Basic Principles of an Effective and Efficient Qualification*)

Suggestions for practice – Part 2: Planning is what counts

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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.

After having clarified the basic principles and the basic understanding of terms in the first part, the topic of planning should be considered in this Part 2. Validation including qualification is characterized by a strictly systematic, formalistic, and documented, i.e., a planned procedure. Precisely these characteristics are one of the great strengths of this quality assurance measure. One does not want to forget or overlook anything, one wants the necessary testing and verification activities to be coordinated with experts, and one wants to have the last verifying check ensured by the binding and responsible signature. Only such an approach guarantees a high level of quality, for technology, processes, and for the product.

Validation or qualification can be highly complex projects when it comes to new construction or alteration measures or the introduction of new products and associated processes. Sometimes, however, it can also be a simple action, for example, if only a single piece of equipment is purchased or only a re-qualification or re-validation is required. The introduced concepts must be correspondingly flexible without compromising the systematics and thus the quality of implementation.

The following article deals with these concepts, the planning, and the essential elements that are at the beginning of each validation project. It is deliberately based on the content – what needs to be regulated, what needs to be described – and only then on the document. If the term validation is used, it is to be understood as an umbrella term for qualification and validation measures.

Agreement on Rules of the Game (Validation Concept)

It is not only a regulatory requirement [1], but it goes without saying that structured and systematic processes can only be ensured if they are defined, described, and communicated to a minimum extent. This applies in particular to the validation process. It is important to have a specific process design that is aligned with the environment (with the company). For the introduction of a validation concept, at least the following topics and processes must be considered, defined, and described:

■ The overall concept

Which elements and which individual steps are established with

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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.

which wording (definitions), and how is the overall process, and the sequence of steps predetermined? Are there special breakpoints and test points (project milestones)? How is the validation process interlocked with other processes (e.g., Engineering), and which interfaces exist? What does the entire document hierarchy look like (e.g., one or more master plans)? How are the "general" competencies and responsibilities e.g., aligned with functions and/or departments? What is the basic attitude towards externally performed activities and their integration? What is the basic concept with regard to risk- and life cycle-based approach? How is the overall overview (qualification and validation scope and status) ensured, and how and where are the annually recurring activities planned and documented? How is "completeness" in the implementation guaranteed (e.g., Traceability Matrix)? It does not matter whether a V-model or a complex flow chart is used as a process model. The steps must be fixed, the sequence must be clearly defined.

■ Procedure of qualification

Which single or combined elements are defined and for which case (e.g., IQ, OQ, or IOQ)? How must or may the individual elements be processed (serial, parallel, overlapping)? Which basic activities are assigned to the individual phases, and which basic acceptance criteria? How do these activities connect to the procurement, installation, or modification of a technical system? How are the documents (forms) structured in terms of content, and how are they numbered? When, by whom, and how are the documents created, where are the proof tests and acceptance criteria derived from and how are they cross-checked? How are the specifications processed, how are the results evaluated, and by whom are they cross-checked and approved? How is a distinction made between complex systems and simple standard devices? How are changes and deviations handled during qualification, and how are they documented? According to which scheme are re-qualification cycles defined and where are they documented? What is the archiving concept?

■ Procedure of validation

What are the basic requirements for starting a validation (software, process, cleaning, sterilization, etc.)? How are the associated plans and reports designed and structured and how are they numbered? Who initiates and who creates the documents? Where are requirements and acceptance criteria derived from? Who checks and who approves in the end? How is the execution and frequency of execution regulated? How are evaluations carried out and on what statistical basis? How are changes and deviations in the validation handled, and how are they documented and evaluated? How are the necessities for re-validation determined and where are they documented? How is archiving carried out? How is a continued long-term evaluation and assessment carried out?

This list is certainly not complete, but each of the questions listed must be answered specifically and concretely for a company or organization in order to map a useful validation concept. General descriptions (prose) should be reduced to what is absolutely necessary for basic understanding. It is important to define who specifically triggers a process when and how and what exactly are the activities to be performed. Statements like "After the IQ comes the OQ. An OQ plan is created for this." are unspecific and not concrete instructions, because e.g., it is not described how OQ is triggered and who actually creates the plan.

