universität wien

MASTER THESIS

Titel der Master Thesis / Title of the Master‘s Thesis

„A brief history of Qualification“

verfasst von / submitted by

Dipl.-Ing. (FH) Oliver Scheiber

angestrebter akademischer Grad / in partial fulfilment of the requirements for the degree of

Master of Science (MSc)

Wien, 2021 / Vienna 2021

Studienkennzahl lt. Studienblatt / Postgraduate programme code as it appears on the student record sheet:	UA 992 580
Universitätslehrgang lt. Studienblatt / Postgraduate programme as it appears on the student record sheet:	Pharmazeutisches Qualitätsmanagement / Pharmaceutical Quality Management
Betreut von / Supervisor:	Dipl.-Ing. (FH) Dr. Michael Zwitkovits, MSc

Content

Abstract

This master thesis charts part of the course of pharmaceutical legislation in Austria, the European Communities and the United States of America leading up to the development of qualification and validation.

It then analyses development of the definition of qualification and validation in detail to help uncover the intention behind the rules and the rule changes.

It finds that the roots of Good Manufacturing Practices can be found in beginnings in the private sector that wanted to improve production and in the government sector where production of private entities had to be controlled.

This is reflected in the comparison of 2 versions of a legislative text detailing the needs for qualification that wants to be compliant to regulatory expectations, where availability and accessibility of information emerges as an important need of the pharmaceutical inspectors formulating these guidelines.

Diese Masterthese zeichnet einen Teil der Entwicklung pharmazeutischer Gesetzgebung in Österreich, der europäischen Gemeinschaften und der Vereinigten Staaten von Amerika nach, welcher zur Entwicklung von Qualifizierung und Validierung führen.

Danach wird die die Entwicklung der Definition der Qualifizierung und Validierung genauer betrachtet um die Intentionen hinter Regeln und Änderungen nachzuvollziehen.

Die Anfängen der Guten Herstellungspraxis werden in privatwirtschaftlichen Produktionsverbesserungsinitiativen und im öffentlichen Auftragswesen, wo die Behörde einen privatwirtschaftlichen Produzenten überwachen wollte, verortet.

Dies spiegelt sich auch im Textvergleich zweier Versionen der regulatorischen Vorgaben für die Qualifizierung wider, wo die Verfügbarkeit und die Zugänglichkeit zu Information als wichtiges Bedürfnis hervorkommt. Da diese Vorgaben von Inspektoren der Arzneimittelbehörden geschrieben werden, kommt ihnen besondere Bedeutung zu.

1 Introduction

This master thesis wants to answer the question which historical setting led to the development of qualification. A history of qualification will have to reflect on the background of the development of the good manufacturing practices and especially on the development of the concept of validation.

Today, the GMP or "Good Manufacturing Practice" is seen as *"'…the part of quality assurance which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use…* [1]".

The first proposed GMP defined it as *"… criteria […] that apply in determining whether the methods used in, or the facilities or controls used for, the manufacture, processing, packing, or holding of a drug conform to or are operated or administered in conformity with current good manufacturing practice to assure that a drug meets the requirements of the act…* [2]".

The quality assurance practices described in the various GMP regulations are mostly abstract. Concrete definitions (like air quality in clean rooms[3] or tolerable levels of elemental contamination[4]) get relegated to annexes or even other guidelines.

This has to be this way, as the field of pharmaceutical production is wide and regulation of every aspect would be burdensome [5] [I].

So basically this boils down to answering the question "…why do you think you can produce an acceptable drug?...".

A producer is forced to document not only the process itself, but also the mastery of the process and all related processes. This is validation, be it cleaning validation – where the successful removal of residues to below acceptable limits is shown; analytical method validation – showing that an analyte can be qualified or quantified as desired; or transport validation – which gives confidence that pharmaceuticals are handled correctly in transit from producer to consumer.

Qualification is a necessary part of validation, as it shows that the systems used to facilitate the to-be-validated process are suitable for the task. In the production of medicinal products qualification and validation are cornerstones of keeping processes in a state of control [6].

