Modern Qualification

Are you ready for this opportunity together with your suppliers?

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Abstract

In a time where pharmaceutical manufacturing and especially the qualification and validation of pharmaceutical facilities is under pressure from new international regulation, new innovative products, and biosimilar competition, it is time to rethink the traditional qualification and validation approach. Many German and European companies are still following very old procedures and project execution models, ending up with facilities that could have been producing months beforehand if they had known the new time and money saving opportunities. A recently released guideline on *modern qualification* enables a customer-supplier cooperation that minimizes repeat testing, enables better product and process understanding for the pharmaceutical manufacturer, and prepares for the new regulatory requirements for quality management and ongoing process verification. Some of these new opportunities are already utilized in China, the US, and elsewhere, but there is still some reluctance in Europe that should be overcome. The new guide can be obtained from European Compliance Academy (*www.gmp-compliance.org*).

Zusammenfassung

Moderne Qualifizierung – Sind Sie bereit für diesen Ansatz unter Mitwirkung Ihres Lieferanten?

In einer Zeit, in der die pharmazeutische Herstellung und insbesondere die Qualifizierung und Validierung pharmazeutischer Einrichtungen und Verfahren zunehmend unter Druck geraten, ausgelöst durch neue internationale Vorschriften, neue innovative Produkte und einem verstärkten Wettbewerb z. B. im Bereich der Biosimilars, ist es notwendig geworden, den traditionellen Qualifizierungs- und Validierungsansatz neu zu überdenken. Viele deutsche und europäische Unternehmen folgen noch immer veralteten Verfahren und Projektabläufen, was sich in Anlagen äußert, die Monate früher hätten in Betrieb gehen können, hätte man bereits die moderneren, zeit- und kosteneffizienten Vorgehensmodelle berücksichtigt. Ein kürzlich veröffentlichter Leitfaden zu *moderner Qualifizierung* zeigt Möglichkeiten auf, wie eine gute Zusammenarbeit zwischen Kunden und Lieferanten gestaltet, und damit der Umfang wiederholter Prüfungen bei Qualifizierungen auf ein Minimum reduziert werden kann. Ein Vorgehen, das gleichzeitig beim pharmazeutischen Hersteller zu einem besseren Produkt- und Prozessverständnis führt und auf die neuen regulatorischen Anforderungen an das Qualitätsmanagement und die fortlaufende Prozessverifizierung vorbereitet. Einige dieser neuen Möglichkeiten werden bereits in China, in den USA und anderswo genutzt, während es in Europa noch immer große Zurückhaltung gibt, die überwunden werden sollte. Der neue Leitfaden kann von der European Compliance Academy bezogen werden (*www.gmp-compliance.org*).

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1. Why Discuss Modern Qualification?

Qualification and validation are important pharmaceutical project activities, but for more than 30 years most pharmaceutical companies have been overdoing qualification activities documentation. They misinterpret the regulatory requirements at a high cost of both money and time.

The FDA issued its first Guideline on Validation in May 1987 [1]. In short, the guideline lists the principles and practices that are acceptable to the FDA for the process validation of drug products and medical devices; but it does not list the principles and practices that must, in all instances, be used to comply with US law. In this early guide, only 2 key terms are defined by the FDA:

1. *Installation Qualification*: Establishing confidence that process equipment and ancillary systems are capable of consistently operating within the established limits and tolerances.
2. *Process Performance Qualification*: Establishing confidence that the process is effective and reproducible.

Since then, the pharmaceutical industry and its suppliers, including engineering, commissioning, and qualification service providers, have continuously expanded those basic FDA requirements to become an extensive money and time-consuming regime considering and working on elements like design qualification (DQ), factory acceptance test (FAT), site acceptance test (SAT), installation qualification (IQ), operational qualification (OQ), performance qualification (PQ), and many more. This was not FDA's original intent and it became very clear in 2011 when the FDA issued the updated Process Validation Guidance [2], which specifies none of these time consuming qualification practices but simply states: *"It is essential that activities performed to assure proper facility design and commissioning precede PPQ. Here, the term qualification refers to activities undertaken to demonstrate that utilities and equipment are suitable for their intended use and perform properly."*

Even though the EU GMP Annex 15, which was revised in 2015 [3], goes into further detail and also lists "new" terms like FAT and SAT as used by the industry, both European and US regulators have stated many times that the requirements and intent of the 2 guides are the same, although their wording is different.

