

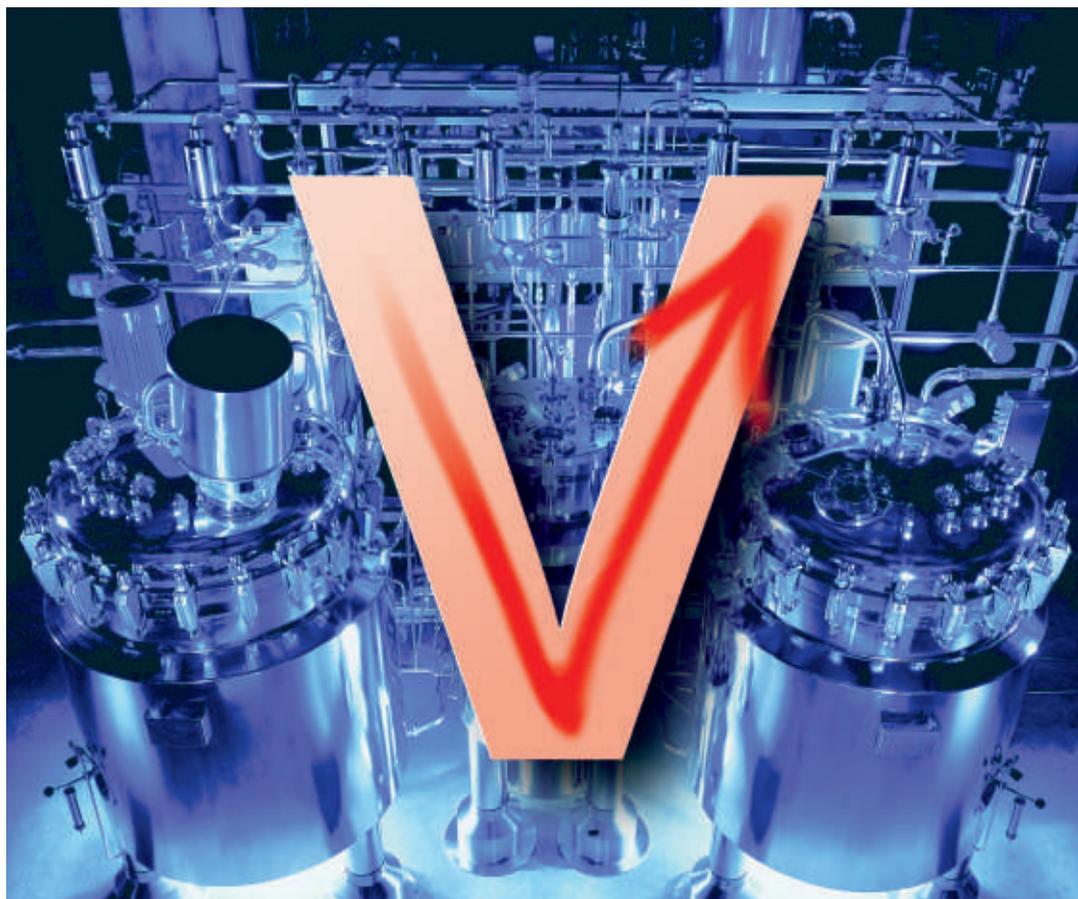
Ralf J. Gengenbach

 WILEY-VCH

GMP qualification and validation of facilities
manufacturing active pharmaceutical ingredients

Principles of Validation

A practical guide



gempex[®]

Table of Contents

3	Principles of validation	67
3.1	Legal principles	67
3.2	Terms and definition	70
3.2.1	Validation	70
3.2.2	Elements of validation	72
3.2.3	Methods of validation	73
3.2.4	Revalidation	75
3.3	Requirements from regulatory frameworks (WHO, FDA, PIC, etc.)	75
3.3.1	FDA requirements for validation	76
3.3.2	WHO requirements for validation	78
3.3.3	PIC/S requirements for validation	80
3.3.4	National requirements for validation	82
3.4	Formal validation procedure	83

3

Principles of validation

3.1

Legal principles

As explained in the previous chapter, the rules of good manufacturing practice address essentially all factors involved in the manufacturing process such as personnel, buildings, premises, equipment, documentation, quality control, etc., that have a recognizable effect on product quality or on its monitoring or verification. However, there is another subject that is not self-explanatory: validation. Those who are involved in GMP nowadays must inevitably confront the subject of validation. In doing so, they will not only recognize quickly that validation is a cost-, time-, and personnel-intensive matter, but they will also be confronted with all the difficulty of obtaining a precise definition and interpretation, as well as the question: “In concrete terms, how do I perform validation?”

Validation as a special quality assurance method is a clear requirement of the GMP rules and nowadays is prescribed by law. This does not only affect the manufacturer of finished pharmaceutical products. The manufacturers of active and excipient ingredients are also subject to validation requirements. From a historical perspective, the subject goes back to the 1980s. Lingnau [60] provides a good treatment of the subject, especially regarding the history of development in Europe. According to his account, the FIP (Fédération Internationale de Pharmaceutique) was already intensively active in the area in 1979 at its conference in Brighton and decided to publish its own guidelines on the subject of validation. These guidelines [61], presented at a conference in Madrid in 1980, were recognized and adopted in 1982 by the Pharmaceutical Inspection Convention (PIC). Initially, the PIC did not work out its own guidelines. According to Lingnau, the core statements of the FIP guidelines are that

- validation is an important contribution to pharmaceutical safety and thus supplements the GMP rules,
- validation is important in the development, manufacture, and control of medications,
- significantly modified manufacture and control methods must be validated,
- validation is the responsibility of the manufacturer, and

- the oversight authority only needs to verify whether the pharmaceutical manufacturer is performing validation according to the state of the art of science and technology.

From these statements, it can be seen that when it came to validation, the initial focus rested on the processes. This is not altered by the fact that the definition of validation issued by the FIP referred to “essential work steps and equipment.” It was not until the “Basic Rules for the Proper Manufacture of Pharmaceutical Products” – PIC Basic Standards – from June 1983 that a distinction was made between the “qualification of equipment” and the “validation of methods” [62]. This distinction is now found in all relevant regulatory frameworks and guidelines.

