Basic Principles of an Effective and Efficient Qualification*)

Suggestions for practice – Part 4: It becomes formal – comparison with the regulations

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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.

There is certainly agreement that after more than 30 years, the topic of qualification requires a fundamental renewal, or at least a significant increase in efficiency. This has been recognized by both the authorities and the industry and has been responded to over the last few years with appropriate publications and recommendations. Parts 1 to 3 of this series of articles, which are published here, also refer to this and are also based on the author's experience with suggestions as to what could be done better, simpler and more efficient. However, these suggestions are neither new, nor special, nor explicitly invented by the author. They are suggestions that are discussed repeatedly at public events, in corresponding committees and in specialist articles, but are not implemented consistently in the final analysis. This raises the question of the "why". Certainly, one of the reasons lies in the fact that once introduced and established, concepts cannot immediately be fundamentally changed, but only in small steps. But even these small steps are often not taken. And the real cause seems to be more likely to be the concern that changes to an existing and tested concept could raise compliance problems and could cause complaints during inspections by the authorities. The resulting damage would then be out of all proportion to the gain from a more efficient qualification system.

The fourth and last part of this series of articles therefore deals with the question of what actual risks exist with regard to the required regulatory compliance if the qualification concept is made more efficient and leaner. To this end, the suggestions for improvement from parts 1 to 3 are briefly summarized again and compared with the requirements of the most common guidelines, regulations and standards.

Essential Suggestions for an Efficient Qualification

If one summarizes the remarks of the previous articles, the essential suggestions for improvement for a

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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.

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more efficient qualification can be highlighted as follows:

1. A clear distinction should be made in the terminology used between "testing", "verifying" and "qualifying". This is not a matter of mere quibbling. It is about the concrete question of what is done differently or more in "qualifying" than in "testing" or "verifying". Only if this is clearly defined, it is possible to differentiate clearly and precisely between what is done by engineers and what is assigned to the quality unit. If one considers "testing" as the actual testing activity, "verifying" as a testing activity against a given acceptance criterion and "qualifying" as a detailed documented "verifying" under control of the quality unit, then already with the choice of words a clear and clean distinction is possible between purely engineering tests (verifications) and particularly quality-critical tests (qualifications). This clear definition should be a common thread running through all further activities.
2. A clear distinction should be made in connection with the unambiguous terminology, also with regard to documentation. For verification activities, i.e., testing activities of engineers, simple documentation, often in the form of checklists or edited technical documents, is generally sufficient. It is self evident that certain basic rules of Good Documentation Practice must be followed (e.g., verification with date and signature, indelible pens, clearly traceable corrections). A detailed, formalized test description – individually separated according to technical systems with plan and report – is probably considered excessive here. Test sequences and procedures are more likely to be found in engineering manuals or in the specific project and quality plans. In contrast, formalism is an essential element in qualification, which ensures that required activities are carried out systematically and completely and that the execution is documented in a comprehensible manner. It requires monitoring by the quality unit and thus the review and release of corresponding qualification plans and reports.
3. The duplication of test executions should be avoided as far as possible and, where appropriate, reference should be made in qualification documents to verifications already carried out by engineers. This applies in particular to "usual" basic verifications, which confirm the proper installation and function of a technical system. This means that the majority of formal IQ (Installation Qualification) and OQ (Operational Qualification) activities can be covered without any further effort. Only process-specific and product quality-relevant tests should be individually and in detail elaborated and controlled by the responsible experts (Subject Matter Experts, SMEs) under the control of the quality unit and the results should be evaluated in detail. The experts on the side of the system suppliers can or should also and especially be brought on board, as their know-how is often very deep and valuable.
4. One should contain the effort from the beginning by clearly distinguishing between a user requirements specification (URS) and a technical specification. The user requirements specification describes what you want for what purpose (*what* and *for what*), while the technical specification focuses on the implementation (*how* and *with what*). The user requirements specification result from the products, processes, application areas and markets for the products intended for production. They contain important information on Quality Critical Attributes (CQAs) and Critical Process Parameters (CPPs). The user requirements can or should also take into account regulatory required protection concepts (e.g., prescribed clean room classes), as far as this results from the products and processes (e.g., products for parenteral applications, aseptic production). Since today every single point of a user requirements specification is systematically and formalistically followed in its implementation – discussion in risk assessments, definition of qualification measures, tracking via a traceability matrix – too detailed a user requirement defining every screw and every fixture leads to an immense and not target-oriented effort.
5. Risk assessments should be carried out in several stages and focus on the product and process-specific risks. The focus should be on the distinction between standard and individual solutions. While standards can be dealt with using common methods (e.g., Good Engineering Practice, verification), individual solutions should be considered more closely (e.g., detailed risk assessment, individual qualification). Standards can be separated from the outset in a first rough risk assessment (risk classification) and then processed more easily (e.g., standard containers, standard laboratory equipment). For non-standard systems, the more detailed risk assessment can be carried out in the form of a Failure Mode and Effects Analysis (FMEA), but this is not mandatory. A detailed numbering system does not always lead to the desired result, sometimes it even distracts from the actual goal.
6. Qualification documents – here plans and reports – should be designed as simple as possible. The key messages focus on: *Who* checks *what, how* and *with what*, and *what* are the acceptance criteria? A plan is of good quality if an inexperienced person knows what to do by pure reading. Today, plan and report are ideally already represented in a single document that is signed before and after processing (entry of the result values). The number of sig-

