.

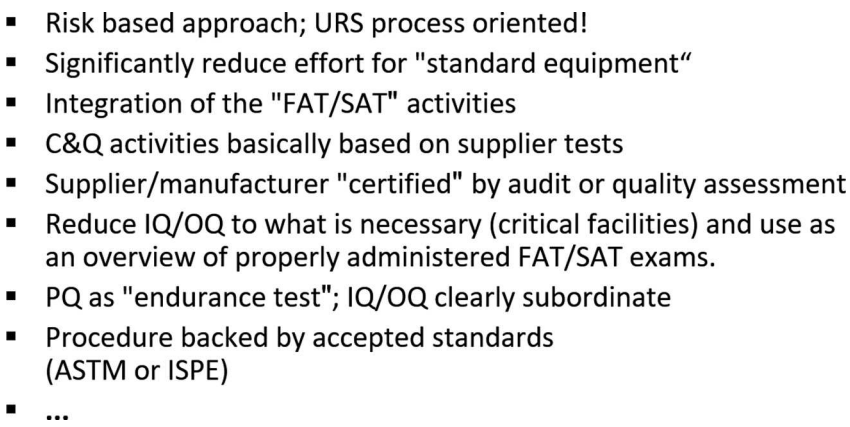
In 2007, ASTM launched a corresponding guide for pharmaceutical and biopharmaceutical plants. The document ASTM E 2500 [5] deals with the specification, design and verification (qualification) of equipment including control and automation systems. In addition to the already known topics of a risk and 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.

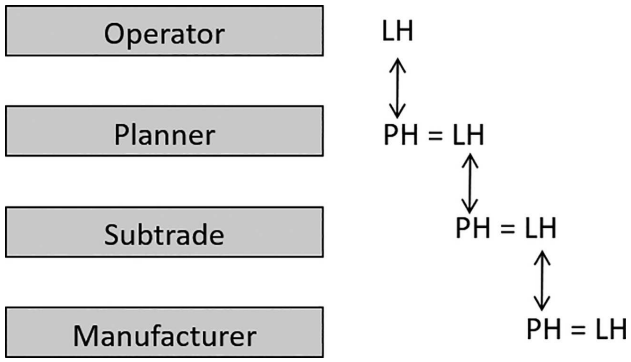
URS is also important in connection with technical change management. Even during an ongoing construction project, it is expected that significant changes – especially regarding GMP requirements – will be discussed, evaluated and documented. When a change exists, this is determined, among other things,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

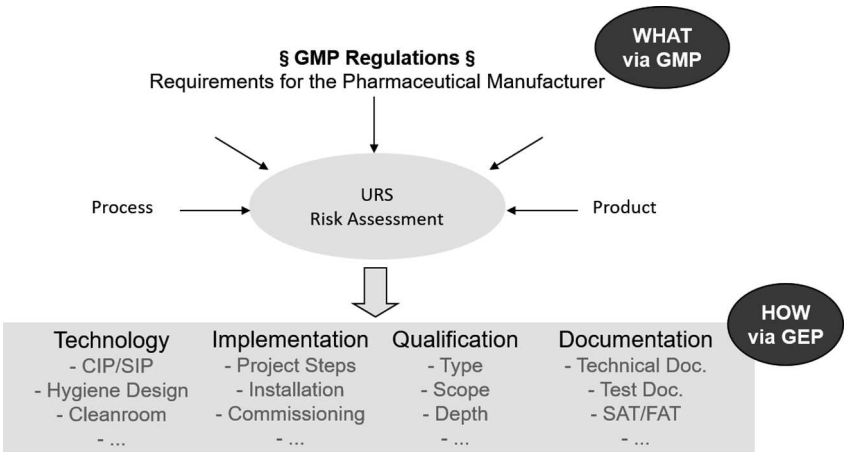
In order to be able to handle the qualification in a reasonable way and to really concentrate the measures on the quality-critical requirements, it is absolutely necessary to distinguish clearly and in a unique way between a "User Requirement Specification" (URS on the highest level) and a technical 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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Qualification 4.0 – Unused Opportunities

How an efficient, time-optimized qualification could work – Part 2[*)]

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■ Risk assessment – playing with numbers

Risk assessment was yesterday, risk management is today. The identification, analysis and evaluation of possible risks with regard to the process, the product and thus for the end user are on the agenda. Review of defined or still necessary measures to avoid or reduce the risks to an acceptable level; ensuring that the measures thus defined are also implemented as a core element of qualification; continuous review and adaptation of the risk assessments to what has been learned in the course of ongoing operation: these are fixed and important requirements in the context of GMP and risk management today.