The legal obligation for validation of finished pharmaceutical products in Germany resulted concretely from the Operational Ordinance for Pharmaceutical Entrepreneurs (PharmBetrV) [63], which in turn had legal force under § 54 Par. 1-2a of the Drug Law (AMG) [64]. The latter had already required in § 5 Manufacture and § 6 Inspection that the processes and devices applied to manufacture and inspection must be validated according to the current state of technology, and the results must be documented. Even the issuance of the new German Ordinance for the Production of Medicinal Products and Active Substances (AMWHV) changed nothing with respect to this obligation. Rather, it dealt with the subject in even more detail. Thus, in § 6 (Hygienic Measures), the admonition can already be seen that the effectiveness of cleaning and sterilization processes must be demonstrated by validation, and likewise according to § 10 (General Documentation), appropriately implemented electronic, photographic, and other document management systems must be validated. The original requirement for validation according to the former PharmBetrV is now found in §§ 13 (Manufacture) and 14 (Verification) of the AMWHV, whereby the scope – with slight restrictions – has already been extended to development products.

A comparable EU-wide requirement has resulted from the “Rules Governing Medicinal Products in the European Community” (Volume 2, “Notice to Applicants”) for the approval of new medications that require the validation of critical processes. However, validation is also a basic condition for the receipt of approval within the US and for export to the US, which is the reason that validation in particular is always a focus of FDA inspections. This requirement for validation is also established in the cGMP rules, 21CFR210/211, which in turn are governed by the Food Drug & Cosmetic Act, Section 501(a) (2) (B) (see also Section 2.3.7.1).

Although the requirement for qualified facilities and validated processes for the manufacture of pharmaceutical active ingredients had already been solidly anchored in the early regulations [65– 67] – albeit in spartan form – in the following years, they increased drastically in importance and occupied more and more space in the published guidelines [68, 69].

Figure 3.1 illustrates this development. For example, the ICH-Q7A guideline, which today is the leading GMP set of regulations for active ingredient manufacturers, devotes a full main chapter exclusively to validation.

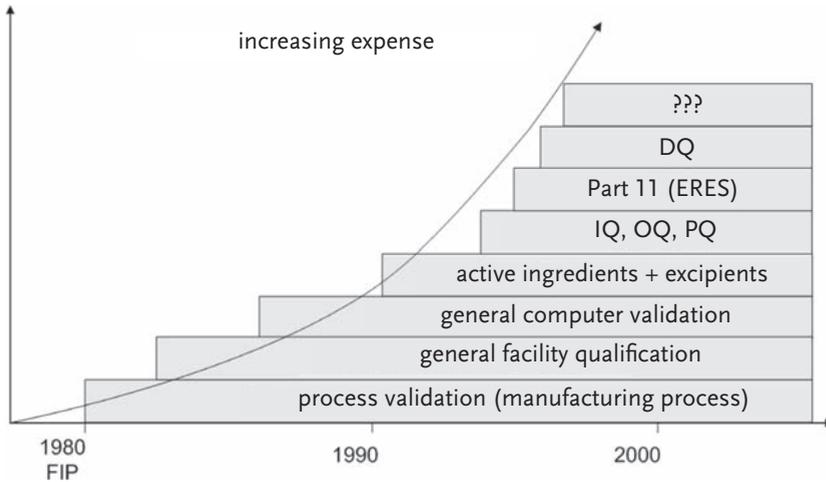


Figure 3.1 Development of validation requirements

Even though for a long time there was, particularly in Germany, no operational ordinance for pharmaceutical manufacturers and thus no connection to a legal basis, the compliance under the “state of knowledge and technology” that the ICH Q7A always represented was at least as binding, so most pharmaceutical manufacturers also devoted themselves intensely to the subject. For delivery of active ingredients to the US, the cGMP rules according to 21CFR 210/211 were and are in force anyway, so in that case, even when other guidelines for inspections were applied, validation was, and still is, always required by law. This became clear through the behavior of the FDA, which in the period from 1992 to 1999 granted a transition phase especially for pharmaceutical manufacturers, during which it was sufficient to present inspectors with a plan for scheduled validation [70]. Today, with few exceptions, it is expected that even older facilities are qualified and all processes applied are validated.

For excipient manufacturers, validation was not clearly recognized as a mandatory consequence of the relevant GMP regulations. However, today the GMP rules of the WHO [71] as well as those of the IPEC (International Pharmaceutical Excipients Council) [72] clearly express that validation is required. While they do not explicitly mention the qualification of facilities, process validation requires a qualified facility, so qualification should be assumed to be self-evident.

It can be said in summary that validation as a method of quality assurance is a central and essential component of the GMP requirements, that validation is required by law, and that it must be implemented by manufacturers of active ingredients, excipients, and finished pharmaceutical products alike. The importance of this subject is a result, in part, of the fact that numerous groups of experts and professional associations have published a full set of further-reaching instructions and guides exclusively in the area of validation. These will be dealt with in more detail in the following chapters.

But what, in concrete terms, does “validation” really mean?

3.2

Terms and definitions

3.2.1

Validation

To understand how to approach validation, it is important to first comprehend in concrete terms what is behind the concept. It is frequently misapplied, even today, so the following discussion will explain in more detail according to the official definitions.

One of the best known definitions comes from the US FDA from 1987. It defines validation as [73]: “documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.”

A further-reaching interpretation that already considers equipment comes from the EU from 1992 and defines validation as: “proof in accord with the principles of good manufacturing practice (GMP) that procedures, processes, equipment, materials, operations, or systems actually lead to the desired results.”

These definitions precisely meet the meaning of the term “validation,” but even after repeated intensive reading, they are often hard for the novice to understand, so the term should be explained with a concrete example.

Sample case: A company buys a new mixer for homogenizing solids. The sequence is clearly regulated. After determining the specification requirements that result from experience with the existing process, proposals are collected and compared, and after one is awarded, the order is initiated. The mixer is planned, built, delivered, and constructed, and is ready for installation. However, before the mixer begins its actual operation, initial test drives are, logically, conducted. Model substances or the actual product are used and a series of samples are withdrawn and analyzed in order to test the homogeneity of the product exiting the mixer. If, after optimizing all parameters (e.g., stirrer frequency, intake), a homogeneous product is obtained, then in the normal case the test will end and the mixer will assume its routine operation.

This is not the case with a GMP operation when the mixing procedure is relevant to quality and must be validated. This is where the real work begins: setting up a program with a precise display that confirms (proves) that the mixer is actually reliable and functions as planned. For example, a product with a demonstrably high degree of inhomogeneity is fed into the mixer and a withdrawn sample shows that, as expected, the parameters previously selected cause a homogeneous product to emerge. The program is repeated many times in order to demonstrate its reliability, i.e., its reproducibility. In addition, more samples than usual will certainly be drawn in order to persuade the last skeptics of the effectiveness of the apparatus. The entire sequence is scheduled in advance in writing, and the results are logged precisely and compared with the previously specified target values – the acceptance criteria. The procedure concludes with a comprehensive report. The mixer is “validated.”