■ Figure 1

Key elements of an efficient qualification (source of all figures: the author).

natures should be reduced to what is necessary.

7. One should distinguish very sharply between a technical defect and a formal deviation. While a technical defect is listed in a simple list of defects (punch list), corrected and the correction confirmed, a formal deviation must be analyzed, evaluated and the further treatment must be followed and documented in detail. The deviation requires the involvement of the quality unit. A technical defect becomes a deviation if it is not found during verification but only becomes apparent in the subsequent qualification or validation activities.

In the previous contributions to this series [1], considerably more possibilities for increasing efficiency were discussed. Nevertheless, the topics listed here are those that have the greatest influence on the scope of qualification, the time involved and the costs. They are clearly listed in fig. 1. The question remains whether these proposals are also in line with regulatory requirements or whether there is a risk that appropriately adapted concepts will be criticized during inspections.

Alignment With the Requirements of the EU

The requirements for qualification in the EU are described for medicinal products in Annex 15 of the EU GMP Guidelines [2]. The essential elements and interrelationships are shown in a simplified form in fig. 2. According to this, procedures and concepts for qualification and validation should be dealt with in a Validation Master Plan (VMP) or comparable document. Activities in connection with qualifications and validations should be described in plans, the results should be summarized and evaluated in reports. These documents are to be reviewed and approved by "suitable" personnel, whereby "monitoring" is explicitly requested by the quality unit. Annex 15 contains all known elements from URS to Design Qualification (DQ), Factory Acceptance Test (FAT)/Site Acceptance Test (SAT) and Performance Qualification (PQ).

In terms of terminology, the guide uses the terms "test", "verification" and "qualification", with specific explanations:

- IQ as "verification of correct installation"
- OQ as "tests to confirm operation ranges"
- PQ as "tests using production materials or substitutes"

Thus, the terminology of Annex 15 does not contradict the suggestions of a clear definition of terms made before.

In its latest version, the Annex also refers to the FAT and SAT tests to be carried out by the manufacturer and explicitly states that tests carried out in this context in the context of an IQ or OQ need not be repeated. Thus, the possibility to refer to "normal" technical test documents in the qualification is created. There are no requirements for the design of these technical test documents.