Regarding the qualification process in particular, it is now clear that even at this stage one does not speak of one single risk assessment, but of a large number of individual risk assessments to be carried out. The entire logistical process, the individual technical systems, the manufacturing, and cleaning processes as well as sterilization and disinfection procedures must be considered. In addition to design criteria and other outputs, the scope and depth of qualification and validation activities can be derived from this (Fig. 5).

Basically, this is reasonable and comprehensible. Nevertheless, risk assessments are unfortunately not carried out in a target-oriented and pragmatic manner in the pharmaceutical environment today. The formalism, the Failure Mode and Effect Analysis (FMEA) with the related evaluation criteria and the fulfillment of regulatory expectations seems to be on first priority. Known technical systems are discussed again and again regarding the same criteria, the numerical FMEA values are determined according to gut feeling, so that the risk priority number finally delivers the result that is already known in advance. Often the User Requirement Specifications (URS) (and sometimes even the technical specifications) are used as a starting point, and the requirements are simply negated as a basis for the risk. "The refrigerator must be equipped with automatic defrosting" – risk: "The refrigerator is NOT equipped with automatic defrosting" – measure: "Check within the scope of IQ and OQ".

And again, it succeeded: A technical requirement that could have been verified by a simple receiving inspection or specification/functional test (Was the right refrigerator of the right type delivered?) has been pushed into formal, extensive qualification. Would it not have made more sense to talk about requirements resulting from the specific planned operation? To clarify which goods are stored in and retrieved from the refrigerator by which temperature condition and with which frequency? What influence this has on the temperature constancy and how critically possible temperature fluctuations for the stored goods are to be evaluated? Wouldn't it have made sense to derive the critical qualification test items from this alone?

Perhaps this will be done in this way in some individual cases. Unfortunately, however, practice shows that the formal and rigid, unreflective procedure described above in particular leads to a senseless and considerable increase in the effort of qualification. Not only the lack of standardization (recurring standard risks that have already been discussed frequently), but also the lack of concentration on operator-specific, and critical requirements makes qualification at this point costly.

Tip: It should be carefully considered whether an FMEA is really needed or whether a simple classification into "low", "medium" and "high" is sufficient. Often the result is the same in the end. Risks arising from the specifically planned operation should be considered. It should be reflected together with the specialists based on experience and the system manufacturer or supplier should be consulted if detailed technical knowledge is required.

■ Design qualification – technical understanding is needed

The topic of design qualification (DQ) was at a late stage introduced into the regulations, and here only

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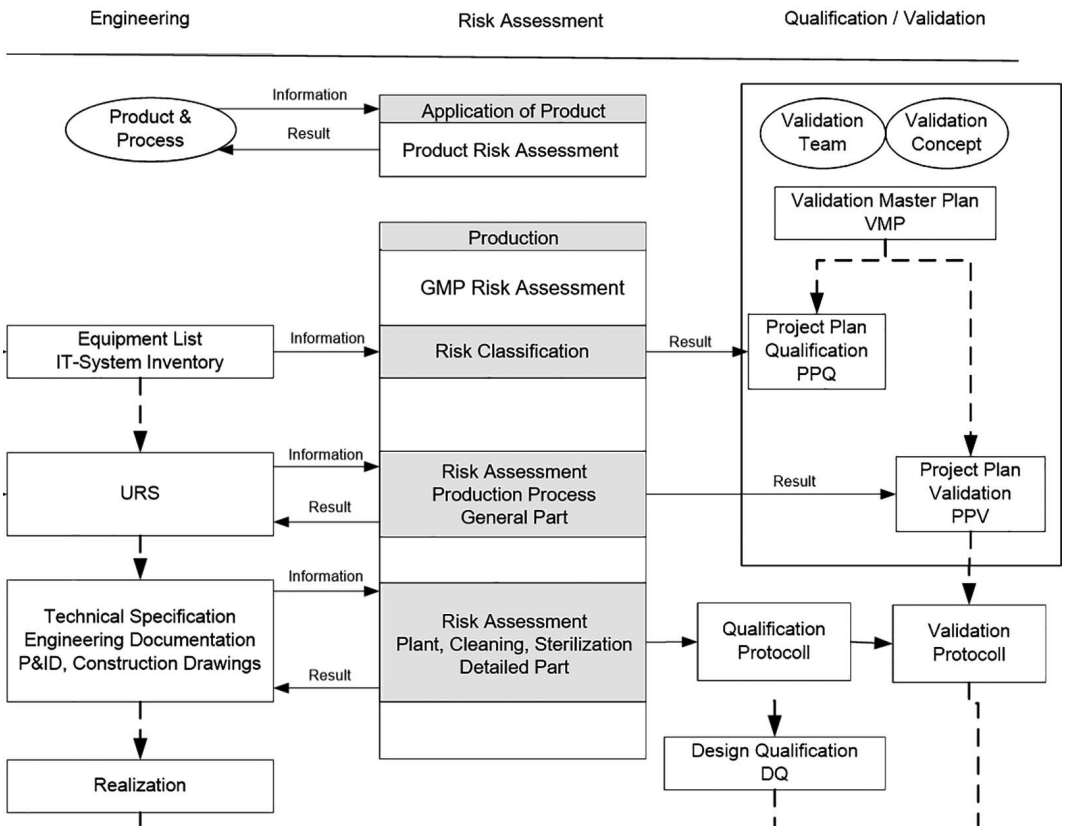
Figure 5