Which individual actions were done? Three important phases must be distinguished:

1. An attempt was made to install a mixer that corresponded to the specifications as closely as possible (production of quality).
2. It was verified to what extent the mixer actually brings about the desired effectiveness (verification of quality = testing).
3. After successful verification, it was proven and documented that the mixer really does bring about the desired effectiveness, time and time again (demonstration of quality = validation).

In the case of validation, one speaks of documented evidence and not of verification; that is, it is assumed that within the framework of previous testing, a positive result has already been determined and the proof is now to be obtained again as additional security that this result can be upheld on a lasting basis. This can occur based on the results of the tests themselves, such as when the test results permit no other conclusion. Thus, a system can be considered fundamentally leak-proof when, in the context of preparing for installation, tests have already yielded this result and the test conditions corresponded to, or at least covered, the conditions under which the facility would later operate. For the documented proof, it then must merely be ensured that the leak-proof tests were completely performed, that the results were acceptable in every case, and that sufficient records – e.g., with regard to measurement results – exist. However, additional worst-case considerations or further experiments may also be required. For instance, the results from the sample withdrawal at the mixer outlet say nothing in themselves about the effectiveness of the mixer if it was already filled homogeneously with product. Validation surely requires a procedure in which it is initially filled with an inhomogeneous product.

A further characteristic of validation is that the previously formulated specifications or acceptance criteria must be fulfilled in every case in the course of producing documented evidence. This requirement confirms again clearly that validation has nothing to do with testing, since acceptance criteria only exist when they have been determined in the context of previous tests.

Ultimately, “documented evidence,” that is, of validation plans and validation reports, is the subject at hand. This is clearly additional documentation specifically for a GMP facility, which later becomes especially important for the operator, since he or she must use these documents to prove to customers and authorities its validity, meaning the reliability of its processes and systems. It is not enough here to point to a specification-compliant product coming from the facility. Validation is clearly more than that.

In summary, one can define validation simply as “documented evidence that shows that something is the way it is supposed to be according to specifications.” Hence, this documentary evidence is clearly more than a simple test.

A vacuum cleaner salesman who pours soot on the Persian carpet of the critical housewife in order to demonstrate the effectiveness of his vacuum cleaner would do well to perform a validation (proof) rather than a test for which, under some circumstances, he may not even recognize the result.

3.2.2 Elements of validation

If one concentrates from the beginning primarily on processes that are reproducible and controlled, which is to say validated, one soon recognizes that validation only leads to reliable and meaningful results when the equipment that is used for each process step functions technically flawlessly and is in proper working order, which is to say it is qualified. Thus, with a look at technical equipment, the concept of validation is expanded by the concept of qualification [74].

“Validation” is often used nowadays as an umbrella term for all qualification of technical equipment and validation of processes. However, the qualification of buildings, premises, and pieces of equipment including support and auxiliary equipment (e.g., water systems) should be distinguished from the validation of manufacturing, cleaning, and analysis processes. In the case of computerized systems (e.g., distributed control systems, ERP systems, document management systems), the term “computer validation,” among others, is used to mean, in general, the qualification of hardware and the validation of software.

Especially in connection with investment projects for new construction or rebuilding activities, the term “validation project” is also frequently used, which then, depending on the project scope, includes either all validation elements or only a few. Figure 3.2 illustrates these connections.

The qualification of technical equipment can be further divided, in turn, into the individual elements:

- DQ = design qualification, as documented evidence that, in particular, GMP-relevant requirements have already been considered in planning a system or an item of equipment.
- IQ = installation qualification, as documented evidence that the system or the item of equipment has been delivered, installed, and connected according to the previously established specifications.

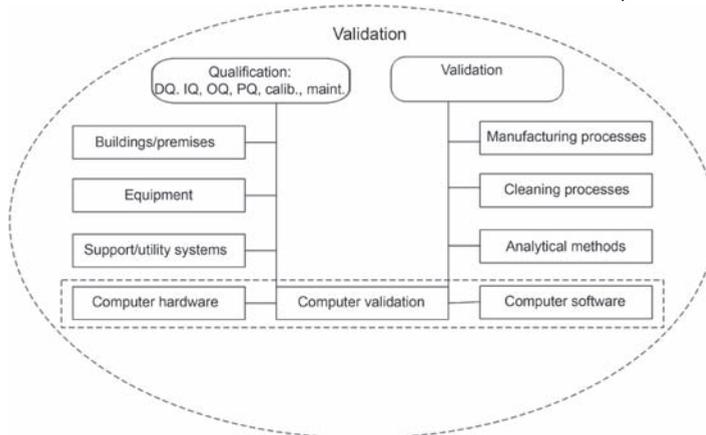


Figure 3.2 Elements of validation

- OQ = operational qualification, as documented evidence that the system or the item of equipment functions reliably in the entire work area, adhering to the previously specified threshold values.
- PQ = performance qualification, as documented evidence that the parts of the system that are recognized within a risk analysis as particularly critical to quality in the entire operating area fulfill the previously established performance requirements.

Activities in connection with the first calibration of measuring devices relevant to quality and the first performance of a maintenance program on items of equipment are formally often assigned to qualification. By contrast, the repeated execution of calibration and maintenance measures is categorized as upkeep of the system, where these measures principally serve to maintain the validated or qualified condition of a system.

3.2.3

Methods of validation

Depending on whether or not the validation activities have been successfully concluded by the point at which a product is brought to market, the following fundamental validation methods can be distinguished:

- Prospective Validation

The qualification and validation activities are performed with regard to a new product, a new process, or a new or rebuilt facility. They must be concluded successfully in a provable (documented) manner before the corresponding product can be sold on the market. The tests necessary for validation are currently scheduled and performed, and the results are evaluated. This type of validation is nowadays preferred by the supervising authority and requires a timely start and good planning in order to avoid time delays and hence losses in profit when bringing the product to market.

