# Basic Principles of an Effective and Efficient Qualification*)

Suggestions for practice – Part 1: Basic principles

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*This contribution is part of a 4-part series of articles. Part 1 deals with basic principles, Part 2 with planning, Part 3 with implementation, and Part 4 is about comparison with the regulations.*

**The article "Qualification 4.0 – Unused Potential" [1, 2] reported that organizations remain stuck on the topic of qualification – which means documented proof of the reliability of technical systems that is required in the pharmaceutical industry. Also that this quite costly, labor-intensive, and time-consuming quality assessment often fails to have the desired effect, and frequently prevents the timely completion of new construction projects. Reasons and initial possibilities for improvements have already been addressed. In the following article, the problems are explored in more detail and concrete proposals are offered for possible solutions regarding especially critical topics. Basic principles that promise a success if they are followed are discussed. This includes proceeding with common sense just as much as focusing on the contents – as opposed to concentrating on forms. Special emphasis must be placed on establishing user requirements and on risk assessments. Both topics are crucial to success or failure early on in a project. The goal-oriented structuring, design, and handling of qualification documents as well as the intelligent integration of documentation from equipment suppliers doing preliminary work are addressed as well. As always, the suggestions still leave room for optimization.**

## What Really Matters

Before detailed suggestions for implementation with examples are discussed, this first part of a planned 4-part series of articles is intended to create a basic understanding of the topic of qualification and the general procedure. This is even more important because today the experts are increasingly losing themselves in discussions about terminology instead of concentrating on the necessary contents and goals. It sometimes seems to be more important to argue about abbreviations like URS (User Requirements Specification), FAT (Factory Acceptance Test), SAT (Site Acceptance Test) and their assignment to GMP and qualification than to think about what should be described in these "content containers" and for what purpose. In the following chapters and articles, we will try to explain the main activities and specific re-

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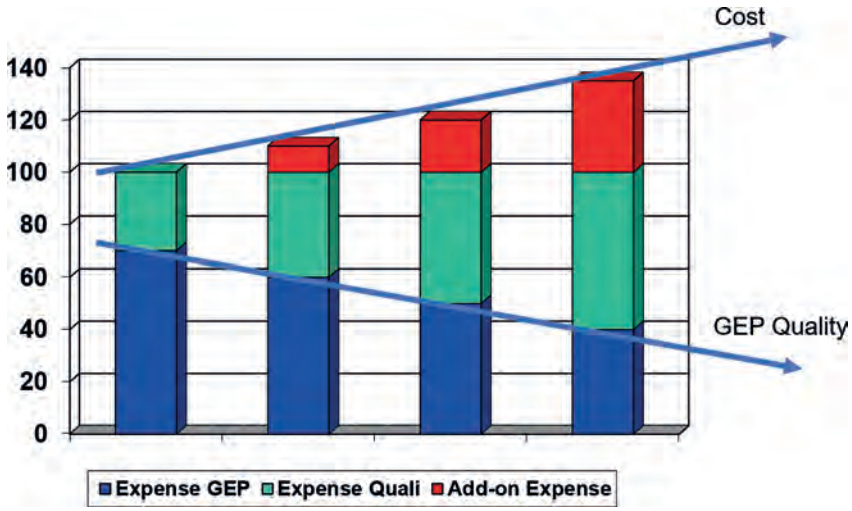
started his professional career in 1987 at BASF AG, Ludwigshafen, after his university study as a chemical engineer at the Technical University (TU) Karlsruhe. For around 10 years he acted as an internal Good Manufacturing Practice (GMP) consultant. Besides establishing an efficient and cost-oriented qualification system, he also was active in numerous technical committees and associations on this topic, among others for the German Institute for Standardization (DIN), the German Chemical Industry Association (VCI), and the Society for Chemical Engineering and Biotechnology (DECHEMA). He was early involved in the preparation and commentary of the "Pharmaceutical Inspection Co-operation Scheme" (PIC/S) document PI006 (validation) and the Q7-GMP guideline of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). After another professional interlude, he founded 2002 the gempex GmbH, an international GMP service providing company, which he still is managing today. In addition to numerous publications, lectures, and talks, he has summarized his accumulated knowledge among others in the book "GMP, Qualification, and Validation of Active Pharmaceutical Ingredient Facilities" published by Wiley-VCH.