Why is this important especially for companies in the EU? It is important because most of them are still misinterpreting those guidelines and still overdoing their qualification exercises. They do not recognize the possibilities offered by regulators to use synergies and still do not partner up with their suppliers in sufficient detail to come to faster, more cost-efficient and effective qualification projects. On the other hand, the suppliers are increasingly struggling as they meet many different and confusing interpretations from their pharmaceutical customers and most of them have a hard time understanding what the *real* requirements are.

While the European industry is struggling, companies in other countries – e.g., in China – have already demonstrated that qualification and validation can be done much faster and more cost-effectively when following modern, risk-based approaches and when working closely with competent suppliers. This is a clear signal for EU based companies to rethink the situation.

The European Compliance Academy (ECA) has taken notice of this

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after completing his university education as a chemical engineer at the Technical University of Karlsruhe, he began his professional career in 1987 at BASF AG, Ludwigshafen. For more than 10 years he acted as an internal GMP consultant. In addition to the establishment of an efficient and cost-oriented qualification system, he has been involved in numerous related expert committees at the DIN e. V., Verband der Chemischen Industrie e. V. (VCI) and Society for Chemical Engineering and Biotechnology (DECHEMA). He was early involved in the elaboration and commenting of the PIC/S document PI006 (validation) and the ICH Q7 GMP Guide. In 2002, after another career break, he founded gempex GmbH, an international GMP service company, which he manages today. In addition to numerous publications, speeches and lectures at universities, he has summarized his experiences in the book GMP qualification and validation of API facilities published by Wiley.

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and has started working on an improved and modern approach considering integrated qualification and validation as well as the intensive cooperation between pharmaceutical manufacturers and their engineering and equipment suppliers. There will also be other guidelines on the market that describe a new generation of modern qualification and validation that will hopefully overcome this obstacle.

2. How Globalization Triggers New Q&V Strategies

It is not a secret that the economy in Asia – especially in China – rapidly increased over the last decade. Money for new investment projects in this area is not a topic and the number of newly built pharmaceutical facilities, especially biotech facilities, can nearly not be counted. Quality is on top, as most of equipment is bought from Western equipment manufacturers and cleanroom technology already is and was a key technology in China. However, this is only one factor. Another is the time needed for building up the facilities, including qualification and validation.

While international pharmaceutical companies have brought in their corporate standards for qualification and validation and these projects typically take as long – or even longer – as they do in Europe or the US, the local pharmaceutical companies take much less time, thereby enabling manufacturing facilities to be operational several months ahead of their Western competitors, raising the question of *how*?

The new Chinese GMP 2010 regulations [4] are based on the same PIC/S [5] core scheme as the European GMP, so the legal requirements are not very different and, therefore, that does not provide the answer. However, the lack of legacy tradition on qualification, the strict focus on bringing the products to market, and a highly pragmatic orientation enables Chinese companies to rethink qualification projects based on the actual requirements and supplier capabilities (including German supplier companies' capabilities) that enable them to leverage significant time, effort, and documentation by not repeating test activities, etc. when not necessary.

In fact, several European suppliers experience significantly more willingness to understand and learn from their capabilities among Chinese customers than among European customers. This seems very similar to the experience in the car industry 25 years ago when the Japanese car manufacturers implemented Total Quality Management (TQM) much faster than their European or American competitors. The lack of legacy thinking in the local Chinese companies and not being stuck to old concepts in a conservative manner have enabled them to implement new practices that provide significant benefits over the traditional overloaded qualification practices. Recent examples from Chinese pharmaceutical projects show that the local companies are fast learners and that the Chinese authorities are also willing to follow modern practices as long as the major targets – good quality and safe products – are reached.