- Retrospective Validation

The product has already long been manufactured in an existing facility according to an established procedure and sold on the market. The validation focuses on data obtained from past production. In general, this involves, depending on the relevant regulatory requirements (EU or US), evaluating data from about 20–30 successively manufactured production batches, which in the case of continuously functioning production operations means that batches must be defined based on a fixed production duration (e.g., one day). However, a retrospective validation is only possible when, within the timespan considered for the evaluation, no significant changes to facility, process, specifications of raw materials and/or products, etc. have been made. Retrospective validation is nowadays only tolerated for those products and processes that were not known beforehand to fall under GMP requirements. This occurs, for example, when a chemical company has been manufacturing a product for a nonpharmaceutical purpose for a long time and now, based on a customer request, demonstrates a new application area in the pharmaceutical domain.

– Concurrent Validation

In some cases, it is not possible to conclude validation before the product is sold on the market, either because too few batches have been manufactured or because too much time elapses between individually produced batches, and the product is not sufficiently stable under storage, meaning that the product from the validation batches would spoil by the time it was actually sold. In these cases, the product manufactured during the validation passes can already be sold, even when the validation has not been fully concluded. The requirement is that the quality of the product is ensured by additional in-process controls, which in this scope need not be maintained after successful conclusion of validation. Here, the concrete method of approach should always be coordinated with the customers accepting the product or even the responsible authorities.

Regardless of the approach that is ultimately chosen, the product manufactured in the course of validation can be sold once validation has been successful. The validation batches themselves must not be discarded. The important thing, however, is that the product quality is ensured and tested.

Even when the individual methods are logically represented as above and can be clearly distinguished from each other in their approach, the reality in many cases is quite different. Thus, it is not uncommon in the pharmaceutical field for projects to already be implemented, i.e., facilities have been built and/or the manufactured product has already been shipped, without the associated qualification and validation having been formally concluded. The reasons can vary widely. One of the most common reasons is that only a negligibly small quantity of the product manufactured at the facility is delivered to the pharmaceutical domain, while most is sold as “industrial goods.” The GMP requirements then usually take a back seat to the other requirements, and the priority shifts toward production.

Such cases, which fortunately are becoming more rare all the time, cannot fundamentally be called retrospective validation, even when the validation activities follow. Nor is it either appropriate or legal to first build a facility, then produce 20–30 batches, and finally, based on their evaluation, perform a “simplified” retrospective validation. Rather, it is the responsibility of the director of manufacturing and the relevant quality unit to ensure that the missing activities are made up as rapidly as possible and handled using the same methods as a prospective validation. Unfortunately, the reality is often that there may be restrictions, since certain actions can no longer be made up, or documents can no longer be procured. Thus, a prospective approach, since it has been planned and test parameters have been established from the beginning, has a significantly greater depth of focus with respect to quality assurance than a retrospective consideration, which will be explored more closely in chapter 4. It would be best in such cases, which can unfortunately not be prevented, if the product then manufactured were exclusively declared as “technical goods” or if this were indicated to pharmaceutical customers. In no case, however, can a pharmaceutical end-product reach the end consumer without these quality assurance measures being performed on the medication.

3.2.4

Revalidation

Validation, including qualification, consists of activities that essentially serve to bring facilities and processes to a secure and reliable condition, and to keep them there. It can be seen that these are not one-time activities that are performed, documented, and then finished once and for all. Rather, there is a legal requirement to constantly monitor the valid state once it has been reached and to maintain it over the lifetime of a facility or process. Thus, one also speaks of the lifecycle of a facility or of the lifecycle model of validation.

A core element of sustaining the valid condition is the change control procedure, which is described in detail in chapter 7. Changes are formally required and evaluated with respect to their effect and the measures that result. For critical changes, revalidation is almost always one of the measures that must be cited. According to FIP [75], a revalidation is strictly required for, e.g.:

- changes of composition, process, or quantity,
- device changes that influence the process,
- use of new devices, and
- changes to process parameters.

Furthermore, revalidation is also required at regular intervals for critical equipment (e.g., sterilization equipment).

Like prospective validation, revalidation is performed according to the entity. This means that in most cases, validation must be successfully concluded before the product from the modified process can be sold. An exception is periodic revalidation, which, like a maintenance process, serves to aid long-term monitoring.

Regardless of whether the “revalidation” is based on changes, the trend even for agency inspections is moving increasingly in the direction of cyclical, change-independent “revalidations.” This is easy to understand, but it is known that process facilities are highly complex and living, which is to say constantly changing entities, and that even the best change control procedures are hardly in a position to formally encompass each change and to assess and evaluate it over the prescribed course. Over time, this results in many “unnoticed” and “creeping” changes, which can only be grasped globally within a routine “revalidation.” Not without reason, the FDA requires an update of the relevant piping and instrumentation diagrams.

3.3

Requirements from regulatory frameworks (WHO, FDA, PIC, etc.)

In section 3.1, the legal principles and binding nature of validation was discussed, as well as the fact that over time, requirements regarding the details of performance of validation, including qualification, have grown significantly. This is seen not least in the increasing number of official (i.e., published by authorities or corresponding industry associations) guidelines and regulatory frameworks.

In dealing with the subject of validation, one cannot avoid dealing with the official documents that handle this specific subject. One must know what is essentially being required by the authorities or the recognized associations. It is of little use to offer the excuse that they offer no practical instructions for individual implementation. In all cases, they contain the basic philosophy and understanding of authority and industry representatives, the general requirements regarding what must be observed, and notes regarding the principles regarding approaches and minimum requirements. For this reason, this chapter also lays out the most important official documents exclusively oriented toward validation and qualification, and their meaning and core requirements are briefly addressed. Emphasis is placed on discussing the generally applicable guidelines and regulatory frameworks relating primarily to validation, while subject-specific documents (e.g., guidelines on validation of cleaning or IT) are dealt with in other places.

3.3.1 FDA requirements for validation

In addition to the FIP guidelines discussed above, the “Guideline on General Principles of Process Validation” [76] published by the FDA in 1987 might be the best known and also the oldest document on this subject. However, as can be suspected from the title, the subject of process validation is in the foreground; hence, technical qualification is less emphasized. It applies to human and animal medications and to medical devices and products. Currently, the FDA is working on an appropriate revision, which is surely long overdue.

The guidelines already specify the most important definitions, some still valid today, especially those regarding validation. The interesting thing is that at that point in time, a distinction was made between the elements of an “installation qualification (IQ),” a “process performance qualification,” and a “product performance qualification,” where the last applied only to medical devices and products. That means that this guide still heavily mixes the concepts of qualification and validation. At its core is the clear statement that for quality assurance, an inspection of the final product is not sufficient and further measures – namely validation – are required. This is demonstrated by simple examples. Even the statement “quality, safety, and efficacy must be designed and built into the product... quality cannot be inspected or tested into the finished product,” which is frequently cited in the literature, comes from this document. Thus, validation is fundamentally considered the key element of quality assurance, although this does not in principle exclude final product inspection.