■ **Figure 1**




*Influence of GEP on costs (source of fig. 1–2: the author).*

cords related to qualification. Which activity is required, why, and what must be recorded and documented? A deliberate attempt is made to use as few terms as possible that are common in this field to avoid the discussions described above. The focus should be on the activity, the reason (why), and the "how-to-do" (how). Only at the end, in Part 4 of the series of articles, the activities are then compared with the "usual" terms. First, however, the focus is on the basic understanding of the topic of qualification.

## Qualification or Testing

Qualification as a sub-item of validation is a documented evidence firmly anchored in the Good Manufacturing Practice (GMP) regulations, which is intended to support pharmaceutical quality assurance and ensure that technical systems, including premises and utilities, function reliably and as required and provide the planned performance. The emphasis here is on "documented evidence", as this is by definition an activity that is intended to demonstrate the reliability of a technical system after successful installation or successful commissioning. Although various checks or tests are carried out or reference is made to them, these activities are not "testing" in the usual sense.

A look at the relevant definitions and their exact wording may clarify this. For example, the EU GMP guideline in its Annex 15 [3] begins the definitions for the qualification of the phases Installation Qualification (IQ) and Operational Qualification (OQ) with: "The documented verification that the facilities, systems, and equipment, as installed or modified [...]." In the corresponding EU-Glossar [4], the definition for qualification is: "Action of proving that any equipment works correctly and actually leads to the expected result [...]." Also in the Guidelines on Qualification of the World Health Organization (WHO) [5], the definitions OQ and Performance Qualification (PQ) are preceded by "Documented verification [...]" and only in the case of IQ is the term "performance of tests to ensure" used, whereby the word "ensure" refers to the verification activity. None of the definitions, therefore, speaks of checking whether something is ok or not, as usual. Rather it shall be proved, that something is ok.

The understanding of this difference is essential since a mixture of the activities – one of the most frequent problems at present – drives the expenditure for the qualification extremely up without a recognizable increase in value (see following chapter). Testing in the usual sense is carried out after a construction or installation process. The activity takes place for the examination of the actual condition, i.e., for the identification of possible still existing defects. If such defects occur, they must be eliminated, and the testing process must be repeated. The qualification (the proof) is carried out after the defect removal – after a completed successful test procedure. Qualification is basically based on the assumption of a faultless technical system, but this must be demonstrated. This additional activity, the qualification, is the "add-on" of pharmaceutical quality assurance. It is designed to produce quality in all elements of pharmaceutical production and not to determine it in the final product by means of analysis.

## The Importance of Good Engineering Practice (GEP)

If the qualification simply is "evidence", then it is self-evident that this requires a high-quality technical product if the qualification is to be carried out quickly and successfully. If this is not the fact, and the technical system shows several errors, then the qualification process will not only be bumpy but also expensive and lengthy successful

This relation is illustrated by fig. 1. Defects that are not discovered as part of normal engineering or that are not even tested for in the first place cannot easily be eliminated and closed with a new test once you get to the qualification phase. Within the qualification phase, every defect becomes a deviation and must be extensively documented, discussed, evaluated, and followed up with appropriate measures. In addition to engineering,

the pharmaceutical manufacturer with its quality unit now also comes into play. There is no need to point out that this means that simple technical defects get into a treadmill of the formalism required in the qualification process with circulations, reviews, signatures, etc. The more activities are shifted from the GEP area to the GMP area, the greater the additional expenditure (see red bars in fig. 1).

But what characterizes GEP, especially in connection with projects in the pharmaceutical or GMP environment? The following list of requirements does not claim to be complete, but contains topics that have proven to be essential in practice:

