Development of requirements to the facilities in manufacturing of medicines

Valery Beregovykh, Moscow Sechenov State Medical University
Oleg Spitsky, Biopharmproject LLC

The requirements of Good Manufacturing Practice (GMP) can be divided into 2 groups, i.e. technical and organizational. The first group relates to materials and products as well as to facilities for medicines production. The term facility usually includes equipment and instruments, buildings and premises, engineering systems and utilities and other infrastructural parts. The requirements to facilities are often considered as one of essential part of GMP guideline basing on the clear principle that good quality of medicines can be achieved by only usage of appropriate equipment, premises, utilities and other relevant facilities. Of course, all the GMP requirements are equally important with no doubt and need to be in compliance for proper quality assurance of medicinal products. However, this focus on requirements to the facilities is not occasional and based on following reasons:

- the most investment costs are required for meeting these requirements
- faults in compliance or execution of these requirements may be hardly (or even impossible) corrected afterwards
- right interpretation and implementation of the requirements to facilities defines execution of the following activities such as qualification and validation, operation and maintenance
- many features of the facilities are critical from the standpoint of impact on quality of medicines
- GMP compliance for facilities is usually inspected carefully

Basic Regulatory Requirements for Quality Assurance

Origin and content of the requirements to facilities in GMP rules is linked to background experience on factors and errors in production of medicinal products leading to their quality deterioration. Such negative impact and errors for quality such as contamination and cross-contamination, mixing and mixing-up can be traceable to practically all the requirements as precaution.

Such requirements as separate weighing room, use of proper materials for equipment parts coming in contact with the product, sinks and drains prohibition in clean rooms, etc. can be listed as examples. Importance and validity of these requirements is obvious and clear with no explanations.

Nevertheless, it is also evident that no guideline or standard can list all the necessary requirements to all possible types of equipment and other facilities. Scope of these requirements can vary depending on types and dosage forms of medicinal products and other factors. For instance, the requirement for assurance of sterile conditions in filling area is obvious for aseptically prepared products but absolutely redundant for non-sterile products. Besides, permanent technological progress leads to development newer and newer features and options for process and engineering equipment and systems that go outside the already established requirements and offer new opportunities for improvement production and quality of medicines. No wonder that many requirements to facilities in GMP rules are formulated such a way to define general or minimal conditions and limits for their parameters and features and need to be specified for concrete application. A requirement for premises to be laid out and connected in a logical order corresponding to the sequence of process operations or a requirement to dedicated facilities for certain products can be given as examples.

Furthermore, general principles should be also taken into account laid down in GMP guidelines in whole for quality assurance and for specific areas in the beginning of each chapter as Principle section. For instance, one of such principles for the facilities is formulated as a requirement for premises and equipment to be designed, constructed, located and operated such a way to avoid cross-contamination and any adverse effect to the quality of products.

From the one hand, this approach lets apply these requirements to various facilities independently on their specific features; but from the other hand, it makes difficult to interpret

them adequately and define whether a GMP requirement should be applied to a specific facility in specific case.

Thus, the above mentioned GMP requirements to facilities can be considered as Basic concept of Quality Assurance of medicines that contains mandatory minimal requirements. It makes GMP rules multi-purpose and more comprehensive but needs simultaneously additional tools and methods for more detailed assessment of the requirements criticality and way for their practical application. The above mentioned filling area for sterile preparation can be illustrative as sample as proper environmental condition in the area is realized many different ways such as:

- open laminar flow A grade in B grade room
- restricted access barrier system (RABS)
- full containment of the area from environment

Cost and complexity level of these solutions differ significantly and an optimal choice should be defined first of all by intended use of the medicine and pertinent requirements to its quality level. It means a tool is necessary to connect technical requirements with intended quality of product. The approach based on quality risk analysis and assessment was identified for many years ago in GMP guidelines as the tool for criticality estimation. This approach was laid down more detailed in the ICH Q6 document Quality Risk Management that is included into Part III of European GMP Guideline now.