A fixed requirement is the production of a detailed, written validation protocol that describes the procedure for validation, including planned tests and data that should be gathered. It is heavily emphasized here that such validation runs should fundamentally consider the widest range of variation that result from operating techniques for facilities at the threshold of the determined parameters. This requirement, which has also become known as worst-case validation, has been extremely

controversial up to the present day, but it is persistently demanded by the FDA again and again in inspections. Even the statement from the FDA, contained in the guide, that the individual systems involved in the process must be validated individually when the final product and/or the in-process controls are not sufficiently meaningful is no longer current to many. A risk analysis regarding validation may not have been explicitly mentioned back then, but it does discuss the necessity of targeted and well-documented product and process development, which is considered the foundation of successful validation and should be ensured by a change control procedure with respect to more extensive changes, such as those pertaining to product specifications.

The assurance of proper functioning of technical equipment is required first in the sequence, as is still common today. Here the term “IQ” encompasses almost everything that today is divided into “IQ” and “OQ,” and sometimes even “PQ.” The critical items of equipment that generally can have an effect on product quality are already discussed, as is calibration including adjustment and maintenance. Execution and documentation of a study with a look at the requirements for the previously mentioned points are expected in particular. This should always be done using the concrete process and the planned products (e.g., which maintenance and calibration requirements result depending on the concrete process and the concrete product). The evaluation of a facility on the basis of its demonstrated functionality in conjunction with another manufactured product is not accepted. It is also mentioned that inspections should be repeated multiple times wherever this makes sense, with a footnote referring to the now widely-disseminated number “3,” though this is deprecated again and again by FDA inspectors themselves as a so-called “mystic number” and hence one that may or may not be correct, when, for example, more runs are necessary to reliably confirm reproducibility. At the end of the technical section, the discussion, interestingly, goes deeper into the meaning of replacement part lists and the necessity of testing these thoroughly within the context of qualification in order to ensure that there is no danger to products from a false replacement part.

Not much more is written specifically on the actual “process performance qualification” or the “product performance qualification,” which logically follows the “installation qualification.” “Intensive testing,” especially the testing of worst-case conditions, is emphasized once more, as is the fact that, in principle, all processes that are validated must be described and specified in detail. The repetition of validation runs is also emphasized. The guide concludes with the subjects of revalidation, documentation, and retrospective validation. With a look at documentation, it is made clear once more that here a system must exist that provides an inspection and a formal release of the validation documents.

In summary, it can be said that while the relatively thin document presents no details regarding execution, it does display many interesting aspects and base requirements from the point of view of the authority; these are still valid today, without restriction.

An additional, quite interesting, FDA document, is the “Validation Documentation Inspection Guide” [77] published in 1993; however, it was never officially

distributed, hence it will only be briefly discussed here. It was essentially initiated and prepared by Ronald F. Tetzlaff, a former FDA inspector. Here the problems relating to the different meanings of the words “validation” and “qualification” are discussed and an attempt made to differentiate between them more precisely. However, in doing this, the difference between qualification and validation is never explicitly mentioned, though various meanings of validation are. This document thus distinguishes between “what” is validated (e.g., auxiliary processes or production processes) and on what basis it is validated (based on manufactured batches or proof of a process being monitored). The eight validation elements discussed are interesting and helpful:

1. goal definition,
2. test execution,
3. recording of results,
4. ensuring the accuracy of the values,
5. comparison with specified values,
6. summary,
7. release of results, and
8. periodic review,

which will here be described as minimum requirements for an acceptable validation sequence. This guide subsequently analyzes these elements in detail, with a special emphasis on the formal requirements regarding the individual documents to be produced. The requirements that should be named here are the use of previously determined layouts, formal review and formal approval with signature by responsible individuals, the need for clarity in the description of content, and the preferred use of flowcharts and graphics in order to simplify the representation of procedures. Even though these are not solid requirements, due to the fact that they were never published, it is still very valuable to be able to understand the thoughts of a long-time FDA inspector. The document concludes with helpful case examples that show which errors – in the opinion of the inspector – appear often in practice.

With regard to the FDA, there is still one last, equally interesting document to be named, the “Compliance Policy Guide, CPG 7132c.08” [78], in which the FDA describes exactly which requirements there must be regarding validation and validation batches for finished pharmaceutical products as well as for the ingredients they contain, so that a finished pharmaceutical product can receive a permit. This underscores yet again the importance of validation for approval in the US. This document says nothing about the content or performance of validation.

3.3.2 WHO requirements for validation

The WHO has compiled its perspective on the theme of validation in the WHO GMP Main Principles for Pharmaceutical Products, “Validation of Manufacturing Processes” [79]. Altogether, this document brings together the extensive knowledge of numerous national and international authorities, including the EU, the US, and

various recognized expert authors, who are mentioned in the bibliography section in a long list. The validity extends to finished products as well as to the ingredients they contain.

It is particularly worth emphasizing the introductory statement, in which the WHO distinguishes in principle between critical processes (i.e., relevant to validation), and noncritical processes, but stresses in a separate clause that, based on previous experience, it basically makes sense for all individual processes involved in the manufacturing process to be subjected to validation. It also emphasizes that validation of a process or a procedure cannot fundamentally improve it, but can only confirm that it runs as desired (or not) and that validation must really always take place at the conclusion of development or a scale-up process. Risk analysis is clearly presented as an important instrument, but its execution is not further described. In addition to giving reasons and advantages that fundamentally argue for validation, it goes into the different validation types (prospective, retrospective, concurrent, and revalidation). With regard to revalidation that is to be carried out in a change-dependent or routine manner, the guide shows a few vivid and easily understandable examples.

Procedure validation takes a prominent role in this document, as it does in the FDA document. In the chapter “Conditions for Validation,” though qualification is mentioned and, interestingly enough, the subject of formulation, meaning the combining of excipient and active ingredients, is addressed, no comments on the actual content or even recommendations for implementation are given. Procedure validation concentrates in particular on the four following approaches or methods: intensive product analysis, process simulations, worst-case studies, and parameter monitoring. These methods are addressed and described in detail. The same is true for the approaches to retrospective validation, the necessary series of 10–25 batches to be manufactured and evaluated, and the trend analyses; emphasis is placed upon the fact that sterilization processes cannot, fundamentally, be retrospectively validated.