- Processes should be defined according to fixed specifications (e.g., in an engineering manual) and follow the usual phases such as Conceptual Design (CD), Basic Design (BD), and Detailed Design (DD).
- The technical documents to be created in each phase should be defined and provided with samples. Usual technical documents such as Piping and Instrumentation Diagrams (P&IDs) should be based as far as possible on existing standards, in which the scope and content of such documents is described (e.g., ISO 10628, flow diagrams for process plants). Documents should then also be produced in this quality.
- Engineering companies active in the GMP environment must be able to create a project schedule that integrates GMP-relevant activities (e.g., execution of GMP risk assessments, qualification activities) in addition to the usual engineering activities. The company must be as familiar with these activities as is expected e.g., in connection with safety requirements.
- There must be a change and deviation management for the technical area, which clearly traces changes and deviations as well as associated corrective measures. This is not necessarily a multi-page and time-consuming form with countless signatures. The documentation can also be done pragmatically and directly in technical documents (drawings) but in a clearly regulated and consistently implemented manner.
- The established test procedures and their documentation are of enormous importance. GEP is characterized by clearly defined breakpoints (gates) outlined in project schedules, at which defined construction and completion tests are carried out and documented in a meaningful/traceable way. In the GMP environment, it is essential that test specifications exist for the planned engineering tests, which define the scope and procedure in detail. The completed documents must be checked by at least one expert. The involvement of the pharmaceutical manufacturer's quality unit is a case-by-case decision. Technical test documents that do not meet these requirements are worthless for a GMP project.
- Another important feature is communication and the underlying documentation. Since construction projects in the pharmaceutical environment are often very complex, extensive, and extremely dynamic, important information and agreements are quickly lost in the hectic pace of everyday life. It is therefore important that a system exists within the framework of GEP, how agreements or meeting results are documented, and open points are followed up (pending lists). Depending on the size of the project, professional companies work here with so-called "Project and Quality Plans", documents in which communication, documentation, numbering systems, and much more are regulated in detail for a specific project.

Besides these points there would be surely still substantially more aspects, like e.g., the construction materials management, the construction site management, dealing with subcontractors, good documentation practices, and others that could be addressed but would go beyond the scope of this article.

It should not be left unmentioned that all the comments on GEP must take into account different areas and levels of application in engineering, which must be considered in the scope and depth of the established quality systems.

For example, engineering, which is active in the area of active ingredients (typically chemical plants), is set up and structured completely differently compared to engineering, which deals with plants for pharmaceutical finished product production. While in the first case the plants are composed of many individual components and there are specialized engineers for different areas (machines and apparatus, pipelines and fittings, pumps, automation, electrical, measurement and control technology) and correspondingly established processes, in the second case it is essentially the architects, cleanroom builders, engineers for technical building equipment and mechanical engineers who act rather independently of each other and therefore often lack the necessary structured overall and interface coordination.

Regardless of the field or scope of a technical project, it is an irrefutable fact that GEP is a basic requirement for successful qualification. It is a fact that errors or quality defects in the field of GEP can only be corrected in the field of qualification at great expense or not at all. Unfortunately, it is also an irrefutable fact that due to the enormous time pressure in such projects today, postponing GEP deficiencies to the qualification stage is not the exception but the rule – and not a single project pushed in this way has really met the time and cost line in the end.

## Efficient Qualification Requires Efficient Documents

Qualification documents are evidence documents and not only serve the pharmaceutical manufacturer as quality documents but are also used in audits and inspections. Correspondingly high demands are placed on Good Documentation Practice, including requirements for traceability and signatures by persons involved in the process.

However, good documentation practice does not necessarily mean complicated and costly documents. Nevertheless, especially in the area of qualification, documents are becoming visibly bloated, formalistic, complex, and increasingly difficult to understand. The involvement of various disciplines (engineering, production, IT, quality, etc.) as well as the results of audits and inspections, which lead to quick, often ill-considered adjustments, contribute to this situation significantly. However, the more complicated such documents become, the more confusing the associated processes become, and the error rate increases.