Another serious gap of the Basic concept is no link between GMP and engineering requirements that are essential part for any facilities by default. Such requirements embrace design, construction, safe and effective operation, maintenance, and others. Although the engineering requirements are out of scope of GMP rules their identification, compliance with GMP requirements and application can be of the same importance for quality assurance of medicines. They are also essential for safety, health and environment protection.

These two issues demonstrate that the basic concept needed to be extended and developed for its application in practice.

Extended concept of Commissioning and Qualification

Pharmaceutical manufacturers and their associations made significant contribution to the development of requirements to facilities. First line International Society of Pharmaceutical Engineering (ISPE) can be mentioned as it published the Basic Guide for Commissioning and Qualification in 2001 [2]. This Guide offers tools and methods for engineering systems classification depending on their impact on product quality. On the basis of this classification requirements are established and necessary activities in commissioning and qualification are defined for assessment of compliance with engineering and regulatory requirements. The Guide sets out extended concept of requirements to engineering systems embracing all the facilities used in production of medicines; that is why it is widely used in the pharmaceutical manufacture until now.

The main components of this concept are approach to criticality identification for systems based on the impact assessment on quality of medicines, and application of GEP and/or GMP principles depending on the result of the impact assessment. Further important tools of engineering management are described in the guide supporting proper execution of engineering and regulatory requirements, particularly these are:

- preparation of user requirements specification (URS) for the facilities
- execution of engineering and extended design reviews
- planning, execution and documentation of activities on equipment commissioning including FAT and SAT
- description of qualification steps (IQ/OQ/PQ) for critical systems having direct impact on quality.

Identification of available engineering systems and definition of boundaries between them is the first step of the impact assessment. This is an important phase as all engineering systems are embraced in this approach and these systems are often close connected to one another.

Then, impact criteria for each system are checked, the criticality is defined and the reason is documented (see Figure 1).

