Qualification 4.0 – Unused Opportunities

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

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■ Risk assessment – playing with numbers

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

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

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

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

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

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

■ Design qualification – technical understanding is needed

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

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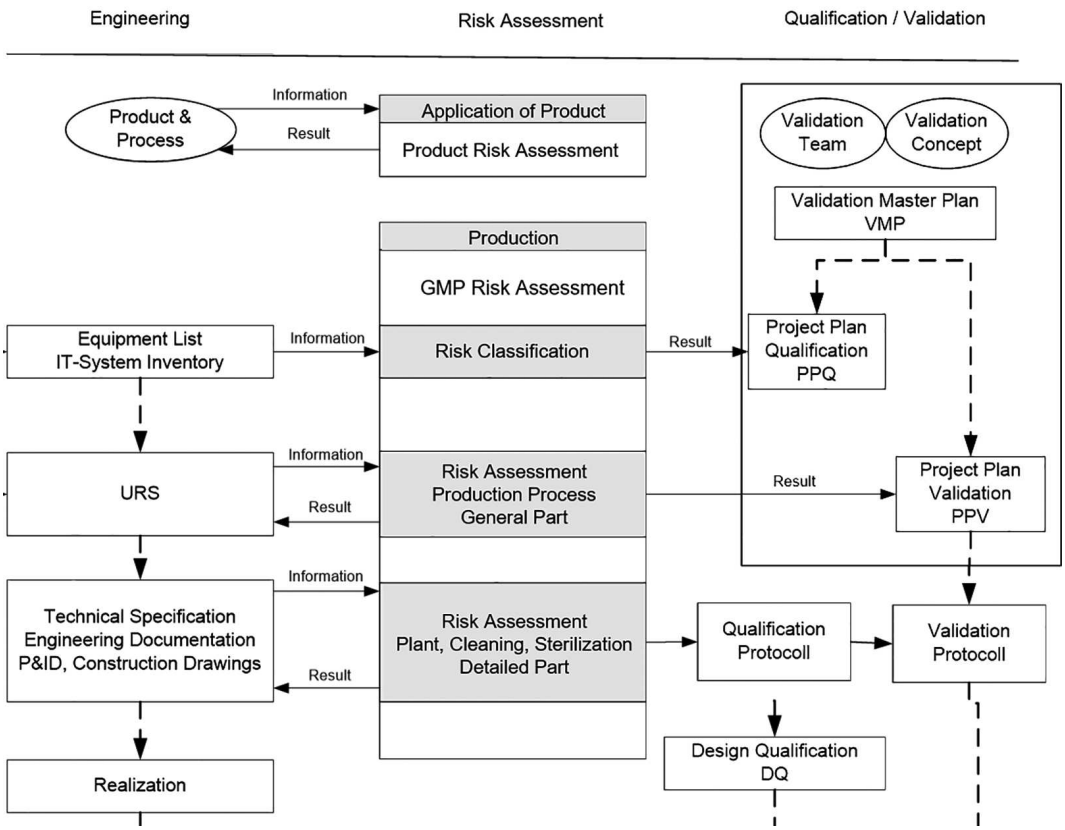
Figure 5



Risk assessment at different levels.

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

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

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

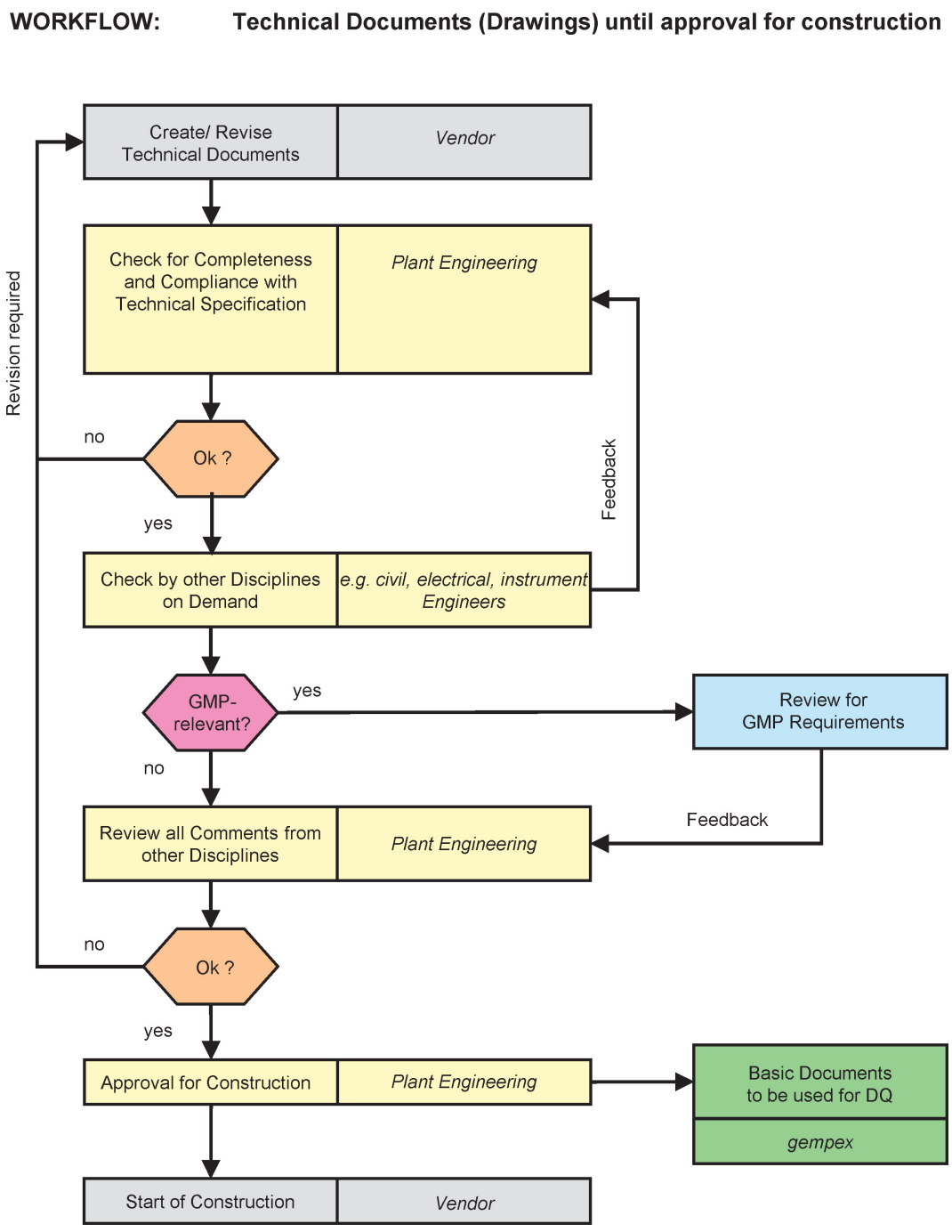
"The next element ... is DQ where the compliance of the design with GMP should be demonstrated and documented. The requirements of the user requirements specification should be verified during the design qualification".

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

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

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

■ **Figure 6**



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

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

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

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

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

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

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

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

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

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

And OQ typically includes:

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

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

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

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

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

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

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

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

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

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

■ How much formalism may it be?

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

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

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

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

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

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

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

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

Qualification 4.0 – what the future holds

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

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

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

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

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

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

Conclusion

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

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

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

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

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

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