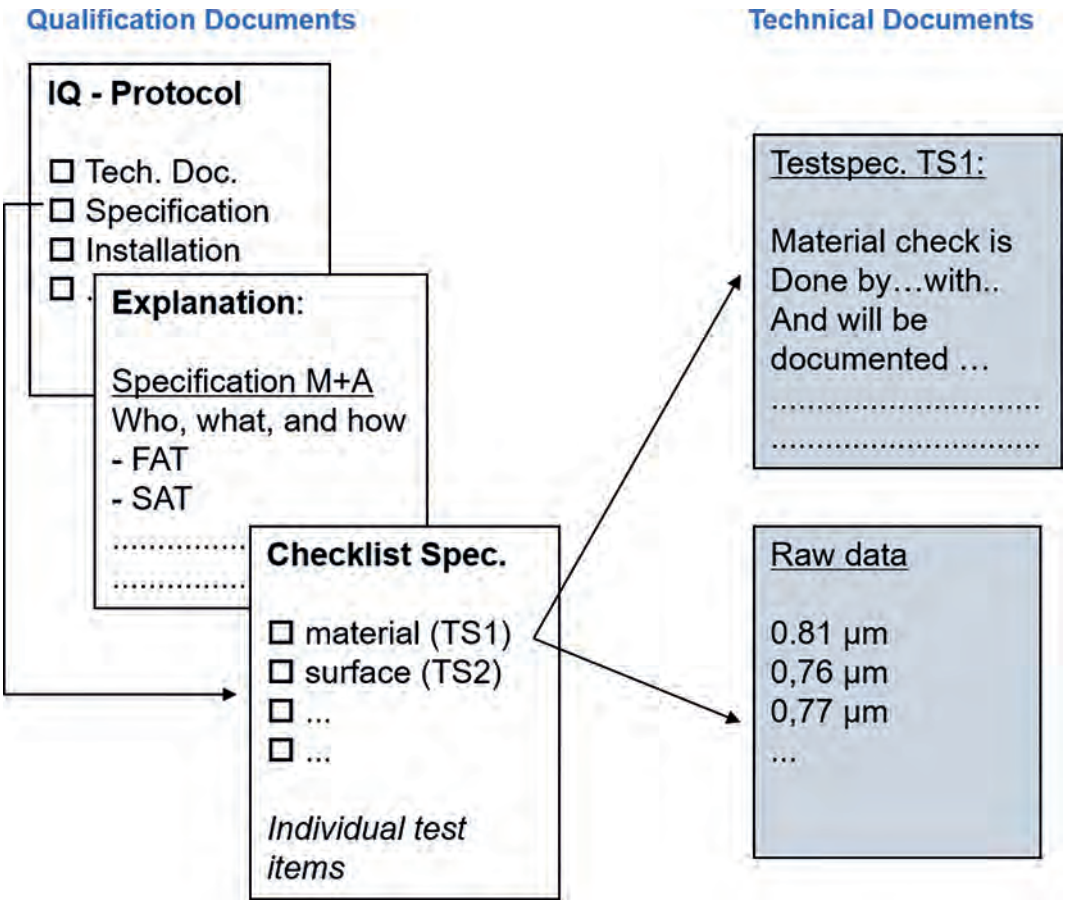
When creating a qualification concept and the associated documents, the following basic rules should therefore be considered:

- First you should start from the content and ask yourself what information it needs and for whom I have to compile this information and for whom this information needs to be compiled. Only in a second step, you should decide in which container (document) you put this information. If it is necessary to describe the procedure for qualification with the individual steps, it would be possible to do this either in a superordinate master document or in individual standard operating procedures. Considering that the qualification of process plants and laboratory equipment is carried out by different persons, it is advantageous to choose the standard operating procedure and divide the topic accordingly so that each party only has to read what they are interested in. The usage essentially determines the document structure.
- Duplication of content should be avoided as far as possible. This is not only to keep the size of the documents small but also to facilitate the maintenance of the documents. Updates then only need to be carried out at a single location. A typical example is the descriptions of technical systems, which are often repeated in different qualification documents at different levels. A change in the description results in the modification of several documents. An individual, single system description, which is then only referenced, is certainly a much better solution here.
- Descriptions in the documents should be short, concise, and specific. Attributes that one would expect to find in a technical environment, but which are not necessarily present during qualification. It is not uncommon to encounter lengthy, textbook-like descriptions, especially when it comes to concept and process descriptions, often simply a copy from the literature or rules and regulations. Instead of "The employee from department XY creates the plan with at least the following test points", one finds the explanation "The qualification is the documented evidence that [...] It usually includes the test for [...]." If a sentence does not describe *who*, *what*, *when*, and *how* something is performed, and *how* and *where it is* documented, then it is not necessarily useful and does not support efficient documentation. Ok – sometimes it can be necessary and helpful to give a short background explanation to the employees in order to also increase the acceptance of the measures. However, this should be well-considered and reduced to what is necessary.
- According to GMP, it is explicitly allowed to reference within certain documents to other documents in order to avoid duplication of information and to make smart documents and maintenance easier. However, there are also limits. For example, despite all the love of smart documents, you should make sure that the amount of references is such that the document can be read as a whole without having to provide entire libraries of other documents.



- Transparency is a delicate issue and not always easy to comply with. This is especially true for documents that are thematically related. For example, if you have a test plan, in which all essential test items are listed for an overview, it is essential that you can easily and quickly assign test items to test descriptions in the more detailed documents in which these tests are described in detail. This is possible if the test description contains the same titles and the same sequence of test

■ Figure 2




***Basic structure of qualification documents.***

items as in the corresponding test plan.