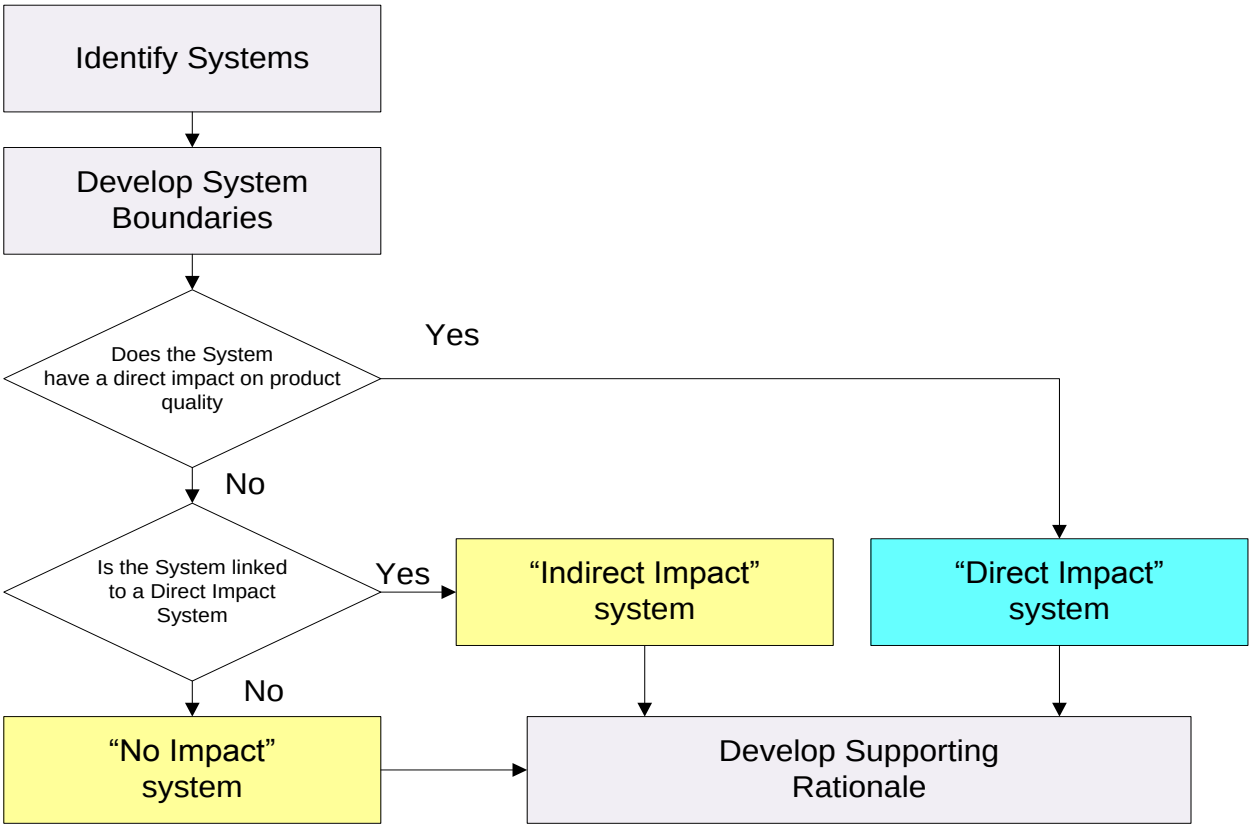

Figure 1: System Impact Assessment Process Overview [2]

Following criteria are listed in ISPE guide for identification of direct impact on quality:

- The system has direct contact with the product
- The system provides an excipient, or produces an ingredient or solvent (e.g. water for injection)
- The system is used in cleaning or sterilizing e.g. clean steam
- The system preserves product status (e.g. Nitrogen)
- The system produces data which is used to accept or reject product (e.g. Electronic Batch Record System, or critical process parameter chart recorder)
- The system is a process control system (e.g. PLC) that may affect product quality and there is no system for independent verification of control system performance in place

For complex direct impact systems an evaluation of criticality of the components may be used, for inclusion of the critical components to qualification scope of the system. The systems and components are divided into groups on the basis of this evaluation. Depending on classification results GEP and/or GMP tools are applied to the systems from different groups as shown on the Figure 2.

Therefore, requirements in the extended concept are established for all engineering systems at the facility on the basis of GEP tools, and for some systems special regulatory requirements (GMP) are added reasoning from their impact assessment on product quality. These requirements should be listed in user requirements specification (URS). Execution of the requirements is checked during extended design review and then, in course of commissioning and qualification of the system.