There is no doubt that Asia and China respectively are also facing similar problems with not always good and qualified support by Chinese vendors and the majority of those vendors are struggling with the correct understanding and details of how-to-do. But by being aware of the speed of development in those countries, it may be obvious that, for EU based companies, the time to think is over and immediate action is needed.

3. The ECA Modern Qualification Guide as a New Initiative for Following Old Stories

Before analyzing old and new approaches, it may be useful to recall the last decade, when there were the first opportunities for modern qualification and validation practices. In 2007, the ASTM E2500 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment [6] was approved after an intensive effort by a number of pharmaceutical companies and organizations, such as International Society of Pharmaceutical Engineering (ISPE), FDA, EMA, and several others. The background was that the FDA's strategic initiative of cGMP for the 21st century had inspired a number of international initiatives, including one by ISPE to develop a standard (in ASTM) and some guidelines that would enable more streamlined approaches to qualification and validation based on the quality risk management principles of ICH Q9 [7] and several other guidance documents. Before, ISPE published a whitepaper [8] on risk-based qualification, which listed 10 core principles for a new qualification approach that became a central part of the ASTM E2500 standard guide (table 1).

The issue of the ASTM E2500 standard guide has been a core inspiration for many other guides and standards, including guides from ISPE, the GAMP 5 guide for automated systems [9], and guides from Parenteral Drug Association (PDA) and from ECA. The ASTM E2500 standard has already been updated several times, but the core of the standard, including the most important definition of critical aspects, is still valid.

So-called "Critical Aspects" are a central part and play a key role in the qualification activities as defined by the ASTM E2500 based approach. In short, this approach can be summarized as the whole qualification project following Good Engineering Practices (GEP) including Good Documentation Practices, based on a clear qualification plan, and that only the critical aspect re-

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Table 1

ISPE's 10 principles for a streamlined Q&V concept.

1.	Focus on what affects product quality
2.	User requirements based on the process
3.	Risk assessment and process development used to identify critical features, functions, and critical process parameters
4.	Only critical process parameters (CPP) will be used as basis for qualification, focusing on product quality and safety
5.	All activities must contribute value to the start-up and delivery of the manufacturing capacity
6.	Risk-based asset delivery combined with Good Engineering Practices
7.	Value-added documents where only data that serves a meaningful purpose should be collected, and documents should mainly serve for operational purposes and maintenance
8.	Use of supplier documentation where the supplier's standard documentation may be used, provided that the supplier is of adequate quality
9.	Test planning where defined tests should only be carried out once (at the agreed location and by the agreed parties, e.g., supplier and customer), although PQ typically requires additional testing
10.	Fostering innovation by flexible programs that apply sound and qualified scientific and engineering judgment

lated qualification activities require the involvement of the pharmaceutical company's quality function (e.g., QA) in order to plan, monitor, and approve those activities as a small part of the whole qualification project.

Some of these principles are not new, but they were never really followed. In almost all guidelines there has been a focus on the qualification of those items, which are critical to the quality of the final product and with the harmonized regulations of quality risk management principles, based on the ICH Q9 guidance [7], there has been a much better understanding on how to apply systematic approaches to criticality across Europe, the US, Japan, and elsewhere, linked to a scientific understanding of the pharmaceutical product and the manufacturing processes.

4. Traditional Approach and Its Limitations

As already identified and outlined in the previous articles [10], there is a high potential for improvement in the qualification and validation section, starting with the installation of a validation project, covering the validation concept itself with all of the organization topics and ranging until the execution, deviation management, and final reporting. When focusing especially on the execution part and the topic of cooperation between the manufacturer (user of a technical system) and vendor (manufacturer of a technical system), additional improvement potential is coming up.