- Signatures are a key to quality assurance in the GMP environment. People take responsibility. Roles and responsibilities are clearly assigned. But it does not always work in this sense. Signatures are often included in the qualification process in order to get the other department "on board" without really defining the scope of responsibility. It escalates into signature campaigns that are time and resource-consuming. In the worst case, it can lead to renewed discussions and document revisions if people – who were not even involved in decisive clarifications of the content – are forced to sign documents. It is therefore essential to think carefully about who is really responsible in the end, who was involved in document creation and who should therefore sign sensibly. If you then also make sure that it is clear what a person is signing for, then GMP requirements are met. With the latter point, it is not uncommon for a person to sign as a "reviewer" but it is not clear what exactly he or she should have checked ( form, content, plausibility, technical issues). It is advisable to describe this clearly below the signature fields so that those responsible are aware of their responsibilities when signing.

A final recommendation – in addition to the above list – is given with regard to the connection between qualification and GEP test documents. Figure 2 symbolically shows the minimum basic requirements. It is usual to provide an overview of planned evidence tests, followed by the test descriptions. Under certain circumstances, this may result in more detailed overview (test) lists. Once the quality (scope, content, and depth) of the technical test documents has been agreed upon within the framework of GEP, the qualification documents can be easily and clearly referenced to the same. In any case, one should make sure to keep the interaction between qualification documents and technical test documents as simple and transparent as possible.

## Risk Assessment and Risk Management

Two keywords influence the process of qualification today – "risk-based" and "life cycle". It is expected that the pharmaceutical manufacturer knows what he is doing and why he

is doing something, that he knows his process exactly, has it under control, identifies possible risks at an early stage, and eliminates them with appropriate measures or at least reduces them to an acceptable level. One such measure is qualification. Accordingly, the scope and depth of qualification today is no longer free to decide but should be defined through appropriate risk assessments. This is also found to a large extent in today's implementation by the firms, but unfortunately often too complicated and not always target-oriented. Even if different methods are described in the ICH-Q9-Guide "Quality Risk Management" [6], the Failure-Mode-and-Effects-Analysis (FMEA) method with its number-based evaluation system has become widely used and accepted.

There is nothing fundamentally wrong with this if it were not for the fact that the people entrusted with the risk assessment are often only focused on the corresponding Excel sheet, on those risks, which are entered in advance, and on the discussions about the numerical evaluation. The view of the essential part of a risk assessment is lost. Risks are often discussed at levels that are neither system-specific nor helpful (e.g., risk: "The construction materials are not suitable").

In principle, it should be noted that in the course of a technical project (new construction, re-construction, expansion or modification) there are certainly a large number of risk assessments to be executed at different times in different forms and with different objectives. At least the following should be considered here:

## ■ 1. Process risk assessment for manufacturing (synthesis and logistics)

On the one hand, the manufacturing process is considered here, i.e., the chemical-physical processes in the production of a pharmaceutical product. The focus is on critical quality attributes (CQAs), e.g., a certain impurity, and on critical process parameters (CPPs), e.g., temperature, and pressure. FMEA can be a suitable method here. All conceivable process parameters at all process stages and possible deviations from setpoint values are discussed.

On the other hand, the logistical process is also to discuss, starting with the receipt, sampling, release, and storage of raw materials and supplies, through their further logistical path to processing to packaging, labeling, and shipping of the finished product. The overall material and personnel flow is considered. Here too, the discussion could be "forced" into an FMEA type risk assessment, but this is not very helpful. Better is the discussion based on material and personnel flow plans, documented in floor plans. A simple record of discussion results in meeting minutes and action lists would already serve the purpose here.

The process risk assessment requires at least a draft document describing the entire project, the product, the process, and the associated GMP requirements as well as initial planning drafts. The risk assessment is used to put the planned protection concept (protection of the quality of the final product) to the test and to improve it if necessary. Performing the risk assessment and adapting the requirements specification (the concept) is therefore interrelated in several runs.