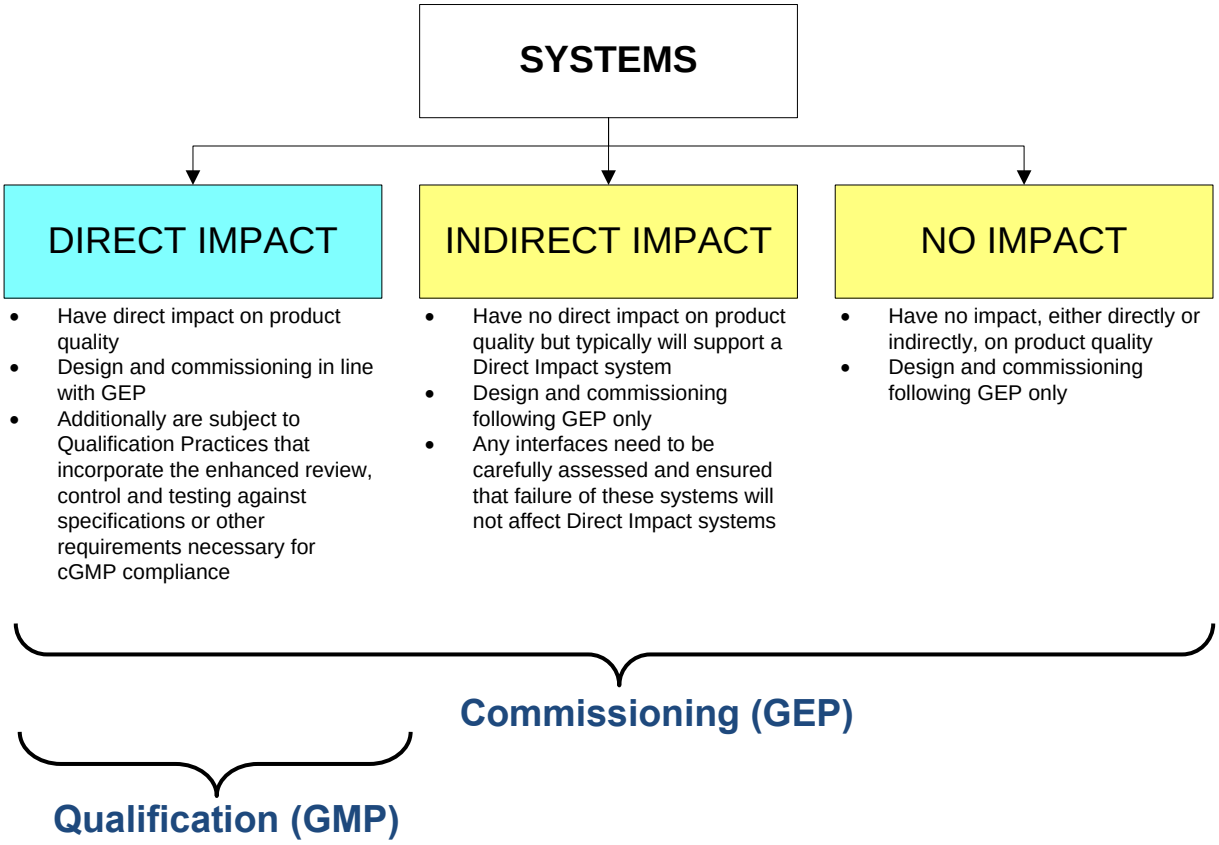

Figure 2: System classification from quality impact

Nevertheless, in spite of considerable progress in the development of requirements the extended concept could not avoid disadvantages complicating and making difficult its application in practice. An uncertainty in system classification may be considered as main shortcoming of this concept. The reason is that impact assessment criteria are based on common experience similar to basic concept. Thus, they are subjective and limited, and link between the systems and product quality is mediate. In practice this leads to displacement of the focus to regulatory requirements; overstating the requirements, scope and documentation volume on qualification; complication planning and execution of engineering procedures and their interrelation to regulatory activities. The concept also does not take into account supplier' experience and competence level which can be used more effective.

Complex Lifecycle concept

Ongoing development of requirements to facilities led to new modern concepts based on:

- consideration of requirements and activities within the facility lifecycle
- identification of their direct links to product quality and intended use on the scientific knowledge and understanding of the process
- taking into account factors and risks affecting the quality.

ASTM E 2500 standard presents this approach where the term 'manufacturing systems' is used for facilities. This standard considers regulatory requirements as a part of general requirements for the manufacturing systems. Both regulatory and engineering requirements are based on knowledge of products and processes for that they are intended (see Figure 3). This approach makes an essential difference between the new concept and other mentioned ones as it makes possible to identify direct link between the parameters of product quality and requirements to the manufacturing system used for the production.