Risk assessment at different levels.

very rudimentary. The PIC/S document PI006 [6] as an example, states in Chapter 2:

"The premises, the supporting utilities, the equipment and the processes have been designed in accordance with the requirements of GMP. This normally constitutes Design Qualification or DQ".

In EU-GMP-Annex 15 you will find the note:

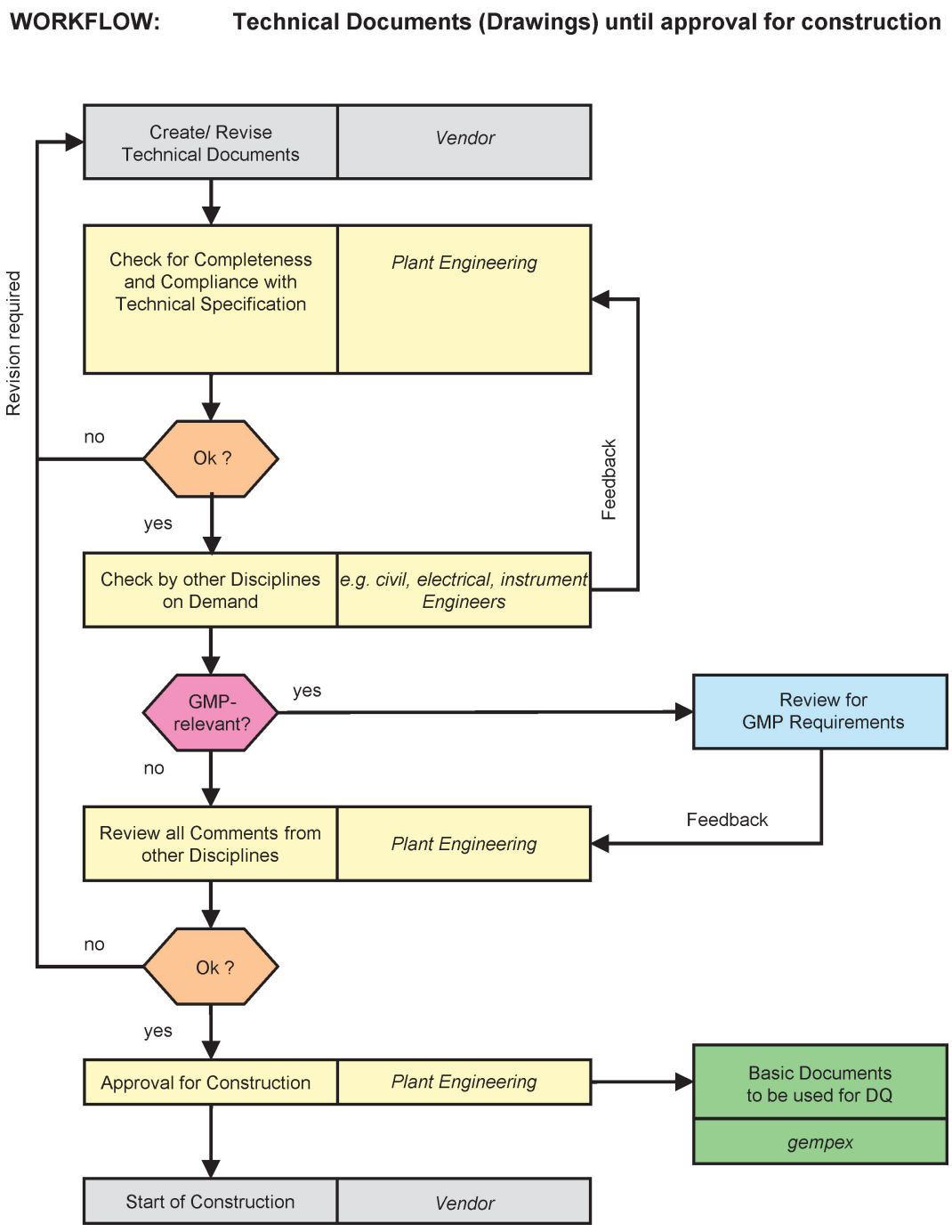
"The next element ... is DQ where the compliance of the design with GMP should be demonstrated and documented. The requirements of the user requirements specification should be verified during the design qualification".