For organization of validation, the WHO also recommends the typical validation team, assembled from the widest variety of technical entities, but also speaks of a validation officer. The guidelines conclude with a proposal for a table of contents for an all-encompassing validation plan. Installation qualification appears explicitly here, too, although it was not previously mentioned, with a brief and pithy reference to “drawings.” Whether this means that the focus of IQ should be inspection of drawings is up to the reader. The section “Qualification protocol/report” does not quite foster clarity, since the further subdivision mentions points that one would expect for procedure validation, but not for qualification. In any case, the appended collection of cited guidelines, regulatory frameworks, and literature is valuable.

3.3.3 PIC/S requirements for validation

The PIC/S Guidelines PI 006 “Recommendation on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation” [80], first published in 1999 under the number PR 1/99, surely describes the theme of qualification and validation most comprehensively. Among all official guidelines and regulatory frameworks, this is surely the document that is most worthwhile to read if one wants to learn a little more about the perspective of the authorities about the individual subjects.

However, one cannot expect that this document will also provide detailed and concrete implementation proposals. To repeat the words of Theo Bergs, a Dutch agency representative and coauthor, at a congress in Berlin, “It is clear... that one will never be able to please industry in any case. If one writes a guideline in too much detail and gives a step-by-step introduction, constraints that apply to some companies will immediately be used to attack it. However, if one keeps the document rather open and offers the necessary room for interpretation, the document is castigated for its lack of depth and the perhaps somewhat fuzzy-sounding formulations, although the shortcoming may have more to do with the ability to contribute the necessary interpretations on a case-by-case basis.”

If one leaves policy aside and considers the contents, one first discovers in this document a clearly structured breakdown of the entire subject, a description of the intersection of the terms “qualification” and “validation” (double meaning of “validation” as an umbrella term and as a term for procedure-specific demonstration) and a clean presentation of the subissues of installation qualification and functional qualification. A vivid figure, which serves to represent these concepts in their totality and in their interaction, rounds out the overall impression of a trail-blazing, well-thought-out document on the subject.

The scope of this guide, which is to be seen as a recommendation, extends to active ingredients and finished pharmaceutical products, where the recommendation-oriented character of the document and its status as “state of the art and technology” are heavily emphasized in the introduction. That means that the user must not necessarily follow the prescriptions it contains if he or she encounters better ideas, but can be assured that using those prescriptions will fulfill the currently applicable minimum requirements for such a system.

According to the introductory definition of all terms – DQ, IQ, OQ, PQ, and procedure validation – the guide deals again briefly with the fact that due to the variety of situations, each company must regulate in writing, for itself, the details, meaning the concrete validation concept, described in the validation master plan; that substantial attention should be directed toward good, thorough documentation; and that one cannot regard the entire qualification and validation program as a “one-time event.” The necessity of the change control procedure and the fundamental lifecycle model are thus discussed. With regard to responsibilities and orga-

nization of a validation project, the PIC/S puts forth the same requirements as the FDA and the WHO, but clearly puts the production manager and quality manager in the foreground as responsible for implementation.

Farther along in the guide, the validation master plan (VMP) is emphasized as the central and strategic document and reviewed with regard to the items it must contain. In addition to recommending which subjects should be handled, and to which level of detail, notes are also given that this must not necessarily be a “closed” document, but rather that one can and should make use of the possibility of using references to go back to existing documents and descriptions.

Installation and functional qualification are then first addressed in more detail with relation to content. Correct installation, in accord with installation plans; directions for calibration, maintenance, and cleaning, set down as tested and approved procedural instructions; the fulfillment of all functional requirements under normal- and worst-case conditions; and the specific training of the operating team together with documentation of the training are identified as the four most important fundamental principles of qualification.

According to the perspective of the guide, areas of emphasis for installation qualification, in addition to a cleanly planned approach following the principles of good engineering practice, are identification of calibration requirements, tests to be conducted at the manufacturer and on site, and the procedural instructions for maintenance and cleaning, mentioned previously, which are to be produced in this stage as a draft. It is explained that while tests performed at the site of the manufacturer of a given item of equipment reduce the effort of installation qualification, they cannot completely replace it. In addition, in this chapter, the subject of change control is first introduced with the section “Planning and construction of facilities.”

Functional qualification, here equated with commissioning, should direct the focus of attention, following further explanations, toward critical functional parameters for the facility. After successful calibration, these functional parameters should be reviewed in tests that were previously established, documented, and approved, and the results should be compared with fixed acceptance criteria. The review of upper and lower thresholds and particularly the review of the worst-case conditions are emphasized and stipulated. Finalized procedural instructions on operation, cleaning, and maintenance, as well as training of responsible coworkers using these procedural instructions, should conclude the functional qualification. Likewise, after conclusion of the full installation and functional qualification, formal approval of the facility for the subsequent validation should occur. The entire chapter on qualification ends with explanations, kept relatively short, of requalification and qualification of existing facilities.

It is worth noting that beyond the definition of design qualification, no further explanations on the subject are to be found. Likewise, the subject of risk analysis is not addressed in terms of content. The other chapters on procedural and cleaning validation contained in the guide will not be addressed in more detail here.

3.3.4

National requirements for validation

One document on the national level that devotes itself to the subject in great detail and deals with both qualification and validation, is the official memorandum “Inspection of Qualification and Validation in Pharmaceutical Manufacture and Quality Control,” published by the Central Authority of the Länder (States) for Health Protection with Regard to Medicinal Products and Medicinal Devices (ZLG) [81], which should by no means go unmentioned. As the title suggests, the focus here is directed at the inspection of such systems. The document itself is conceived as a harmonization of the inspection principles within Germany and aims its focus on final pharmaceutical products. With certain restrictions, however, it can also be applied to the active pharmaceutical ingredient area, or at least it can serve to familiarize one with the manner of thinking of the inspectors.

As opposed to the documents cited previously, the level of detail in this memorandum is immediately noticeable. Not only does it introduce important statistical quantities with associated equations for quality evaluation, but it names and briefly explains concrete execution models, widely known in the literature, relating to risk analysis, which is handled here in a very clear and targeted manner. For the validation master plan, a concrete table of contents is recommended, as well as a basic structure for qualification and validation plans and reports. In sections, e.g., relating to the qualification of facilities, the document breaks down the requirements all the way to the details, which usually can only be found in the specific annexes to GMP regulatory frameworks or in relevant industrial standards (e.g., bacterial counts in various areas). However, this should be used carefully, since, as previously mentioned, the document places final pharmaceutical products in the foreground.