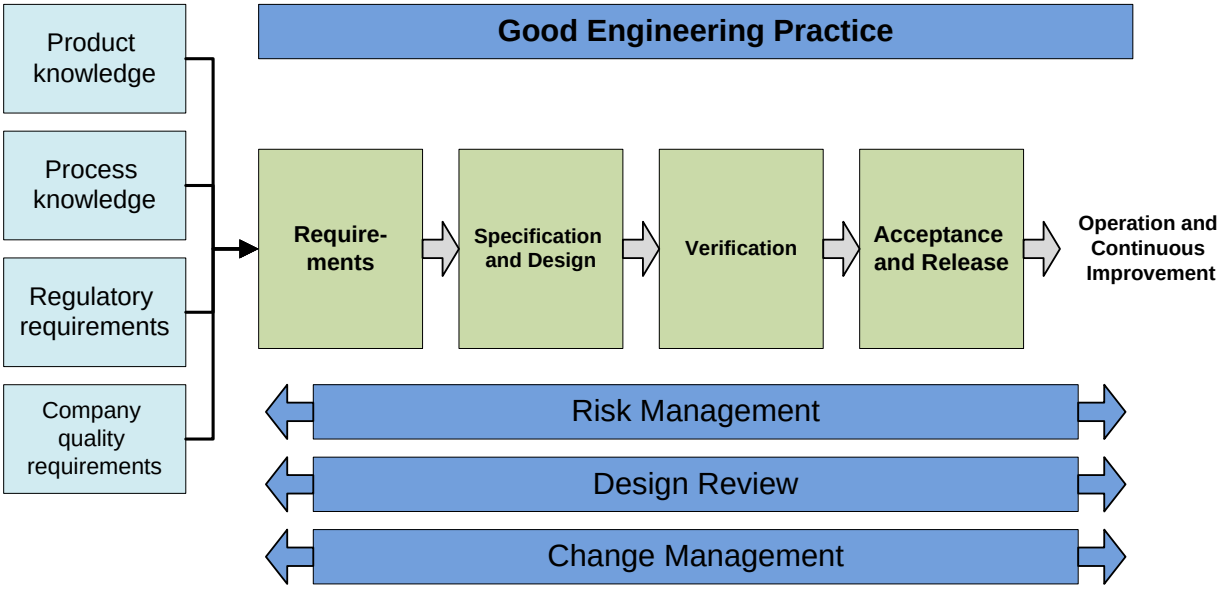

Figure 3: The Specification, Design, and Verification Process [3]

Besides, this concept matches a modern approach Quality by Design (QbD) that establishes quality already on the initial life cycle phase of research and development of medicines. According to QbD the quality should be based on knowledge of product and process by definition of Critical Quality Attributes (CQA) and Critical Process Parameters (CPP) and establishment Control Strategy. The QbD concept is based on ICH Q8 Pharmaceutical Development [4] and targeted to ensure efficient and manageable process in order to obtain proper quality of the product. Similarly, the ASTM E2500 concept is also targeted to design and construction a manufacturing system that provides efficient process management and proper product quality. Obviously, these tasks are interrelated and the only difference is the form of the outcome: material form, if we speak about the manufacturing system, and non-material, if we speak about the production process (Figure 4). In this case we can say the manufacturing system and corresponding production process are adequate as well as the requirements established for them. For instance, the requirement to ensure control of the production process can be realized through determination and implementation of proper requirements to the process equipment, such as in-line detectors and/or a control system for the equipment operating parameters that control the production process.