Traditional qualification concepts, especially in the pharmaceutical industry, are normally not leveraging the supplier's knowledge and test activities, which are done either in the factory (FAT) or on site after delivering and installing the technical system (SAT). Rather, the pharmaceutical manufacturer is going to describe all of those tests in a detailed, accurate, and as required manner with all of the pre-defined acceptance criteria as IQ, OQ, or PQ tests by themselves in the related qualification protocols, which means, they are repeating those tests just on a higher formalistic level. Technical details – like e.g., nozzles of a mixing vessel, their position, number, and size – are taken from technical drawings, transferred into the related checklist, and later on used on site for the verification of correct design. Accordingly, the resources of validation engineers are needed for the preparation of qualification protocols as well as for the final execution, whereas the said validation engineers in most cases are lacking specific technical know-how and for this reason, they need some time until the task can satisfactorily be finished.

In the traditional qualification, the user requirement specifications (URS) as well as the system specific technical risk assessments are also executed prior to ordering the system, which means, without the involvement of the target vendor. Validation engineers involved in this kind of tasks know how challenging it is to search for all of the needed details for a lot of different technical systems and, therefore, spending most of their time on internet and literature research and – finally – also for talking with potential vendors.

Facing those obvious time consuming and time-wasting problems, the pharmaceutical industry has already started trials to use the vendors' knowledge for different cooperation models. In most cases, offers from vendors to execute the system specific qualification were followed with different new challenges and new experiences. The most challenging question that arose was how to integrate the vendors' qualification package in the best way, especially when facing a situation wherein qualification packages are ordered from a wide variety of vendors. Different models appeared and have been tried with more or less success.

Some companies handed over their internal qualification documentation templates to their vendors, and then required them to fill it out as usually done by the pharmaceutical manufacturer's valida-

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tion engineers. Problems appeared as vendors were not familiar with the forms and, therefore, making many mistakes. In addition, the costs for vendors increased dramatically due to these additional complex work requirements. Other companies decided to take the qualification documents unchanged as offered by the vendor, with the result to face big problems during inspections as questions from inspectors could not accurately be answered in a short time. Finally, some companies decided to use the vendors' qualification documents, but created own additional reference documents to make traceability easier and to avoid problems in inspections. Even though the last model seemed to provide the best solution, it did not really reduce the workload, time, or cost expenditure. In saying this, it becomes obvious as to why most pharmaceutical manufacturers turned back to the old qualification approach, doing all of the activities by themselves. And with the intention not to have any risks, no differentiation is made between the critical and non-critical aspects. Everything is put on the same level of qualification effort and documentation.

5. Modern Approach, Solving the Problems, Bridging and Closing Gaps

The ECA Modern Qualification Guide takes a new way to solve a problem that has existed for 30 years. The guideline does not have the intention to invent a totally new approach or deviate from the long-known and established philosophy to concentrate qualification activities on the critical aspect items. However, the experts of the ECA qualification and validation group deeply analyzed the situation, and it ended up that the following facts seem to block the transition to a new approach:

- The models as described in standards like ASTM E2500 are still too abstract and not providing sufficient details for the how-to-do.
- Leveraging of vendors' know-how and expertise will not be possible if vendors do not fully understand the different needs, not being able to speak the "GMP-language" and not being able to distinguish by themselves on what is legally required independent of their customers' different interpretations.
- The breakdown of the qualification process should be more granular concerning individual and typical engineering tasks and activities including but not limited to the correct sequence of executing those activities.
- Good templates for related engineering as well as qualification documentation are missing.

Therefore, the *modern approach* as considered in this article, will still follow the concept that all qualification projects should be done under GEP, while only those parts characterized by the quality critical aspects should focus on the involvement of the quality unit of the pharmaceutical manufacturer. And to bridge the gap, the ECA Modern Qualification Guide is going to have one section explaining the details to be considered by the user (the pharmaceutical manufacturer) and one section with the details to be considered by the vendors.