As the topic of validation remains existing even after an initial project (e.g., a new building), it is recommended to describe these procedures in individual documents (e.g., Standard Operating Procedures, SOPs) within the quality assurance system and to maintain and optimize the documents and processes continuously.

Procedures validation concept

- Execution of a validation project
- Qualification of equipment
- Qualification of devices
- Validation of computerized systems
- Validation of manufacturing processes
- Validation of cleaning processes
- Validation of analytical methods
- Validation of transport processes
- ...
- Implementation of risk assessment
- Change control C&Q

The first green box lists typical titles that are at least required to describe a validation concept. The division of topics into individual documents should be based here on the working method and organization (e.g., qualification of laboratory equipment is carried out by laboratory staff and is therefore ideally a separate instruction). However, a warning is given against too detailed a division, as it makes the documents difficult to read and carries the risk of duplication.

The Allocation of Roles (Validation Team)

The definition of responsibilities broken down to the assignment of tasks by name is essential for a functioning system, not only in validation. Responsibilities at different levels must be named as follows:

■ Superior responsibility

The superior responsibility lies purely legally with the Production

Management and the Quality Unit and should also be described as superior in the concept instructions described above or in a site-specific master plan. Additional units and functionaries can be named and listed, depending on the organization and their involvement. This can extend to a separate department for qualification and/or validation. However, the concrete mention of names should not be made in the documents themselves. It is better to refer to current company organization charts because this provides greater flexibility and easier maintenance.

■ Project specific responsibility

The project-specific responsibility is usually assigned to a team or individuals, depending on the size of the project, and includes the higher-level managers. The naming is typically and correctly done in a project-specific master plan or a higher-level validation plan. Here, too, it is recommended not to list the names explicitly in the document, but to refer to a project organization chart or a simple list of names, which is also easier to handle.

■ Responsibility for execution

Execution responsibility lies with the persons at the execution level who create documents, execute instructions and evaluate results and summarize them in reports. Every person involved in the actions – whether internal or external to the company – must be identifiable. Here, too, it is recommended to dispense with naming them by name directly in the documents and instead work with an attached signature list that is filled out and signed after processing. It makes only limited sense to specify people by name in advance, as changes in staffing can quickly occur for a wide variety of reasons. In the end, the decisive factor is the identification of the performers and the assurance that these persons were instructed in the activity before the performance.

■ Test and release responsibility

The responsibility for testing and approval clearly lies with the production and/or laboratory management and quality unit but can include any other specialist departments. These persons are usually listed in advance by name on the cover sheets of the qualification and validation documents. It should be noted that

- the number of signatories is reduced to the absolute minimum, e.g., a political "security culture" is to avoid.
- ideally it is specified for what a person is signing for (e.g., check for formal criteria, check for technical feasibility, check for compliance with acceptance criteria).
- it is clear who is ultimately responsible for releasing the document for execution or storage (multiple signatures should be avoided here, alternatively the meaning of the release or approval should be defined accordingly).

If it concerns smaller measures (e.g., procurement of an individual device), then the responsibilities are stated in the specific qualification and/or validation plan, whereby the before-made remarks apply also here.

The complexity of processes and technical equipment today makes it necessary for technical specialists to sit around the table and round off the "validation team". This is correct and important, but it requires that

- specialists are only called in when it is really necessary (efficiency of the meeting).
- especially suppliers of technical systems are included (the actual specialists who know the finer points).
- sessions in the larger circle are used exclusively to obtain comments and clarify open questions, since elaborations in the large circle are inefficient and basically not possible.
- it is clarified that there is exactly one decision maker, all others only have the right to comment.

It should be pointed out again at this point that the actual responsibility ultimately lies with production, the quality unit has a control function, and the specialists must cover the professional and technical background. A comparison with motorists (person responsible), traffic policemen (monitoring), and car repair shops (technical expertise) may illustrate this clearly.