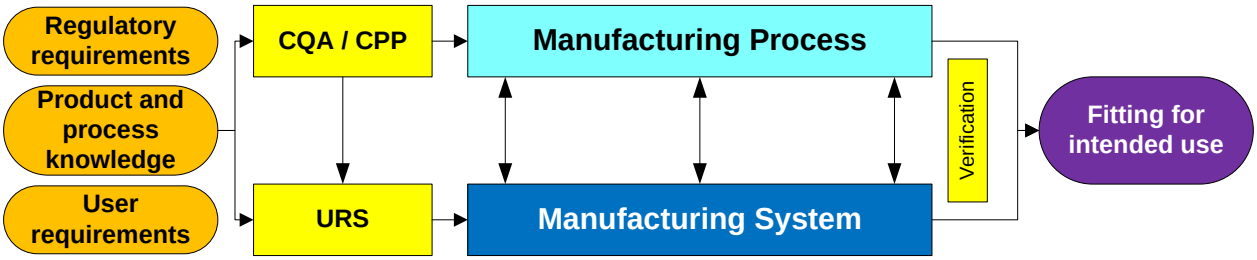

Figure 4: Interrelation of the requirements to manufacturing system and process

So, the **complex concept** outlined in ASTM E2500 includes the ideas of the basic and detailed concept, such as compliance with regulatory requirements, quality risk assessment, utilization of good engineering practice as a basis for all manufacturing systems, change control system, design review. Herewith it represents a totally new level because of the following reasons:

- considering the manufacturing system within its life cycle
- determination of requirements to manufacturing systems basing on the product and process knowledge taking into account regulatory requirements and the Client's (User) requirements;
- manufacturing system approach similar to QbD approach in product and process development;

- refocusing from verification requirement compliance (commissioning and qualification) to the initial phase of determination and formulation of requirements to manufacturing system.

In addition, this concept includes new principles that develop and supplement the previous principles:

- management and participation in all critical activities at different steps of the manufacturing system life cycle by subject matter experts (SME)
- verification of established requirements in order to confirm compliance of manufacturing system with its intended use without specific tests simulating its operation;
- usage of suppliers' documentation for verification;
- continuous improvement of manufacturing systems.

These concepts guarantee predefined efficiency, reliability and predictability of manufacturing system operation and, correspondingly, ensure reliability and manageability of process executed with their help. This results in a more stable functioning of systems and consistent product quality. Moreover, the complex concept includes redistribution of costs and resources by their focusing on more critical manufacturing systems and gives a possibility to use the already available suppliers' information about the systems for requirement verification. This provides cost savings during the system life cycle.

Comparative concepts analysis

Particularities and differences of the reviewed concepts are shown in the table below.

Concept	Basic	Extended	Complex
Document	GMP Guideline	ISPE Guide [2]	ASTM E2500 standard [3]
Requirements scope	Regulatory (GMP)	Engineering and regulatory	Critical for product quality and patient safety
Systems	Critical for product quality	All engineering systems in production	Pharmaceutical and biopharmaceutical manufacturing systems affecting product quality and patient safety
Source of requirements	Accumulated experience from production	Engineering experience	Product and process knowledge Regulatory requirements Client's requirements
Methods for assessment of requirements	Quality risk analysis	Impact assessment on product quality; Project risk analysis	Quality risk management; QbD; GEP; SME (Subject Matter Experts)
Statement of requirements	Not described	User requirements specification (URS)	Specification of manufacturing systems (URS)
Verification of design compliance	Design qualification (DQ)	Enhanced design review (EDR)	Specification and design reviews; supplier qualification
Verification of system fitting to intended use	Qualification (IQ/OQ/PQ)	Commissioning (FAT/SAT) and Qualification (IQ/OQ)	Verification
Execution	Not described	Maintenance service; Quality unit; Project approach	Project approach; SMEs participation

As we can see in the table, the differences of the described concepts refer not only to the identification of requirements, but also to all other activities regarding manufacturing systems. Besides, a life cycle approach to the manufacturing systems leads to convergence and merging of various requirements and methods. So, for example, the basic concept includes the requirements only for the critical facilities affecting the quality. The extended concept covers all

engineering systems but uses for the engineering and regulatory approaches different terminology, measures, documents, tests, i.e. commissioning and qualification plans, protocols and reports; commissioning plan and validation plan; engineering change management and quality change management, etc. The complex concept uses the same approach for all manufacturing systems. However, the scope and content of the measures will depend on the system purpose and criticality.

Analyzing the development of requirements from the basic concept to the complex concept allows us to systematize the approaches to the facilities for production of medicines and use the results of this analysis to find the optimal approach depending on the company purposes.