DQ is also discussed for the first time in an official document with regard to the items it contains. It even names the main subjects about which acceptance criteria should be formulated in a user requirement document or functional specification document. However, one may have reservations again where the statement is given that DQ ends with reconciliation of the user requirement and functional specification documents, which once again is only true for typical pharmaceutical facilities, which often are bought “off the shelf.” By contrast, the test points and approaches proposed in this document for IQ and OQ can also be extensively extended to active pharmaceutical ingredient facilities.

The performance qualification, which is not handled by the PIC/S document mentioned above, either, is clearly declared here as its own building block between OQ and procedural validation. However, the memorandum correctly explains that in many cases, the PQ inspections can be done during the OQ and sometimes also during the procedural validation, but a PQ never replaces a procedural validation.

All in all, therefore, this is a document that goes still deeper into detail than the PIC/S document, but has only limited applicability to active pharmaceutical ingredient facilities.

**3.4
Formal validation procedure**

Regardless of how many official documents one studies, or the country or organization from which they originate, the core essence of evaluation of all regulations is that validation, including qualification, is a strictly formal procedure that must be planned, organized, and documented. It matters little that one can read, correctly, in PIC/S Document PI 006 that most activities and procedures are not new at all and many manufacturers have conducted them before, though unfortunately without the necessary documentation. Whoever devotes him- or herself to the subject today cannot get around a minimum measure as a formalism. Figure 3.3 shows the fundamental steps and the documents to be produced on this subject that must be laid on the table for every inspection, and whose quality eventually determines whether such an audit runs successfully or not.

Today, these essential steps can be distinguished:

1. Validation planning

In the first step, the fundamental determinations of the validation concept are performed, meaning the company-specific and detailed approach to qualification and validation. Likewise, the concrete responsibilities, either general or specific to an existing project, are determined. It must be decided who has the overall responsibility, who should be involved in the current validation team in the first place (validation team), and who, according to the size of the pending project, monitors or controls all tasks and sequences (validation coordinator). The organization and the fixed dates must be clarified, and the scope of the project must

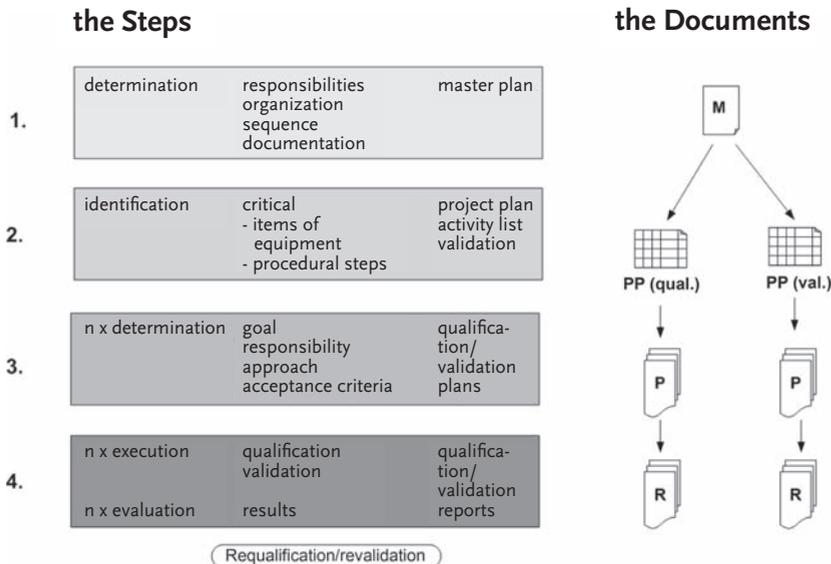


Figure 3.3 Steps and documents for validation

be described. The layout of all documents to be produced must be determined, and the sequences with regard to production, inspection, approval, and review of documents must be arranged. All these and further regulations are generally compiled into a superordinate strategic document, the validation master plan. This is the first definitive document that must be created and formally approved, i.e., with the signature of the persons responsible, before beginning the actual activities. It is this document that is first requested by the corresponding authorities and that frequently provides the first look at the topic.

2. Determination of the scope of validation

As mentioned in the preceding chapter, the authorities place most importance on the systems that are critical to the quality of the products in question and/or to the functions to be considered in the context of qualification and validation. Hence, one must not subject everything to the effort-intensive procedure. An essential tool for identification of the critical systems and functions is risk analysis. The result is usually a series of various lists of facilities to be qualified, measurement instruments to be calibrated, and processes to be validated. Some companies use their own so-called project plans, which they maintain separately over the course of the project. Others integrate the result directly into the validation master plan, where it appears yet again in the form of lists or so-called qualification or validation matrices. Regardless of the form, it is true that a clear determination and delineation of the scope of work (a quantity structure) must be given so that nothing is forgotten, but also so that the necessary financial and time framework, i.e., the resources, can be planned.

3. Qualification and validation plans

For every individual activity so identified, the necessary testing scope must be determined in a targeted manner, in writing, in the next step. In particular, the goal, the personnel responsible for execution, the planned approaches, and in any case the acceptance criteria, must now be fixed very specifically in writing. If there are, say, ten different systems to qualify, there are at least ten individual qualification plans to produce. If DQ, IQ, and OQ are separated accordingly, this will already result in 30 documents, which then, after appropriate inspection, must be formally approved, with signature, for review. Naturally, there are also possibilities for reducing the effort, e.g., by compiling similar items of equipment in a single common document, but the general mountain of papers that inevitably is created in connection with validation remains unmistakable.

4. Qualification and validation reports

Once the individual activities have finally been executed and all qualification and validation inspections have been successfully reviewed, the raw data thus created (notes taken by hand, printer output, etc.) must be brought together, results evaluated, and the validation status determined in a comprehensive assessment. At this point, too, it is the first priority to conclude the report formally with the signature of the individuals responsible.

If at the end of the whole pile of work and validation, one believes that one can now lean back, satisfied, one is quickly disabused of this notion if one determines, for example, that the validated status can only be maintained with a well-functioning change control system, which brings with it mandatory permanent revalidation, as long as one does not entirely forgo changes or especially critical parts of the system. This closes the so-called lifecycle of validation, which is not concluded until the facility is shut down or manufacturing of the GMP-relevant product ceases.