The Project Takes Shape (Master Planning)

The master plan topic is not new and not specific to validation. Every major urban development project starts with a master plan in which the project is comprehensively recorded, explained, and roughly planned. It is a basic document on which further detailed planning and implementation is built. This is also the case with validation. Especially for larger and more complex undertakings (new construction or reconstruction), the project must be described, structured, and pre-planned as a whole (e.g., milestone plan). The persons responsible for the project must be named and the necessary resources must be provided. It has to be determined according to which concepts is proceeded concretely and – as the core element of the master plan – which project scope is to be discussed, which then has a direct effect on the necessary resources. This and more can and should be the content of a validation master plan.

Today, however, the subject is somewhat more complex in that there are not only master plans for projects but also site-specific master plans. Figure 1 shows an example of how different information can be maintained in a structured way.

For a site or an individual facility, it must e.g. be specified who is responsible for the topic of validation – independent of ongoing projects. The basic concept according to which validation is carried out at

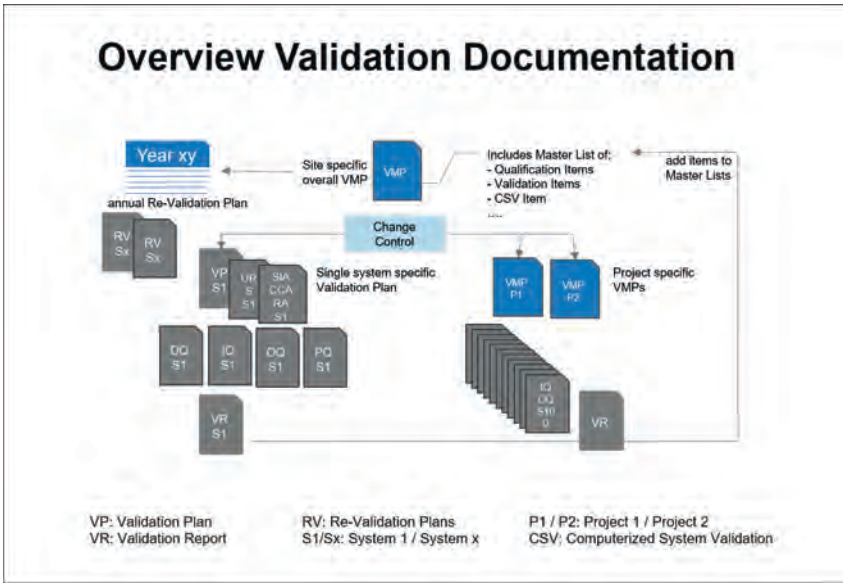
the site must be defined. And there must be overviews for the site that show which technical equipment exists, which processes and products are established, and what the associated qualification and validation status is. The list of content items in Annex 15 of the EU GMP Guide to the Validation Master Plan (VMP) should be understood in this direction [2]. Depending on the organizational structure, this superior VMP can contain subordinate master plans, e.g., a qualification master plan (with the list of the technical systems to be qualified) and/or an IT master plan (with the list of the IT systems to be qualified or validated).

In the life cycle of a site or facility, there will be smaller and larger projects which, depending on their character, may also involve qualification and validation activities, usually triggered and evaluated by a change control program. If these are larger projects (e.g., installation of a new production line), it makes sense to describe the project in a project-specific validation master plan (fig. 1). If it is a smaller project (e.g., procurement of a laboratory device), it will be sufficient to define the project in a validation plan (VP) only. In both cases, it is important that after completion of the project or the individual action the systems and/or processes are included in the site-specific lists, i.e., in the site-specific VMP.

Within the framework of a life cycle model, the recurring actions must also be planned, ideally annually. Here it has proven to be useful to derive a separate annual VMP or corresponding action lists from the site-specific VMP and/or its superior master plans.