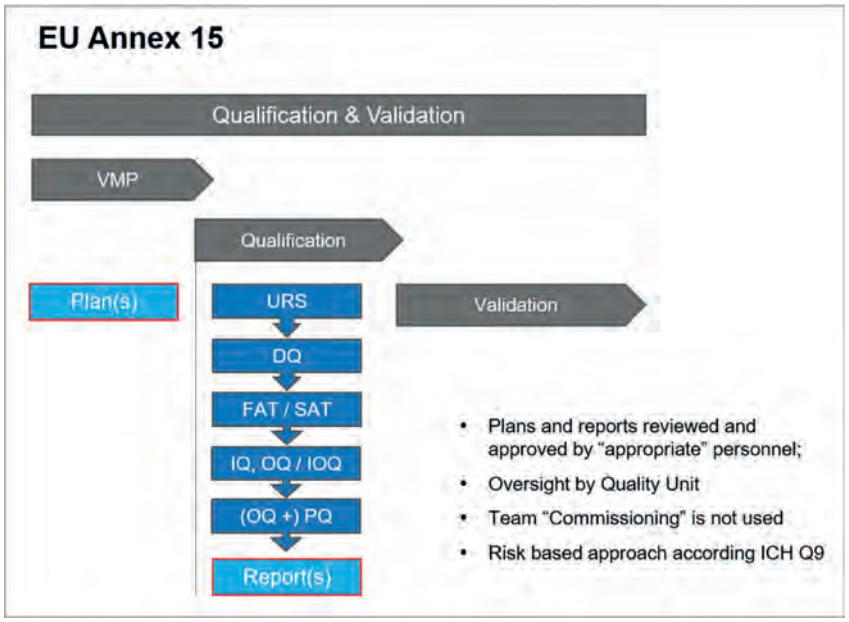
With regard to User Requirements Specification (URS), Annex 15 also contains a short section stating that specifications for equipment, facilities and supply systems should be described in a URS and/or in a functional specification. This does not express a clear and unambiguous separation of user requirements specification from technical specifications, as described above. The addition that the description can also be made in functional specifications, however, at least offers the possibility to make the separation at one's own discretion.

Finally, we would like to take a look at the topic of risk assessments. Here the Annex 15 speaks in principle of a "risk-based" procedure with reference to the ICH Q9 Guideline. Also, the embedding in a general quality risk management system as well as the necessity for the repeated revision of already existing risk assessments (Lifecycle Approach) is addressed. The Annex 15 does not provide detailed instructions on the different stages of risk assessment or the method. Thus, the user is given all conceivable degrees of freedom as long as the following goal is achieved: Quality risks that are not acceptable are mitigated or minimized to an acceptable limit. Furthermore, the scope of the qualification must be directed to the quality-relevant systems, properties and functions.

Comparison with the Requirements of the USA

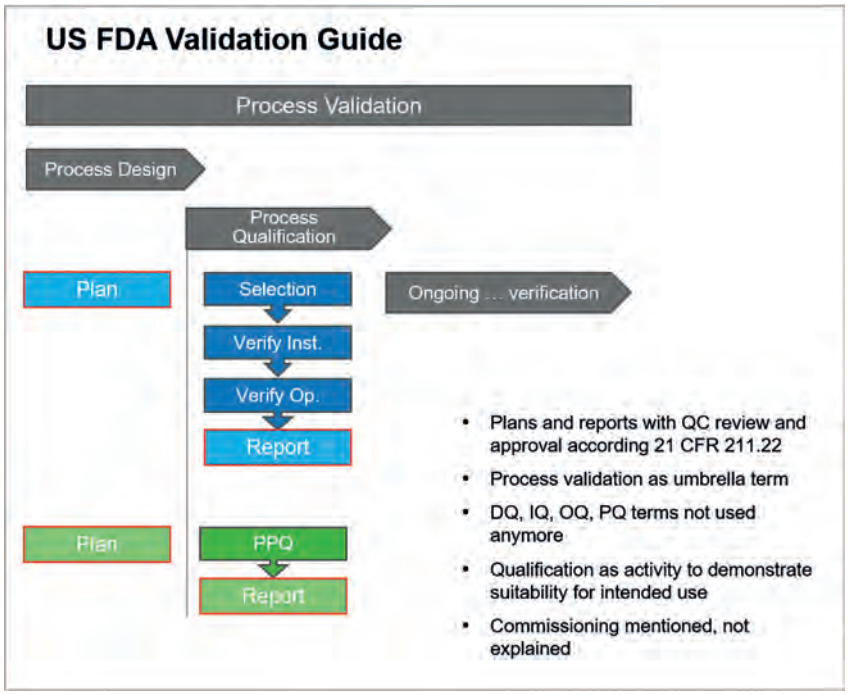
In the USA, qualification and validation requirements are described in the FDA Validation Guide [3], which was reissued in 2011. With the replacement of the old guide pub-