All documents described above go through essentially the same procedure, portrayed in Figure 3.4

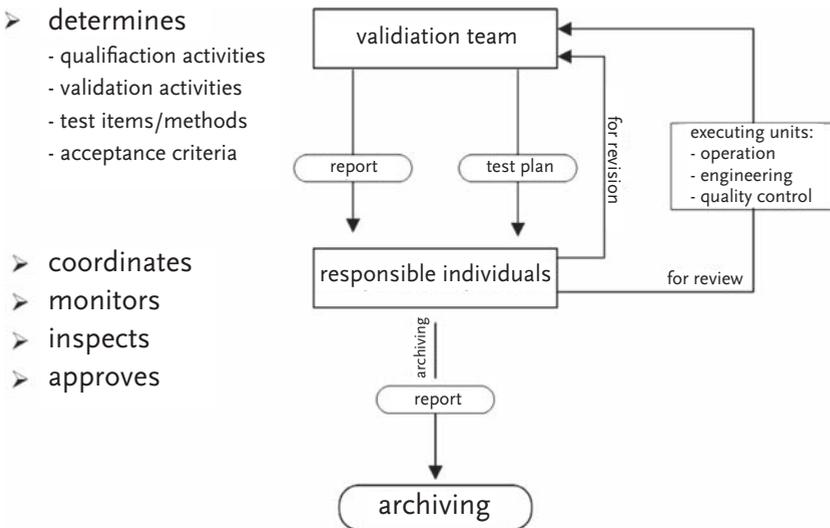


Figure 3.4 Flowchart for validation documents

The document is generally created by the validation coordinator, by other individuals selected for this purpose, or by external companies. The coordination relating to contents, approaches, and especially acceptance criteria, occurs in the validation team, which here assumes an important key position. The authorities place a particularly great value on the very fact that this “documented evidence,” i.e., the qualification and validation activities, is coordinated by the responsible experts, namely the individuals who generally know the facilities, processes, and products the best. That should guarantee the highest measure of confidence and reliability.

It is important that the sequence of review of the individual documents also be strictly observed. Within the context of inspections, the so-called data integrity is constantly inspected, whether, e.g., the validation master plan, risk analysis, qualification and validation plans have been produced in the prescribed order, and the signatures for test plans, test executions, and reports have been provided in the cor-

rect chronological sequence. This also includes the inspection of compliance with “decision criteria,” which must be fulfilled if one wants to move from one action stage to the next (e.g., changes from IQ to OQ to PQ and to procedural validation).

The superordinate monitoring in order to guarantee the implementation of all necessary measures, including the formal approval of all plans and reports, is undertaken by those responsible for validation, predominantly the production quality unit manager together with the manager. They perform the final evaluation and document with their signature whether a qualification or validation was ultimately successful and thus can be concluded as a partial or overall result.

Admittedly, the sequence described here is highly simplified and represented linearly. However, it does show the minimum requirements that are placed upon form and structure of a formal validation by the authorities and the necessary steps that no one nowadays needs to discuss, since they are strictly required by the regulatory frameworks. They are the state of the art and of the technology and are a must for anyone who devotes oneself to this subject. In reality, the sequences and relationships, especially the interaction with other entities, such as engineering, are naturally significantly more complex. The following chapters will intensively explore these issues and the question, which is certainly a gripping one, of how validation is ideally implemented under aspects of optimization.

Literature

- 60** J. Lingnau, Allgemeine Grundsätze der Validierung, Vortrag anlässlich des CONCEPT-Symposiums Validierung im Rahmen europäischer Richtlinien, October 15–16, 1990, Frankfurt/Main
- 61** FIP-Richtlinie in Sucker, Heinz, Praxis der Validierung unter besonderer Berücksichtigung der FIP Richtlinien für die gute Validierungspraxis, Paperback APV, Wissenschaftliche Verlagsgesellschaft, 1983
- 62** J. Lingnau, Allgemeine Grundsätze der Validierung, Vortrag anlässlich des CONCEPT-Symposiums Validierung im Rahmen europäischer Richtlinien, October 15–16, 1990, Frankfurt/Main Section 2.2
- 63** PharmBetrV – Pharma Betriebsverordnung
- 64** AMG – Arzneimittelgesetz
- 65** WHO, Good Manufacturing Practices for Pharmaceutical Products, Technical Report Series, No. 823, English Version, Chapter 18 (1992)
- 66** PIC (Pharmaceutical Inspection Convention), Richtlinie für die Herstellung pharmazeutischer Wirkstoffe, June 1987 (PH 2/87)
- 67** Guide to Inspection of Bulk Pharmaceutical Chemicals, Office of Regulatory Affairs and Center for Drug Evaluation and Research, Rockville, MD, Sept. 1991, Revised May 1994
- 68** FDA, Guidance for Industry, Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients, draft guidance, March 1998
- 69** ICH Q7A, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, issued by FDA, August 2001
- 70** E. R. Martinez, An FDA Perspective on BPC GMPs, Control and Validation, Pharm. Eng., May/June 1994
- 71** WHO, Ergänzende Richtlinie für pharmazeutische Hilfsstoffe in WHO Technical Report Series No. 885, Annex 5, 1999
- 72** IPEC, Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients (BPE), the International Pharmaceutical Excipient Council, Rev. Edition 2006
- 73** FDA, Guideline on General Principles of Process Validation, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Center for Devices and Radiological Health, Rockville, MD, May 1987, Reprinted May 1990
- 74** J. Lingnau, Allgemeine Grundsätze der Validierung, Vortrag anlässlich des CONCEPT-Symposiums Validierung im Rahmen europäischer Richtlinien, October 15–16, 1990, Frankfurt/Main Section 2.5
- 75** Sucker, Heinz, Praxis der Validierung unter besonderer Berücksichtigung der FIP-Richtlinien für die gute Validierungspraxis, Paperback APV, Wissenschaftliche Verlagsgesellschaft, 1983
- 76** US Food and Drug Administration, Guideline on General Principles of Process Validation, May 1987
- 77** US Food and Drug Administration, Validation Documentation Inspection Guide, CDER, 1993, never approved and never officially published
- 78** US Food and Drug Administration, Sec. 490.100 Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (CPG 7132c.08), ORA, 1993, Rev. 2004
- 79** WHO, Guidelines on the validation of manufacturing processes, WHO Technical Report Series, No. 863, 1996 neu aufgelegt in Technical Report Series, No. 937, 2006
- 80** PIC/S, Recommendations on Validation Master Plan, Installation Qualification, Non-Sterile Process Validation, Cleaning Validation, PI 006-3, September 2007
- 81** ZLG, Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten, AideMémoire 07121104, Inspektion von Qualifizierung und Validierung in pharmazeutischer Herstellung und Qualitätskontrolle, 2004