Regardless of how you design the model and how you use the VMP document, you should always be careful not to duplicate information. Referencing is explicitly allowed in Annex 15 [2]. For example, you can refer to the Standard Operation Procedures (SOP) described above for

■ **Figure 1**



Overview of validation documents (source of all illustrations: the author).

the validation concept. The same applies to a project description that may already have been prepared in connection with other official approvals.

Detailed recommendations on the contents of a VMP can be found among others also at the PIC/S (Pharmaceutical Inspection Co-operation Scheme) [3] and from the WHO (World Health Organization) [4].

Wishes May be Expressed (User Requirement)

Every house builder knows this: Everything begins with wish pictures and first sketches, perhaps also already with a first quickly drawn floor plan. Only when the architect comes on board do you gradually begin to structure your ideas and wishes, if necessary, with the help of a checklist provided by the architect. And it's the same in pharmaceutical construction, at least when it comes to the first big ideas. You have a product, a process, and the first necessary equipment in mind, which the engineers quickly put down on paper - usually in the very early concept phase. The first block and process flow diagrams, floor plans, and installation drawings are created. This is normal and quite legitimate but should be more systematized when moving into the basic planning phase. Now is the right time to set down in writing the user requirements, taking into account the product and process characteristics as well as the regulatory framework. In doing so, the user requirements define what one wants to do, to what extent, and for what purpose (e.g., one wants to produce a certain number of painkillers for a certain market) and not how this can be achieved in detail. The user determines the use, the engineers determine how the technical implementation is carried out. This does not exclude that the user also has some technical wishes and of course has to formulate these (e.g., certain stainless-steel claddings or floor coverings). This should not, however, result in the user producing a detailed technical specification at the end, as otherwise all further actions derived from the user requirements (e.g., risk assessment, change control C&Q) will be lost in infinity.

Content user requirements

- Which products should be manufactured?
- How are these applied later (orally, parentally)?
- What are the product specifications?
- Are several products manufactured in the plant?
- Is the manufacturing process open or closed?
- Are critical IT systems in use?
- Where should the products be sold?
- What are the quality critical parameters (quality attributes, process parameters)?
- What are planned quantities, and production cycles?
- Are special processes in use (biotech)? etc.

The second green box lists typical questions that are usually answered in a superior user requirement specification (e.g., for new constructions). This can and should be extended by the user to include specific requirements derived from the rules of Good Manufacturing Practice (GMP) for subsequent operation (e.g., that certain activities must be carried out in a specific cleanroom environment).

Of course, there are also user requirements for individual technical systems when they are newly acquired or replaced. Since we are already at the individual system level, these requirements are more technical in nature, often mixed directly with a technical specification or a manufacturer's datasheet. Here, too, major problems become apparent in the further course of validation if the user requirements go down to the last technical detail. It goes beyond the reasonable scope of any risk assessment based on the user requirements. Therefore, the basic principle of user-oriented questions also applies here:

- What do I want to do with the system?
- Which ease of use (degree of automation) would I like to have?
- What performance requirements (capacities, throughput, availability) do I have?
- What special requirements are placed on the system or its design (e.g., good cleanability, easy to dismantle, smooth surfaces)?
- In which environment should the system be used (e.g., indoor or outdoor, high temperatures, humidity, space requirements, accessibility)?

It is ultimately the task of the engineers to transform the user requirements into more detailed technical specifications based on the required technologies – such as e.g., clean room technology, sterile technology, and hygiene design. In doing so, the engineer makes use of a wide range of norms and standards that already offer extensive assistance. It cannot be the user's task to specify all technical details and it cannot be the quality unit's task to check all technical details for adequacy, just as it is not the car buyer's task to specify or check the dimensional accuracy and tolerances of piston rings. Unfortunately, however, this is exactly what is happening today in the GMP environment and is one of the basic causes of the inefficient and ineffective processes.