A strong recommendation is given in this guideline to clearly differentiate between a pharmaceutical product and process URS (PPURS) and the following more technically oriented URS, which allows from the outset to identify and concentrate on the critical aspects, critical quality attributes (CQA), and critical process parameters (CPP) of the pharmaceutical production process. Accordingly, and in line with the new GMP requirements, a critical aspects-based risk assessment (CARA) model is introduced and explained, which is not a once-through activity but rather follows the whole project from beginning to end. In addition, the fact that qualification and validation activities finally constitute a project is taken into account by explaining the need and the content of project quality plans (PQP), an instrument essential to managing such projects. Most importantly, the ECA guide will provide a wide variety of examples and actually used templates to help the industry on both sides for a better understanding and to move from theory to praxis.

Finally, efficiency is characterized by doing the right things in the right way; in other words, for efficient qualification projects, including the selection of items, which need or do not need qualification as well as the assessment to which amount the qualification is meaningful is also needed. Several procedures and tools already exist (fig. 1). The decision on what is GMP and non-GMP relevant is mostly done in the early stages and described ideally in the PPURS. In a further stage, ISPE offers in the commissioning and qualification guide a so-called impact assessment tool that helps to identify

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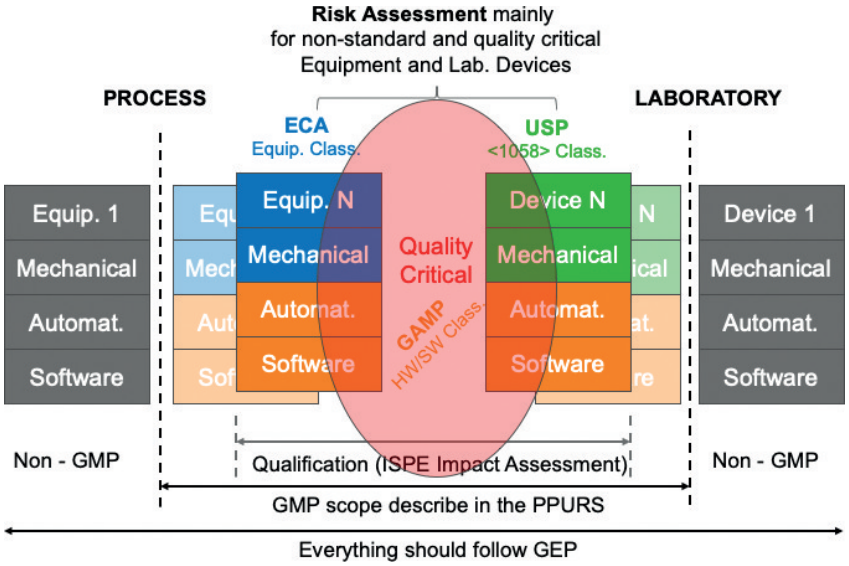
■ **Figure 1**



Tools and procedures to classify systems and define the scope of qualification (Source of the figure: the authors).

which of the GMP relevant systems need qualification and which one only needs GEP testing. The GAMP 5.0 guide for computerized systems finally offers a methodology to do a classification on the automation and software part for hardware as well as for software to define the degree of activities related to the qualification. Something similar is proposed by the United States Pharmacopeia (USP) section <1058> to differentiate between standard laboratory equipment needing nearly no activities and high customized and complex devices needing thorough and intensive qualification work. The ECA guide will go to close the last open gap, which is the classification of the non-automated part of process equipment by even doing the same to differentiate between standard equipment and high customized and complex equipment and to recommend the level of qualification activities commensurate with the complexity.

6. Integrated Qualification and Validation: Harvesting the Benefits

The benefit of an integrated approach to qualification and validation, which includes the involvement of the vendors and other suppliers, including engineering service providers, is that a common approach to GEP and quality risk management principles can be applied across a small or large project, independent on whether existing or new facilities are in the scope.