In addition, the comparison of various facilities requirement concepts allows us to better understanding the activities related to manufacturing systems during their life cycle. For instance, the difference between the equipment and processes tests and checks in basic concept called “qualification” and “validation” and requirement for “verification” in the complex concept as described in ASTM E2500 [3] and FDA guidelines on process validation [5]. Sometimes these terms are mixed and used as synonyms that can be freely applied to identify the same activities or completely replaced by a unified term, for example “attestation”, “tests”, etc. However, there is a principle difference between the terms “validation” and “verification” and this principle is based on different levels of manufacturing system knowledge and understanding.

ISO 9001 [7] provides a requirement to process validation, that validation should be carried out only for specific processes that cannot be verified. Comparison of terms “validation” and “verification” in ISO 9000 [6] does not provide a clear understanding because the difference is only in several words:

“3.8.4 verification: Confirmation by providing objective evidence (3.8.1) that the *established requirements* (3.1.2) have been fulfilled”

“3.8.5 validation: Confirmation by providing objective evidence (3.8.1) that the *requirements* (3.1.2) *dedicated for certain use* have been fulfilled”

The comparison of the “basic” and “complex” concepts helps to understand why a validation of processes and equipment (called “qualification”) is required in the first case, and why it can be replaced by verification in the second case, as well as the difference between these two terms.

As it was above mentioned the basic concept requirements to facilities are “prescriptive” based on the previous experience and defined only in general or as restrictions. They determine a limited range of required parameters and features of the facility that define only its application frames. This set of requirements cannot guarantee the facility compliance with its intended use, i.e. consistent product quality. In this case, the equipment and the process can be interpreted as a “black box”, which outcome cannot be guaranteed based only on the established requirements. This means that a simple check that the equipment is compliant with the established requirements (verification) in order to confirm its utilization according to its intended use is not sufficient and process validation is needed, including simulation tests during intended application of the facility (Figure 5). This means a well-known process run involving the equipment operation, where incoming and outgoing attributes and parameters are checked related to raw materials, products and the process including “worst case” tests.

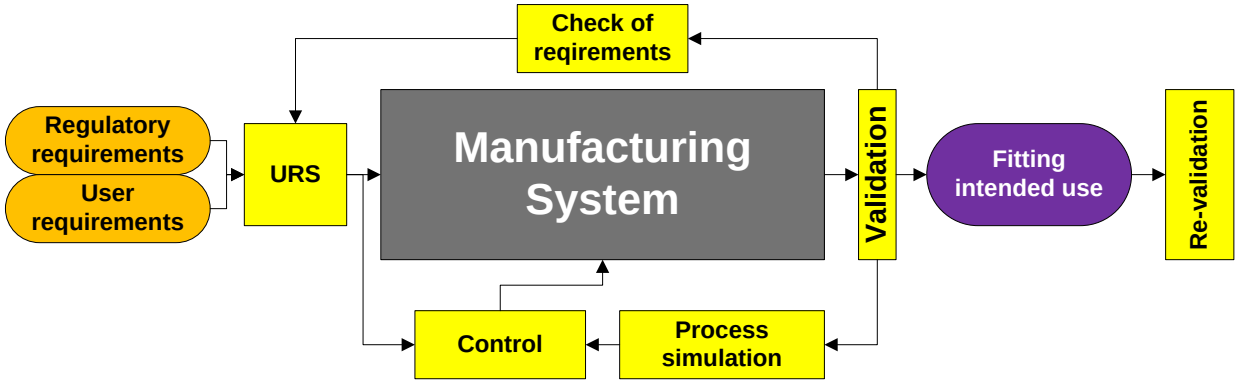

Figure 5. Validation of manufacturing system confirming its intended use

Unlike the basic concept, the complex concept presumes that there will be established a full set of requirements to manufacturing system prior to the design development process, which are determined basing on the product quality attributes, process parameters and include existing regulatory requirements and Client's specific requirements. This set of requirements should be sufficient to determine certain usage of the manufacturing system and identify its "behavior" in the process. It increases "transparency" of the manufacturing system operation and predictability of its outcome (it is not a "black box" any more), when it is possible to say that compliance with the established requirements already guarantees its fitting to intended use and results to desired product quality level. That is why compliance of the manufacturing system does not have to be confirmed through tests with process simulation (validation), but it can be done by only checking compliance with the defined requirements to the system, i.e. verification (Figure 6).