A Last Look at Security (Risk Assessment)

"Risk-based approach" is certainly one of the most frequently used terms in the GMP environment today, and not without reason. To analyze what is critical and to concentrate your measures on it is logical and makes sense and is what authorities today expect from past experience. A risk assessment is neither a one-time nor a uniform action. Especially in connection with new projects and the associated qualification and validation, the necessity arises to carry out risk assessments and analyses in different forms at different times.

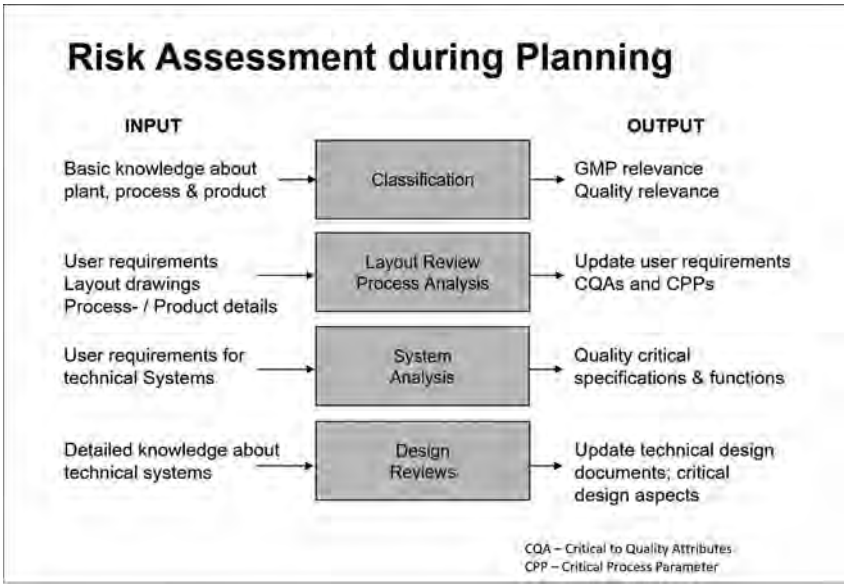
■ Classification

Classification is a first and very early type of risk assessment. Already at the beginning of a project, it can be decided with simple means and logical justifications whether a certain technical system is subject to GMP requirements at all (e.g., a wastewater plant) or whether it is quality-critical in terms of GMP or not and therefore has to be subjected to qualification (e.g., a secondary heating/cooling circuit). It would definitely be exaggerated to use a Failure Mode and Effect Analysis (FMEA) for these decisions. A simple discussion among experts based on simple process diagrams with subsequent documentation of the decision and justification in the form of a meeting note should be sufficient here. This can be created e.g., as an attachment to the user requirement specification. Of course, there are also tools, as far as GMP-criticality is concerned, such as a questionnaire [5] offered by the ISPE in its new baseline document, which is very useful for early classification.

■ Process risk assessment

The process of risk assessment is then a further and deeper level of risk assessment. Here, a distinction should be made between 2 types of processes (here with regard to a typical new construction or reconstruction project): the logistical process and the chemical or physical manufacturing process. In the first case, it makes sense, when user requirements and initial planning documents are on the table, to go with all experts through all logistical processes - i.e. material and personnel flows - in detail along the process flow and check them for risks of contamination and/or mix-ups. Experience has shown that direct documentation in the planning documents combined with meeting notes is efficient and effective. The

■ **Figure 2**



Risk assessments in planning.

results should then be used to update the user requirements. If desired, the meeting points (the discussed risks, e.g., of a mix-up) can be listed in tabular form afterward and, if necessary, evaluated with the help of key figures. It remains to be seen whether this provides more security. At least it makes it possible to classify similar risks in the same way. This type of risk assessment is often referred to as the first "design review", which is certainly applicable and should then be defined as such in the validation concept described at the beginning.

For the assessment of the chemical or physical manufacturing processes, FMEA seems to be more suitable. Here, every single manufacturing step has to be discussed in detail, and especially deviations from quality attributes and process parameters have to be discussed. Actually, this information should already be available at the time of the creation of a user requirement, e.g., from research and development or from test productions. Not infrequently, however, there are changes in scale and equipment during the implementation in a commercial production plant, so that a renewed "tapping" of especially these critical and essential values makes absolute sense. Again, the results should lead to an update of the user requirements.