Figure 2



Qualification concept according to EU-Annex 15.

Figure 3



Qualification concept according to US-FDA.

lished in 1987, the concept, which runs under the main title of "Process Validation", was completely changed and divided into today's 3 phases (fig. 3). Thus, a distinction is now made between the phases of Process Design, Process Qualification and ongoing Process Verification. The topic of qualification is found in the second phase.

Qualification is described by the FDA as *"documented evidence that utilities and equipment are suitable for the intended purpose and function as desired."* The widely known abbreviations DQ, IQ, OQ and PQ no longer appear. They are only indirectly referred to by specifying the qualification activities in more detail like:

- *"Selecting ... based on whether appropriate*
- *Verifying ... correct installation*
- *Verifying ... correct operation"*

Plans and reports are required for qualifications, whereby the FDA leaves it open whether individual, system-specific plans or an overall plan for a qualification project will be created. Some essential content points for the plans are specified as follows:

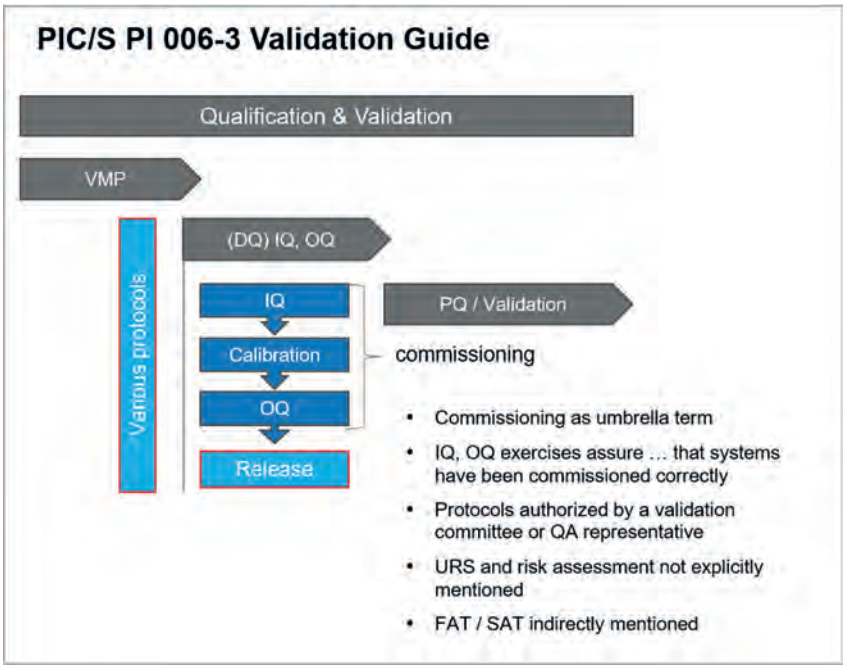
- intended studies or tests
- criteria for evaluating the result (acceptance criteria)
- scheduling of the qualification activities
- responsibilities of the divisions and the quality unit
- procedure for documentation and release of the qualification

Unlike in the EU, the FDA mandates that these plans must be reviewed and approved by the Quality Control Department. Pure monitoring (oversight) is not sufficient here.