There is no more information on how to carry out or even document the DQ activities. The picture that emerges with regard to implementation in industry is correspondingly very different.

Up to now, it has become almost commonly accepted that for DQ one compares the user requirement specifications (URS) with the functional and detailed design specifications (FDS, DDS) or at least tries to do so. In cases in which the supplier uses the URS at the same time as an answer document, and thus as FDS/DDS document, possibly supplemented by comments, the procedure is quite simple. In other cases, where the supplier prepares his own documents as part of the offer and order phase, it is already not so simple. The difficulty already begins with the question of what or which documents constitute the FDS and DDS respectively. Is it only the offer, is the accompanying correspondence also to be included or do the documents of the next planning stage also belong to it? While some people quickly complete the task of comparison by making a short-term statement, others go to the trouble of numbering the URS according to the specification items and making a detailed comparison based on this. Then there are cases in which the FDS/DDS documents are even written by the ordering party (the pharmaceutical manufacturer) itself – certainly a procedure that must be questioned with regard to independent comparison and review. In addition the question arises, how one deals with standard equipment (e.g., refrigerators, balances). Often brochures are retrieved for this, converted into an URS and at the end again compared with the brochure – as quasi-DQ – which makes only sense if one would like to test its own "transmission work". It remains to be seen whether one can define this as DQ.

The so far described URS – FDS/DDS comparison did not yet consid-

■ **Figure 6**



Example of a technical process with GMP review points (excerpt).

er the fact that the URS often represents only the highest level of the further to be developed documentation. The URS normally is followed by the elaboration of detailed plans and technical drawings, which are used for construction and installation later. Considering that DQ was introduced to ensure that GMP requirements – e.g., requirements for good cleanability – are sufficiently taken into account already in the design phase of a technical system, then it becomes obvious, that this can ultimately only be ensured in the detailed technical documentation and only if the involved and reviewing persons have sufficient technical expertise. Now one can plan to subject each technical document and each developing version

to a "GMP review", possibly still under integration of the Quality Unit. But anyone who has ever been involved in technical projects will know that the number of such documents can quickly increase immensely, and the task can become a mammoth task. It is therefore important to think carefully in advance about which technical documents should be checked at which stage. Certainly, the most important check is the one carried out before a drawing is released for construction. Prior to this, it is up to the company to decide how many previous versions will be subjected for review. Also there is little point in including the Quality Unit in the review itself if it does not explicitly bring a certain expertise. Rather, it should be the Quality Unit's task to ensure and then confirm in the DQ document that these review tasks have finally been performed. And proof of the review by the technical expert can be provided e.g., by means of a simple inspection stamp or inspection note – "Reviewed for compliance with the relevant GMP requirements" – on the respective drawing.

So, it is obvious that the effort in DQ can vary extremely with the chosen procedure: from almost none to an immense effort. Since a project usually involves several specialist disciplines (e.g., architecture, technical building equipment, automation, process equipment), it is inevitable that the procedure of when which documents in which version are ejected from the usual technical workflow for a GMP review must be discussed and defined very intensively with each of these specialist disciplines even before the project starts. For this purpose, it is recommended to work out corresponding flowcharts as shown by an example in Fig. 6.