■ System assessment or technical risk assessment

System assessments or technical risk assessments are carried out based on user requirements and detailed specifications for individual technical systems (e.g., risk assessment tablet press). This is possible at the earliest when the planning is more advanced and the equipment is selected, the supplier and the system type are known. Only then will all the information required for a successful risk assessment be available. This process often takes place in two stages. In the first stage, the assessment is based solely on the user requirement, limited to the level of detail described there. Once the system type and thus the supplier is known, the supplier is brought to the table to finalize the risk assessment that has been started. An absolutely recommendable procedure.

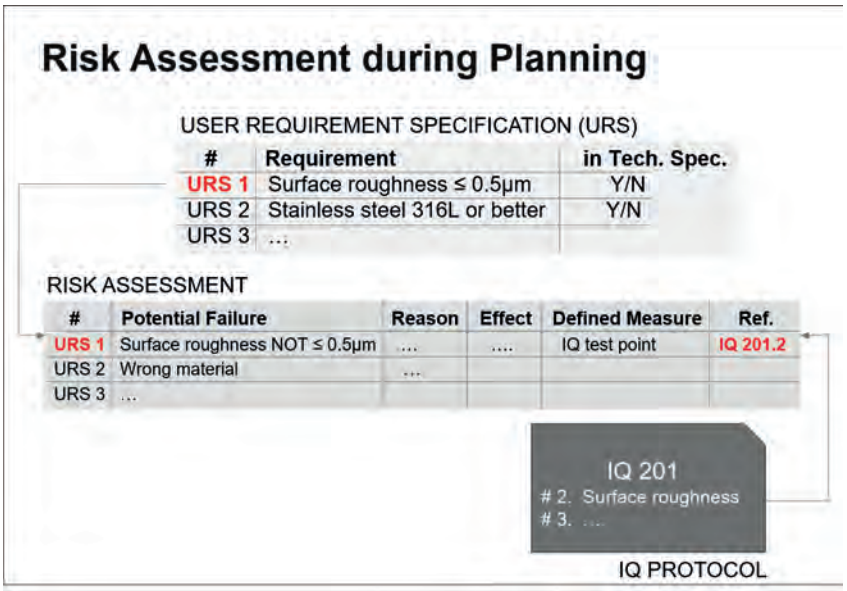
In technical risk assessments, it is important to focus on the specific application and less on technical standards that are already regulated by norms or the state of the art. What risks could there be with regard to the intended use and the mode of operation – e.g., in a water system? Can connected consumers and their planned mode of operation lead to malfunctions – e.g., recontamination in the distribution loop? Can simultaneous excessive offtake lead to backflow in the distributor loop? The fact that high-quality stainless steel with a corresponding surface quality is used as material for the pipe is an established standard and does not have to be questioned and discussed for the umpteenth time.

The technical risk assessment will then be continued in the form of detailed design reviews, parallel to the elaboration in the detailed design. However, this step is already part of the qualification, specifically the design qualification, which will be discussed in the next part of the series of articles.

Further risk assessment concern specific processes such as cleaning, sterilization, or disinfection. Risk assessments are also required in connection with computerized systems and their software. These all assume that the processes to be considered are established and described and are therefore carried out at a rather late stage in the project.