At no point do these regulations speak against a terminology as suggested above. Again, the term verification is used as a testing activity against an acceptance criterion, while the term qualification is closely related to the formalism of plan and report preparation and the integration of the quality unit. There are no detailed specifications for the structure of a qualification plan, nor are there any specifications for the implementation of a risk assessment. However, reference is made here to both the ICH Q9 Guideline and the American standard ASTM E2476 [4] (ASTM International, orig. American Society for Testing and Materials)

References to the integration of engineering activities (e.g., FAT/SAT) are also not given in the docu-

■ Figure 4



Qualification concept according to PIC/S PI 006-3.

ment. However, there is a reference to the ASTM E2500 standard [5], which deals intensively with this topic (see below).

Thus, the US-FDA Validation Guide offers maximum degrees of freedom in the implementation of a qualification. Here the focus is exclusively on the goal to be achieved – all equipment must be suitable for the intended purpose.

Alignment with the Requirements of the PIC/S

It may also be worthwhile to take a look at the Validation Guideline of the Pharmaceutical Inspection Cooperation Scheme (PIC/S) [6], which is older, but at least serves as an opinion poll among the inspectors of the PIC/S member states.

Structure and terminology here still correspond to the traditional scheme as shown in fig. 4. The qualification consists of the elements DQ, IQ, and OQ, followed by the PQ, which in this document is set almost equivalently to the process validation. Above all, the Validation Master Plan is enthroned, the content of which is described in detail in the document.

In terms of terminology, all qualification activities are referred to as "documented evidence" that the design meets GMP requirements, the systems are correctly installed and working properly. However, the term "commissioning", which is common among engineers, appears here for the first time and is seen as an umbrella term for all activities that are carried out, among others, within the framework of IQ and OQ. This combination of terms and the statements in section 2.5.2 *("The concept of equipment qualification is not a new one. Many suppliers have always performed equipment checks to confirm functionality of their equipment to defined specifications, both prior to and after installation.")* show that the qualification activities are closely related to engineering. This becomes even clearer when, e.g., the IQ and OQ activities are explicitly attributed to the engineers.

The FAT and SAT are not directly addressed. However, Section 5.3.4 "Checking of Suppliers" states that there are tests at the manufacturer's premises which do not necessarily have to be repeated as part of the qualification activities.

Protocols are required for different levels, with the expectation that they will be prepared by the different disciplines and authorized by a validation committee or the quality unit. At various points it is described that the different tests can be documented directly using the technical specification documents and the typical piping and instrument flow diagrams. Further, the qualification protocols are not detailed.

User requirements specification and risk assessment are also not explicitly mentioned. In the case of the latter, reference is only made to the fact that critical manufacturing and control equipment should be qualified.