[I] „*FDA does not intend to set acceptance specifications or methods for determining whether a cleaning process is validated. It is impractical for FDA to do so due to the wide variation in equipment and products used throughout the bulk and finished dosage form industries.* [5]"

Example: A new tank is used for a production process involving vigorous mixing. Product solution splashes on the cover. Will the cleaning procedure remove the splashes and so remove the risk of carryover from one batch to the next? To test the process, it has to be clear what equipment, in what state, will be used – and this clarity should be delivered by qualification.

Medicinal products have most impact on the life of people not at peak health – qualification and validation are an integral part of the process that helps to keep this vulnerable population safe.

1.1 Let my subjects be healthy! A short history of medication and its regulation and laws in Austria

Use of medication predates humans, as animals are known to self-medicate[7] and intricate production methods are clearly old, as exemplified by, for example, $K[AuI_2]$, a synthesised gold compound that has been used in India as a medicine as early as 500 years BCE [8].

The promise of being made whole again, that comes with medication, seems to have always attracted quack-salvers looking to make a quick profit and thus has inspired rulers to legislate about medication.

In Austria this starts with the “Gesundheitsordnung für alle k.k. Erblande“ in the year 1770. There were earlier laws in the empire, the “Gesundheitsordnung” itself was inspired and, to a large extend, copied from a law of Bohemia from 1753, but the “Gesundheitsordnung” was the first law applicable to the whole country – thus raising health laws from a regional to a national level.

This body of rules (developed over many years) aimed to define the duties of medical professionals (physicians, surgeons, midwifes and also pharmacists) towards their customers as well as towards each other, how professional credentials were to be obtained and how conduct of duties was to be controlled and sanctioned.

Concerning pharmacists, the first relevant paragraph starts with "*As everything depends on the preparation of the drugs, operation of a pharmacy shall be allowed no one whose competency has not been examined and certified by an imperial university that hosts a medicinal faculty.* [II] [9]" This is revolutionary, as it makes university education for pharmacists compulsory in the empire.

Paragraph two details the need for obedience of pharmacists to god, the "Sanitätskommission"[III] (sanitary commission, the newly established disciplinary body for doctors, midwifes and pharmacists) and the books (detailing how to prepare and what medicinal products to have ready for use). §2 also promises a new pharmacopoeia, this was realised with the "Pharmacopoeia Austriaco-Provincialis" 1774.

§3 prohibits the pharmacist from treating patients himself (except in cases where a physician is not available) and compels him to have a certain amount of product in stock.

§4 urges them to be nice to other people – to medics and midwifes, to their personnel and to serfs that fetch medicine for others.

§6 Defines prescription requirements for certain substance classes, §7 regulates how sale of arsenic (As_2O_3) is to be restricted and documented, §8 stipulates that doctors in small places have to make medicines available if there is no apothecary, §9 compels pharmacists to make medicines available by having apprentices or journeymen dispense them "during night and day", at least in time of pestilence (if it is a small operation with only one journeyman) and finally §10 bans druggists, chymists and traveling snake oil salesmen from selling pharmaceuticals.

[II] „Da an der Zubereitung der Arzneien alles gelegen ist, als solle eine Apotheke zu führen niemand erlaubet werden, der nicht gleichfalls auf einer erbländischen Universität, der eine medizinische Fakultät einverleibet ist, ordentlich examinieret worden und das Zeugnis seiner Fähigkeit erhalten. [9]" Author's translation

[III] Although there were sanitary commissions in some cities (e.g. Graz, established 13. May 1753), the law from 1770 made them mandatory everywhere in the empire.