## ■ 2. System risk assessment (process equipment and auxiliary facilities)

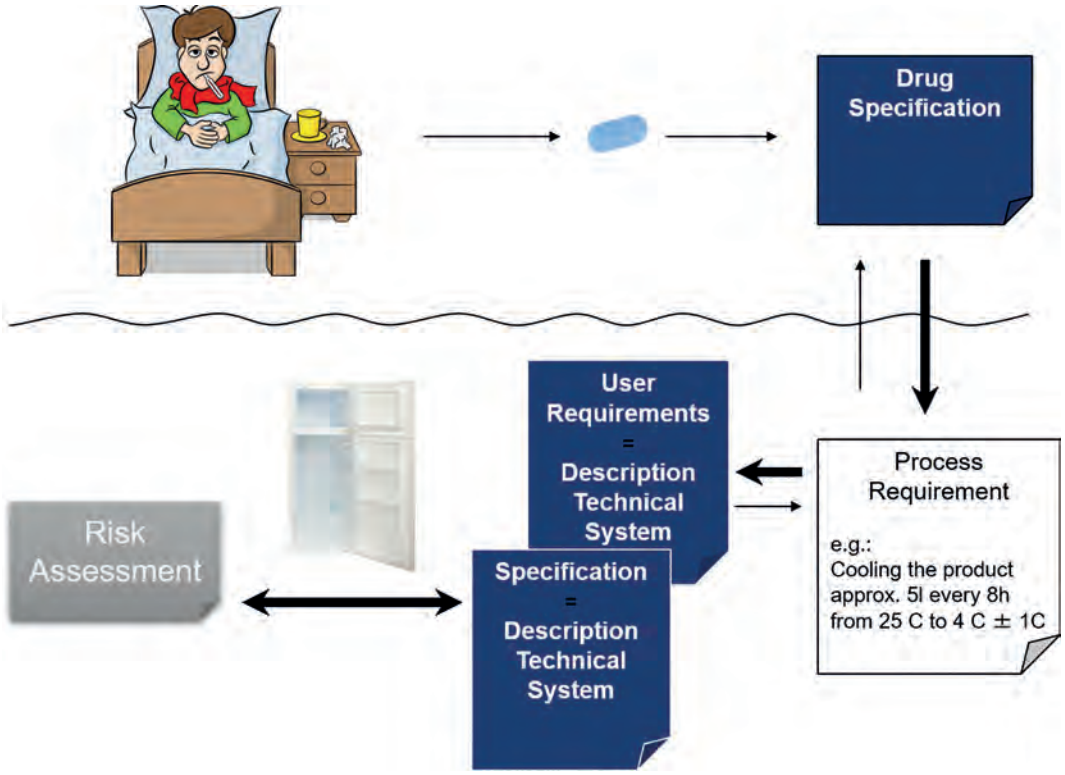
With the concretization of the process requirements and conditions, the hardware required for this is usually also concretized, i.e., the necessary rooms, process equipment, and necessary auxiliary facilities (water, steam, gases, etc.). Risk assessments are also required here and can be carried out by means of FMEA. However, one should consider carefully whether such a risk assessment is required for all systems. For example, an analytical balance as standard equipment has certainly passed through many test instances and topics such as correct and trouble-free installation and initial calibration are actually a matter of course. To ensure this again by an FMEA is certainly more than questionable.

It is probably self-explanatory that the need for risk assessments increases with the degree to which the technical system is individually designed (i.e. no standard equipment). However, this again only makes sense if this technical risk assessment is specific to the equipment and the intended use. Instead of asking what happens when a refrigerator's power fails, it would be more important to question whether the device can provide the necessary cooling capacity for the intended use (e.g., considering the frequency of door openings, the temperature of the contents during storage) in order to quickly set required temperatures and keep them within predefined limits. Since the special knowledge of the equipment manufacturer and/or supplier is often needed here, a procedure makes sense, with which a first rough draft of the risk assessment is provided by the later user and this is then discussed in a second round with the specialist, i.e., the equipment supplier or manufacturer.

## ■ 3. Process Risk Assessments for supporting Processes

Once the equipment has been discussed and finally selected, a further step can be taken to begin risk assessments on topics such as equipment cleaning, disinfection, sterilization, etc. An FMEA is certainly conceivable, but with certain limitations, since in these processes, the fundamental deviations (incomplete cleaning, insufficient sterilization), as well as the associated effects, are always the same for all individual points discussed. The focus here

■ **Figure 3**




***Risk analysis traced back to the patient (source of the illustration: the author; source of the image elements: AntiMartina_iStockphoto.com, AndrzejTokarski_ stock.adobe.com and agcreativelab_stock. adobe.com).***

should be on what can lead to a deviation and how likely this is. However, these risk considerations presuppose that the associated processes are available at least in written draft form.