Once a science- and risk-based approach to qualification has been understood and implemented, the next option is an integrated approach to qualification and validation in pharmaceutical companies. Many pharmaceutical companies make a clear separation between qualification and validation activities and some even shift the teams from the qualification to the validation activities, like when a racing team shifts its members during the pit stop of a car race. The result is a slow and inefficient transition from qualification to validation, thus putting the whole project timeline at risk.

Integrated qualification and validation enable a number of benefits and emphasizes the fact that the two have more in common than when separated. The science- and risk-based approach to qualification starts with the product and the process in mind. The CQA of the product and the CPP of the process are important for identifying the critical aspects of the qualification program. They are equally important for the process validation, since they are the most important aspects of the whole manufacturing process, per definition.

In other words, the "mother of all risk assessments" in the science- and risk-based approach is the identification of the CQA and CPP. There are other important requirements that are needed to confirm both for qualification and validation but understanding the CQA and CPP is the ultimate MUST. Risk assessments should be repeated several times during a project as part of the risk management activities and some of the most significant risk elements should be addressed by e.g., mitigation, and this is common for both qualification and validation activities.

When keeping in mind that the critical aspects of the qualification and the CQA and CPP come from the same original risk assessment, the whole project life cycle of both qualification and validation can be streamlined. The main purpose of the qualification is to demonstrate that the system is fit for its intended use, before the process validation activities starts and long before the commercial distribution of the product can be possible.

Once these product attributes and process parameters are identified, there can be a "red thread" through the overall project of qualification and validation and all the way into the ongoing process verification, in which the CQA and CPP remain one of the focus set of process characteristics to be trended and evaluated regularly as part of continued/ongoing process verification as well as part of the regular EU required product quality review (PQR) or US required annual product review (APR) reporting.

The implementation of a cost-effective and integrated qualification

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and validation program is not complicated. It is actually easier than the patchwork of process and product rationales that many pharmaceutical companies currently use in their qualification and validation programs. However, although it is not complicated, one must be careful about terminology because unfortunately FDA and EMA use slightly different terminology regarding both qualification and validation. The European term Process Validation corresponds to the FDA term Process performance qualification (PPQ) and the European ongoing process verification is the same as the FDA's continued process verification. There are other examples, but the point is simply to emphasize that it is straight forward to integrate qualification and validation activities – at least when being clear on the use of a common qualification and process validation terminology.

7. Conclusion

Validation including qualification is a 30-year-old story. It is suffering from being inefficient, ineffective, and very time consuming. Attempts to change practices have not had a broad international impact yet. Regulators and associations have pointed out many times that all systems and parts of systems must be worked on and tested in a good qualitative way, simply stated as GEP but only less systems, the quality relevant ones, must undergo highly intensive qualification. Critical aspects, CQA, and CPP should be identified as a core exercise by using a risk-based approach. Knowledge and experience from vendors could and should be used in the best way to achieve good results.

However, until today, industry is lacking a transformation to this new approach, apparently suffering from vendors not fully understanding the GMP requirements in this aspect, which is only partly true. Moreover, it seems that the transition is blocked due to some inflexibility and conservative thinking of the pharmaceutical industry. Nevertheless, globalization and fast development especially in the Far East does not allow the industry to keep this status.

ECA's new Modern Qualification Guide is a new attempt to change this, having all the history, legal requirements as well as already developed approaches in mind. The main target is to help the industry to find the best cooperation between the users and manufacturers of equipment, to use the knowledge and expertise of both parties to achieve the best results in a short time. It is not the intention of the guideline to develop a new approach rather than provide more details, practical instructions, and especially case studies and templates to make it possible to "walk on the already prepared road".

The next step has been a new version of the guide called "Integrated Qualification and Validation" with a focus on integrating the qualification and validation activities and it is the first industry guide to address the integration and enable customers and suppliers to cooperate based on a common, standardized approach. For companies that may be reluctant, studies into recent projects in Asia, e.g., in South Korea and China, may be a source of inspiration. The projects there have been much faster in adapting the new opportunities to save project time and money. Maybe your company should be interested, too?

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