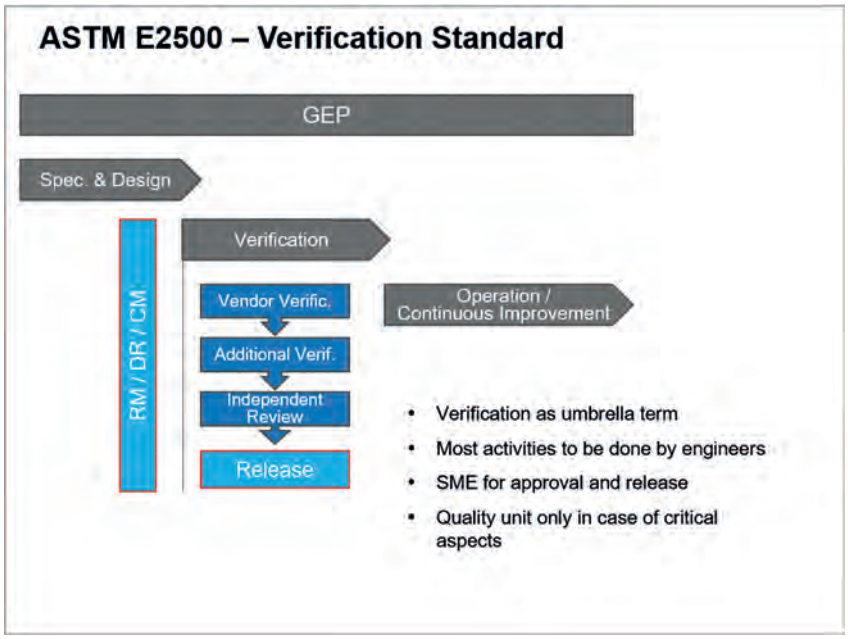
This "recommendation document" also leaves enough degrees of freedom open and encourages the intensive involvement of the engineers with their routine activities as an important support in the qualification process.

Comparison with the Requirements of Generally Applicable Standards

Even if not published by regulatory authorities, standards and association documents often reflect the current state of knowledge and technology, which is why 2 important documents should be considered at the end. The first is the ASTM E2500 standard in its latest version [7], which was developed in response to a white paper on qualification published by the International Society for Pharmaceutical Engineering (ISPE) [8]. The second is the ISPE Baseline "Commissioning & Qualification" [9], which was reissued in 2019.

Both documents see the qualification activities very closely related to technology and only the critical

■ **Figure 5**



Qualification concept according to ASTM E2500.

and release-relevant activities are the responsibility of the quality unit. Figure 5 shows the basic scheme proposed in the standard ASTM E2500.

Here the topic "Good Engineering Practice (GEP)" dominates, which is seen as an essential basic requirement throughout the entire qualification process. The overall process itself is divided into the phases "Specification & Design", "Verification" and "Operation/Continuous Improvement". Of equal importance to the GEP are "Risk Management (RM)", "Design Review (DR)" and "Change Management (CM)", which also span the entire qualification cycle.

The term "verification" is used here – somewhat unusually – as an umbrella term for all qualification and validation activities. This also includes commissioning activities, but this does not necessarily contradict the explanations given at the beginning. In fact, all tests that are performed against an acceptance criterion can be called verification across the board, regardless of the point of time and responsibility. The terms or abbreviations DQ, IQ, OQ and PQ do not appear in the document.

A URS is not explicitly mentioned in the standard, but "requirements" in general are dealt with and here in particular the product and process-relevant requirements reflected in the CQAs and CPPs. The structure of qualification documents (here called "verification documents") is not described in detail. However, it is pointed out that it is basically possible and also recommended to use the documents of the system suppliers, provided that the suppliers are sufficiently qualified. All in all, the suppliers and the technical specialists (SMEs) play an important role, since the entire verification work is expected from them, while the quality unit comes on board very late. And only if the respective system is to be seen in the context of "critical aspects" that can influence product and/or process quality.

The topic of risk assessment is only dealt with in general terms. The focus is on risk management with reference to the ICH Q9 Guideline, emphasizing that the topic covers the entire life cycle and should focus in particular on the "critical aspects".

The ISPE document for Commissioning & Qualification (C&Q), like the standards document, also focuses on the pursuit of Good Engineering Practice and the testing activities to be performed in this context. Here the term "commissioning" is assigned to engineering activities, while qualification activities are placed under the supervision of the quality unit. As before, the term verification is generally used as a test against acceptance criteria. ISPE also tries to integrate the tests carried out by the suppliers within the scope of FAT and SAT in a meaningful way and not to repeat tests unnecessarily. The scope of the tests should be described in a C&Q plan, which in turn can refer to other documents and test plans. The usual IQ and OQ protocols and activities are deliberately avoided, because the claim is made that these activities can be easily covered in a more targeted C&Q process, taking into account Good Engineering Practice.