The three above-listed areas for risk assessments are certainly logical and widely known. In addition, however, there are other risk considerations that are not always immediately recognized as such and are therefore often not sufficiently documented. E.g., it is the preselection, of which technical systems fall at all under GMP and which not (e.g., GMP starting point in active substance manufacturing processes, exclusion of wastewater and exhaust air treatment), as well as the typical review of technical documents with a focus on GMP aspects (Design Reviews) which fall into the category of a risk assessment and therefore must be comprehensively documented.

A critical aspect when conducting a technical risk assessment is certainly the question of how far back the focus should go back to the risk for the patient, for example, as often indicated in GMP regulations?

Figure 3 illustrates how this recourse to the patient actually takes place and what a technical risk assessment should focus on. For example, for the direct application of a drug on a patient, a product risk assessment is carried out in early phases, the product is tested extensively, and the product specification is derived from this.

This in turn is the basis for the development of a suitable process with the corresponding critical attributes (e.g., homogeneous distribution of active ingredients) and finally also the process parameters (e.g., pressing force during tableting). This means that, if the critical process parameters are adhered to, critical process or quality attributes are also adhered to and, ultimately, the product specification is met. The technical risk assessment must therefore focus exclusively on compliance with the given system-specific specifications and critical aspects derived from the product and process. Thus, possible risks for deviation from the technical specifications are discussed rather than the direct impact on the patient. This recourse results from the causal chain described above.

One last note is dedicated to the term “risk management”, which, following the modern age, is used nowadays on almost every occasion, including technical risk assessment. It is to be understood that risk management is a superior process to be established at the pharmaceutical manufacturer and technical risk assessments are a part of it. Technical risk assessment alone does not constitute risk management. Rather, the technical risk assessment, which is

created for the first time within the scope of a newly installed facility, must be maintained in the pharmaceutical company after the end of the project and, if necessary, supplemented with newly identified risks as experience increases.

## Summary – Key Elements for Efficiency

Efficiency results from the mere fact that one does not lose sight of the actual goal – i.e., to prove that technical equipment is properly designed, installed, and functioning. All documents generated are merely aids and containers for information that support this proof. Accordingly, one should concentrate on doing only what is necessary for this purpose and create documents for support and not as an end in itself. The previously made statements can be summarized as follows:

1. Qualification is a documented evidence of a desired condition and not a check whether the condition has been reached or not. This basic understanding is essential for an efficient qualification since technical tests are not repeated but referenced to the same. Under no circumstances should any technical tests be postponed to qualification since technical errors are thus stylized as GMP deviations. It would be ideal if there were a formal release for qualification, which would be issued when the engineers have completed the technical tests positively and corrected technical defects.
2. GEP is the basic prerequisite for a successful, but also efficient qualification. Poor engineering leads to a costly or even impossible qualification process. The result is illustrated in fig. 1. GEP can significantly support the qualification process and make it efficient if the technical processes are well organized and documented, if there are functioning technical change and deviation management systems and if the technical design and test documents are of a quality that allows them to be easily referenced from the qualification documents.
3. Qualification documents themselves must be designed in a simple, easily understandable, transparent way and, if possible, without multiple repetitions. The simpler the system and the documents, the less error-prone and the faster the processing of the associated activities. Not to forget that a simple, clear, and comprehensible document system scores correspondingly high in audits and inspections.
4. Risk assessments – the central tool, not only to identify critical aspects for qualification but also to exclude non-critical aspects from qualification – must be carried out at the right time with the right tool. You should think very carefully about what you are discussing and have the courage to move away from the generalities and towards the specific system characteristics. FMEA is also not always the tool of choice and especially starting with an Excel sheet is not recommended. A brainstorming, a general consideration in a team with specialists and a collection of comments are often the best start for a valuable result of a risk assessment.

Certainly, there is a whole range of other topics and aspects that could be listed and discussed with regard to efficient qualification. However, the statements made in this article concentrate on the main critical points and on the basic understanding that is absolutely necessary to understand the topic of qualification comprehensively and to tackle it efficiently. In Part 2 of the series of articles, the topic "Conception and Planning" of qualification will be dealt with and solutions will be shown, starting from this basis.

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