Although in regulations and literature in connection with DQ, the comparison of URS and FDS/DDS is always given priority, it is actually the review of the technical execution documents that are of central importance and ultimately determine the quality of the technical system. Errors in the URS primarily have an effect in the commercial sector, but not necessarily in the quality of the technical system, if the error is then detected in the drawings. In such a case, the supplier will maybe insist on his FDS/DDS documents as a commercial "contractual basis" and link the corrections of defects to his additional budget requirements. For GMP and efficiency reasons, it therefore makes sense to concentrate on reviewing critical design documents and pragmatically documenting this with e.g., a stamp.

Tip: DQ should be focused on the review of critical technical drawings and design documents. In advance, the workflow should be discussed with the respective engineering disciplines and it should be determined when which document at which development stage will be ejected for review. Not every version of such a document should be considered. Usually, the first version to determine the direction, an intermediate version check and, of course, a check of the "release for construction" version would be sufficient.

■ Qualification versus technical testing – or if the FAT is misunderstood

Design qualification usually is followed by the installation qualification (IQ) and operational qualification (OQ). IQ as proof that a technical system is specified, designed and installed as planned. OQ as proof of correct functionality. It is certainly the elements of qualification that have the longest history, and which are now largely known and firmly established in all companies, including suppliers. The individual test items and the scope of testing also follow a widely comparable standard.

E.g., IQ covers the following typical checkpoints:

- Documentation (completeness and actuality)
  - Technical documentation
  - Operator documentation
- Specification (compliance with the requirements)
  - Component Identification
  - Certificates
- Installation (assembly and connection)
  - Location of installation
  - Installation of the individual components
  - Connection and environmental conditions
  - Overall condition

And OQ typically includes:

- Preliminary tests for commissioning such as
  - Leak tests
  - Testing of mechanically moved parts
  - Testing of switches, alarms, interlocks
- Automation tests like
  - Sequence controls
  - Functions of local controls and/or distributed control systems
- Operating parameter tests in connection with
  - Water runs
  - Routine parameter tests
  - Critical parameter tests challenging upper and lower limits

Regarding OQ, shifts in individual tests can be observed either from PQ to OQ or from OQ to the PQ phase, depending on the company's philosophy.

Now the qualification is defined as *"documented evidence to show that something is as it should be"* and not *"to test whether something is as it should be"* – there is a crucial difference. While in a test the result is still open (good or bad), in a qualification one expects in principle a positive (good) result. Formally correct, a technical system would therefore first have to be tested and, if the result is positive, then be qualified to confirm the result. And in the qualification – because it is known – the result can be predefined as an acceptance criterion.

If you look at the checktpoints listed above, you will see that these are actually nothing special and cor-

respond to at least 90 % of the already usual tests that are made in case of good engineering. A leak test e.g., is required with and without GMP. If it is once carefully executed and documented, one can assume a leak-tightened system and a repetition of the test (then in the context of the qualification) would not necessarily bring more quality. However, the emphasis is on "carefully" and "documented", i.e., on Good Engineering Practice (GEP).

This is the crux of the matter. Following the recommendations of the ASTM E-2500 standard and following common sense, it would actually be more than sufficient to focus on well-documented and carefully performed technical tests (GEP), and in the context of qualification, to simply check and confirm that those technical tests have been performed. A qualification plan based on such test documents would therefore be simple, pragmatic and target oriented.

However, the practice is far from this. The checkpoints listed above can still be found in their entirety in the qualification documents, even if reference is made in parts to technical test documents from FAT and SAT. Worse still, it has now become commonplace – partly driven by the pharmaceutical industry, partly proactively caused by the suppliers – that FAT and SAT documents are increasingly taking on the character of a qualification document. There are signature lines for the Production Manager and the Quality Unit, bloated, perfectly shaped checklists with acceptance criteria, deviation lists and much more. The effects in terms of effort, time and costs are devastating. The benefit is only marginal. While in the case of technical tests, if an error occurs, it ends up on a punch list and can be rectified and the test repeated without much formalism, in the case of qualification or the "qualification like" FATs and SATs, this draws huge loops and employs hosts of personnel. There the error is then a formal deviation with risk assessment, root cause analysis and many signatures.

The objection that FAT and SAT documents are also subject to certain requirements in GMP-regulated facilities is absolutely justified. E.g., it is not acceptable to look at what has been done in the FAT during the qualification process and then to align the qualification plan accordingly. Referencing to FAT and SAT is only possible and acceptable if the scope, depth, and documentation of the tests have been agreed upon in advance with the supplier and/or the engineering department. This can already be done within the scope of the order (as requirement in the URS or in the purchase order) or by preliminary review and approval of FAT and SAT documents, whereby this approval is, however, carried out by the Technical Specialist and not by the Quality Unit, at most in coordination with the latter.