The ISPE document also takes a very firm stand on URS and describes what is meant by it and what a URS should not be. According to the baseline document, a URS should contain product- and process-relevant requirements. It should explicitly not include any design specifications.

With regard to risk assessment, ISPE offers the "Impact Assessment", which has been known for a long time and precedes a risk assessment, and which has now been considerably simplified in the new baseline version. Thus, only a distinction is made between "Direct Impact" and "Not Direct Impact" systems, whereby only the former are subject to qualification. All other systems only undergo a simple technical test, known as commissioning.

The baseline document itself then provides a large number of very de-

tailed execution proposals, underlaid with corresponding samples and working templates. These are all to be understood as "can", but not as "must", which is why they will not be discussed further here.

Last but not Least/Conclusion

An in-depth analysis of the essential regulatory, but also normative requirements and recommendations shows that the topic of qualification is handled quite openly and offers a wide scope for interpretation and implementation. All documents speak of tests, verifications and qualifications, whereby it is uniformly recognizable that qualifications always require the involvement of the quality unit. Recent documents show the clear trend towards the sensible use and integration of engineering test documents in order to avoid the duplication of test activities. Good Engineering Practice and the use of supplier know-how are of decisive importance in this context. Regardless of how a URS is formally defined – the fact is that all technical projects start with the user's requirements resulting from the product and process as well as the applicable regulatory requirements. These must be defined and communicated in writing at an early stage so that all further requirements and technical specifications can be derived from them in a meaningful way. These requirements must then be put to the test with the help of a formal risk assessment. Today, it is a continuous and uniform requirement that risk assessments are to be seen in the overall context of risk management and thus do not represent a one-time activity. Risk considerations and risk assessments take place in a wide variety of forms and at different project phases, whereby the exact method and form can be freely chosen. One is just as free in the design of test and qualification documents. However, it is increasingly being pointed out that it makes sense to use standard technical test documents here and not necessarily to create one's own checklists, which is costly and prone to errors.

In conclusion, there is nothing from the regulatory or normative side that would contradict the aspects of a modern qualification and thus the proposals made in this series of contributions. There is nothing to justify the fear of compliance deficiencies and thus nothing that would prevent concept optimization. So, it is solely in the hands of the industry, in the hands of the pharmaceutical manufacturers, whether they consider the problem of a complicated, cost and time-intensive qualification to be critical enough to do something in the direction of "simplification" here. Even if the status quo is maintained according to 30 years, the problem of excessive requirements cannot be in reality as great as it is often presented. And if it should be so great, then all that remains is to express it with the words attributed to old Goethe: *"Success has three letters (in German language): TUN" (which means "Do" in English).*

LITERATURE

[1] Gengenbach R. Grundprinzipien einer effektiven und effizienten Qualifizierung – Teil 1 Grundprinzipien. Pharm Ind. 2020;82(1):62–71. – Teil 2 Auf die Planung kommt es an, Pharm Ind. 2020, 82 (4):452–460. – Teil 3 Es geht los – die Umsetzung, Pharm Ind. 2020;82(7): 837–848.

[2] EudraLex, Volume 4, EU GMP Annex 15, valid since Oct 2015.

[3] Guidance for Industry, Process Validation: General Principles and Practices, US-FDA, Jan 2011, Rev. 1.

[4] ASTM E2476-09 "Standard Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture".

[5] ASTM E2500-7 "Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment".

[6] Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-sterile Process Validation, Cleaning Validation, PIC/S PI 006-3, Sept 2007.

[7] ASTM E2500-13 "Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment", May 2019.

[8] A Whitepaper on Risk-Based Qualification for 21st Century, ISPE International Society for Pharmaceutical Engineering, 9 March 2005.

[9] ISPE – Baseline Commissioning & Qualification Vol. 5 (2nd edition), 2019.

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