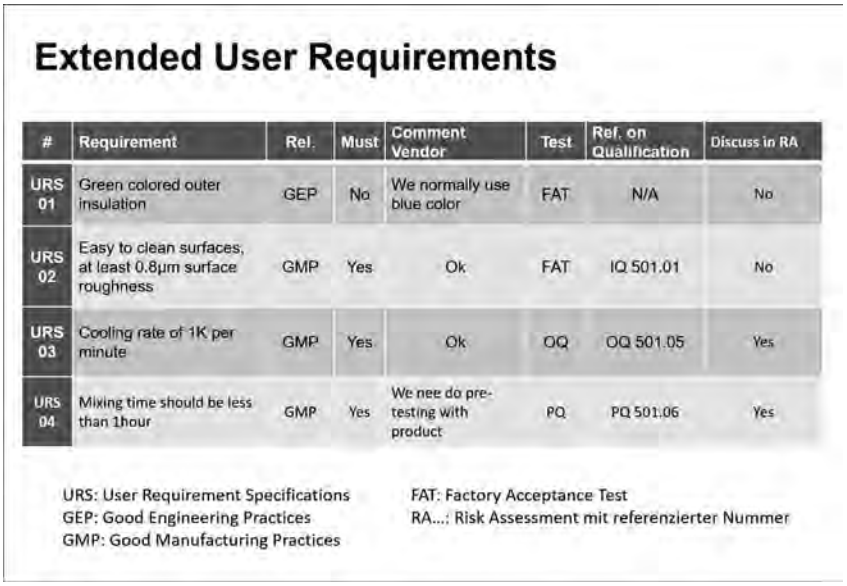
Common to all risk assessments is that they are used to question existing requirements and their planned implementation and, if necessary, to optimize the design with regard to process and product quality. The results lead to the adaptation of the corresponding user requirements and specifications. Likewise, critical design attributes are identified, which must be paid special attention to in the context of the latter qualification. Figure 2 shows again the risk assessments that play a role, especially in validation planning.

■ Figure 3



Traceability.

■ Figure 4



Extended user requirements.

Do Not Lose the Overview (Traceability)

Of course, the requirements and measures defined in the validation planning must not be lost sight of at the end of a project. This is certainly not an easy undertaking in the case of extensive and complex projects. It is important to ensure that all specifications defined in a user requirement are met and implemented at the end of the project. It is also important to ensure that all measures defined in the risk assessments have been implemented. Especially since all defined qualification and validation activities have been incorporated into the corresponding plans and protocols. In order to guarantee this consistency, the tool of the traceability matrix has been established over the last years, in principle one or more Excel tables, which connect requirement points with the points discussed in the risk assessment and checked in the qualification. Figure 3 shows exemplarily such a connection between user requirement, risk assessment, and the qualification plan.

Basically, there is nothing wrong with such traceability, but there is some objection to the way the implementation has degenerated. So, today enormous, unmanageable Excel tables are provided, which do not only contain the points of the catalog of requirements and the risk discussions; meanwhile, even details from technical documents are registered, in order to manage the cross-connection. One can hardly assume that real traceability and transparency are still given here, not to mention the amount of work involved.

It is certainly more sensible and advisable to pay attention to the issue of transparency and traceability already when designing the source documents – the user requirement and/or the risk assessment – and to create the possibility of links by inserting one or more columns.

Figure 4 shows the example of a tabular user requirement, which refers to the appropriate lines of the risk assessment as well as to the qualification items. In the risk assessment itself, a column can be added at the end, in which after implementation of all measures this is confirmed with date and signature and thus the complete processing.

The Complete Package Validation Planning

As with all projects, planning is crucial to the quality of the final result. In case of validation of a pending project, the planning includes the elements:

- Validation concept
- Validation team
- Validation master plan (site/project related)
- User requirements (project, technical system)
- Risk assessments
- Traceability Matrix.

Experience has shown that today most mistakes are made in connection with user requirements and risk assessments, which leads to significant time delays and excessive project budgets. It makes sense to take a closer look at these documents, their meaning, and their design before starting a project. In the above explanations, some hints were given on how this could be done pragmatically. Other models are certainly also possible. In any case, the complete package should be available – starting with new construction or reconstruction projects – at the latest by the end of the basic design phase before moving on to the implementation phase, which will be examined in part 3 of this series of contributions.

LITERATURE

[1] EudraLex Vol. 4, EU GMP, Annex 15, point 1.
[2] EudraLex Vol. 4, EU GMP, Annex 15, point 1.5.
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