Even if reference is made to technical test documents, of course, there are still points that can only and exclusively be proven within the scope of qualification. Typically, these are points from the late OQ or already from the PQ phase, e.g., if it is a matter of proving the performance of a technical system at the operating parameter limits or under real conditions (e.g., with product or simulated substances). These tests should have been identified beforehand by means of a risk assessment and should only be carried out by and under the responsibility of the future operator and with the involvement of the Quality Unit.

Tip: The risk assessment should be used to identify the really relevant points of the IQ and OQ phases that need to be proven during the qualification process. All other points, especially routine tests, should be moved to the technical area, FAT, SAT and commissioning activities. The scope, depth and documentation of the technical tests should be agreed with the respective technical units at an early stage. It should be ensured that the technical test documents are orderly but pragmatic. References to the technical tests should be made from the qualification documents. The Quality Unit should only be involved where it is really necessary (qualification documents).

■ How much formalism may it be?

Qualification is a systematic, planned, coordinated, controlled and thus formal process. This is precisely one of the strengths of this tool, which supports Quality Assurance. The systematic approach and formalism are necessary to exclude unacceptable risks as completely as possible. It is important – like e.g., in space technology – not to make any mistakes that could have fatal consequences in the end. The only thing that helps is to work through checklists that have been prepared by specialists and checked and approved several times. But how far can and should the formalism go? For sure, only as far as it still serves the cause.

The concepts originally presented, mainly from the USA, have always been characterized by their extreme checklist character. Everything that had to be tested – or more precisely proven – was banished to a checklist. A tank e.g., with all its connections and nozzles was reflected in a checklist, each individual nozzle was listed with its identification and dimension. The presence and the correct dimension were prompted. The creator of the checklist naturally used a design drawing or a P&ID as a source of information. The employee working through the checklist then checked the situation on site (and hopefully not on the previously used document) when he fulfilled his task responsibly. Initially, there was nothing to object to. But the question remains, does this really make sense? Isn't it more purposeful and ultimately more reliable to carry out such a check directly on the basis of the technical drawing, which anyway

must be correct and valid in the end? Isn't the error rate higher, the level of detail lower when transferring to a checklist?

Even though such checklists are still widely used, testing – based on original technical documents and performed by Subject Matter Experts (SMEs) – should clearly be preferred today. The fact that this also leads to enormous time and cost savings is just one positive side effect.

Another phenomenon after more than 30 years of development history in qualification is the fact that even today qualification documents are still being reinvented, redeveloped, and discussed again and again. That enormous energy is still being spent on how to design forms and checklists and how to set up and structure qualification plans. This does not only apply to small companies or newcomers. Even within large companies there is sometimes no agreement and different concepts, forms, and checklists are used in different areas of the company. It's like in art, everyone has his own view and perspective and wants to enforce them. Whether it is helpful in the end is highly doubtful.

When it comes to signatures, the discussions become even more intensive. The argument *"I would like to have Department X or Y on board, they should also take responsibility."* or the claim *"Without my signature nothing is allowed to go on!"* often leads to overcrowded signature pages and thus to circulation times that can hardly be justified. Quite apart from the fact that, in the worst case, the actual responsibility is even not clear.

In an age in which almost everything is standardized, normed and stored in databases, it is strange that such a simple task – uniform and simply structured qualification forms – seems to be unsolvable. The hope remains that a solution will be found in the age of Industry 4.0.

Tip: The focus should be on the contents of the qualification and not on the forms: What should be proven, how should it be proven, who should do it and what are the acceptance criteria? The documents should be designed as simple as possible – less is more. The minimum number of signatures should be insisted upon. The persons responsible are clearly regulated according to GMP. Unnecessary checklists should be avoided, and as much as possible original technical documents should be used as inspection basis. A first sample document should be read by an inexperienced person: If this person understands the basic principles, the document is good.

Qualification 4.0 – what the future holds

To use the title *"Qualification 4.0"* was already daring. Putting the topic in the context of Industry 4.0 and describing future visions is much more daring.