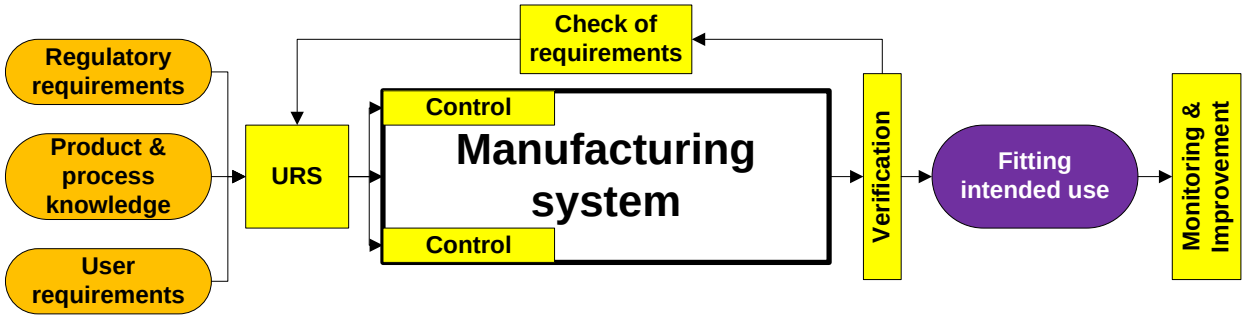

Figure 6. Verification of manufacturing system confirming compliance with established requirements

Therefore, the transition from validation to verification in this case is justified by the increased controllability of the system and process, which is based on the better knowledge and understanding of the product and the process reflected in the requirements to the corresponding production process. This approach provides high reliability and consistency of the equipment operation and process execution and guarantees a certain quality of the product. Verification is supported by collection and processing of statistical data needed for evaluation of tendencies during the life cycle of the manufacturing system and process.

Knowledge and understanding of various levels of requirements to the facilities, their origination and development provides a justified approach to execution of tasks and activities related to the facilities in QA system. Herewith, we should understand that only basic concept requirements, listed in GMP guideline, are mandatory and their fulfillment should be traceable for all critical facilities. However, the optimal internal facilities control system can be provided through various approaches and tools from above mentioned concepts, particularly for organization and execution of the following tasks:

- evaluation and classification of the facilities depending on their impact on product quality;
- development of quality risk mitigation measures to acceptable level through the facilities;
- determination and planning of necessary activities and cost evaluation within the life cycle of manufacturing systems.

These approaches allow us to understand better the intended use of the facilities, necessary requirements to them, to identify the relation between the technical measures and QA activities, to determine the required level of attention to various facilities depending on their role in the infrastructure and their impact on achieving the proper product quality.

References

1. ICH Tripartite Guideline Q9. Quality Risk Management. ICH, 2005.
2. ISPE Engineering Baseline Guide, Volume 5: Commissioning and Qualification. ISPE, 2001.
3. ASTM E2500 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment. ASTM, 2007.
4. Pharmaceutical Development, Q8(R2), ICH Harmonised Tripartite Guideline. ICH, 2005/2009.
5. Process Validation: General Principles and Practices. Guidance for Industry. US FDA (CDER, CBER, CVM). January 2011.
6. ISO 9000:2005 Quality management systems - Fundamentals and vocabulary.
7. ISO 9001:2008 Quality management systems - Requirements.