The fact that the pharmaceutical industry is conservative is well known and is certainly also due to the fact that changes of any kind are only reluctantly seen, since they immediately affect the approval of products and thus the market success. In view of the fact that qualification today is a not inconsiderable cost factor, a time guzzler and a project brake, one would actually have to expect that there will be significant developments towards optimization and increased efficiency. But far from it. People still act as they did at the beginning, developing forms, checklists and qualification concepts again and again. You still have your problems in processing, you struggle with innumerable deviations, not at least because technical tests are pushed into qualification, because essential information is missing, because it has not been identified exactly what is really critical, and last but not least, because the focus is more on satisfying the interests of authorities than on actual process safety. This may sound provocative, but it is what is still frequently found in practice.

Industry 4.0, the *"Internet of Things"*, networking and the provision of data of all kinds: this is the topic that is currently trending in industry, the topic that shows new ways to efficiency and process optimization. To get to this point with the qualification, a lot of preparatory work is certainly still necessary. For example:

- The basic concepts of qualification – what is and what is not permitted by the regulatory authorities – would have to be described more closely and concretely in the relevant regulations, and the technical aspect would have to be given more consideration. Degrees of freedom are helpful, but if they are too great, the opposite is achieved. And industrial standards do not necessarily provide more security here.
- Standardization would have to be driven forward for the recurring, typically used equipment. The basic operations are well known in both the pharmaceutical and active ingredient industries, as are the machines and apparatus required for them. There is no need to reinvent the wheel again and again.
- Data and information on qualification tests derived from norms and standards (e.g. cleanroom tests according to ISO 14644) should already be easily accessible from the Internet today.
- Vice versa, the information, results and experience gathered during qualification would have to be stored in the cloud. This should be unproblematic since the vast majority of this data does not represent critical know-how.

If we pursue the idea of Industry 4.0 further, it would of course be a dream to be able to obtain all the information and data relating to the qualification of a specific device, machine or apparatus from the Internet on day X by means of barcode matching. Whether these are the technical specifications, detailed

drawings, certificates, FAT results or even test specifications for basic IQ and OQ tests, it would in any case be a gigantic step forward that would make a significant difference in time and cost savings. Some of this information is already available (e.g., manuals, specifications), but unfortunately only partly and not specifically for a certain machine with an individual serial number.

Conclusion

The qualification currently looks back on a history of more than 30 years. Starting from simple, technically oriented checklists, the basic elements DQ, IQ, OQ and PQ have been developed. The methodology of a risk-based approach has been introduced in order to focus the qualification more on the goal of patient safety and not just to produce paper. Life cycle models were designed to ensure that Quality Assurance is maintained over the service life of the technical system. The link to engineering has been established by including elements such as user requirement specifications (URS) and FAT in the guidelines. Constructive criticism was expressed by competent parties on the formalism and paperwork and resulted in technical standards and recommendations that are increasingly based on Good Engineering Practices (GEP).

Nevertheless, the formalism has remained, the mountains of paper, the effort, the not always meaningful and goal-oriented approach. What remains is that qualification is a cost and time factor that is not always in reasonable proportion to the result. What has remained is that the link between GEP and GMP is only sporadically successful, and the advantage of good engineering is still not realized. In this context, the term Qualification 4.0 must certainly be deleted from the vocabulary until further notice.

However, for all those who want to increase the efficiency and meaningfulness of the qualification, regardless of modern aspects and cloud philosophies, some suggestions and tips were given. These should be emphasized once again:

- To get away from formalism, to reduce it to a minimum – less is more.
- Ensure good engineering with associated good documentation and make maximum use of it.
- Clearly distinguish between what is technical testing and what is worth being covered in the qualification. In particular, a URS should be a user-oriented document and not a technical specification.
- Performing risk assessment with common sense and focused on specific concerns.
- To involve the Quality Unit only where critical GMP aspects are really at stake.

Finally, the recommendation remains to stick to the equally 30-year-old principle: GMP = Common Sense

LITERATURE

[1] FDA, Guideline on General Principles of Process Validation, May 1987.
[2] A White Paper on Risk-Based Qualification for the 21st Century, ISPE, Mar 2005.
[3] Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment, ASTM 2500-07, revised 2013.
[4] GAMP – Good Automated Manufacturing Practice, A Risk Based Approach to Compliant GxP Computerized Systems, GAMP 5.0, ISPE, 2008.
[5] Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment, ASTM E 2500, Aug 2007, revised version 2013.
[6] PI006-3, Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation, PIC/S, Sept 2007.

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