The most interesting paragraph is §5, in the original it reads as follows:

"*Die Ingredientia Medicamentorum und Simplicia aus allen dreien Reichen müſſen, ſobald man ſelbe zur Korrupzion ſich zu neigen verſpüret, weggeſchaffet, ſo wie jene, welche an ſich ſelbſt mit der Zeit ihre Kraft verlieren, alle Jahre friſch und in hinreichender Menge und Güte angeſchaffet, zu rechter Zeit eingeſammelt, mit allem Fleiße ausgetroknet und gereiniget, und in ſauberen Gefäßen aufbehalten, die alten und verdorbenen Präparate aber, welche nicht durch chimiſche Handgriffe wiederum verbeſſert werden können, ausgeſondert und an ihrer Statt friſche verfertiget werden; und da es beſonders bei den Medicamentis chemicis gar oft auf gewiſſe wohl kündige Handgriffe ankommt, als werden die Apotheker ſolche und alle Composita nach maßgebiger Anleitung des Diſpenſatoriums zubereiten und dabei alle Vorſichtigkeit gebrauchen, auch da ihnen ein oder anderer Handgriff nicht vollkommen wiſſend wäre, ſich bei den Land - Fiſikern oder anderen geſchikten Medikern Rats erholen, keineswegs aber in Zubereitung der Azneien auf die Geſellen allein ſich verlaſſen, ſondern bei Zuſammenſezung und Verfertigung der Rezepte mit allem Fleiße darob fein, damit dieſelbe vorgeſchriebenermaſſen gemacht, und nichts davon vernachläſſiget, weder eine andere Spezies eingemenget werden möge.*

Vorzüglich iſt unter ſchwerer Strafe zu ſorgen, daß die Gefäße, Tiegel, Mörſer und dergleichen, worin die Arzneien zubereitet werden, wohl gereiniget und jenes Unheil vermieden werde, welches hierinfalls durch den Einfluß ſchädlicher Materien entſtehet, und oft mit den Arzneien die empfindlichſten Folgen nach ſich gezogen hat.

Im Falle ein oder anderes vorgeſchriebenes Ingrediens wicht vorhanden wäre, ſo haben ſie ſolches dem betreffenden Mediker des Endes, auf daß er ſelbſt an deſſen Statt ein an deres von gleicher Wirkung anordnen könne, zu melden, die Rezepte hingegen fürnemlich, wenn darin Ingredienzien von ſtarker Operazion befindlich wären, keinesdings dem Lehrjungen, um nicht etwa durch Unbehutſamkeit oder andere Fehler dem Kranken zu ſchaden, zur Verfertigung anzuvertrauen [9]"

If you look closely and squint, some GMP seems contained in there:

Handling of expired medicines ("*…ſobald man ſelbe zur Korrupzion ſich zu neigen verſpüret, weggeſchaffet…*"),

Use of standard operation procedures ("*…werden die Apotheker ſolche und alle Composita nach maßgebiger Anleitung des Diſpenſatoriums zubereiten…*"),

Handling of highly potent substances ("*…wenn darin Ingredienzien von ſtarker Operazion befindlich wären, keinesdings dem Lehrjungen…*")

Prevention of contamination or cross-contamination ("*…Gefäße, Tiegel, Mörſer und dergleichen, worin die Arzneien zubereitet werden, wohl gereiniget und jenes Unheil vermieden werde, welches hierinfalls durch den Einfluß ſchädlicher Materien entſtehet, und oft mit den Arzneien die empfindlichſten Folgen nach ſich gezogen hat…*")

And it should be noted that this law prescribes the use of suitable equipment ("*…Tiegel, Mörſer und dergleichen (…) jenes Unheil vermieden werde, welches hierinfalls durch den Einfluß ſchädlicher Materien entſtehet…*") by demanding that crucibles, mortars and the like are from materials that do not negatively influence the prepared medicine.

What is omitted, compared with the current good manufacturing practices of today, is a generic prescription how to determine if equipment is suitable. Ideally, the descriptions of suitable equipment would have been part of the pharmacopeia, but they were missing. Even the descriptions for the preparation of medicines and reagents were sometimes so brief that "*it is not possible to work with these instructions and preparations fail* [10]".

This has to be seen in conjunction with the new need for pharmacists to study at university and demonstrate chemical knowledge [11] in front of a board to be allowed to run a pharmacy – a pharmacy where operations would have been regularly inspected by members of a sanitary commission, who would decide if premises and equipment were suitable.

This state of affairs continued into the 20th century, e.g. the pharmacy bylaw of 1934 for the operation of pharmacies states in §3 that "*…premises, furnishings, containers and equipment have to be in order and suitable for use as well as clean…* [12]" but does not define what suitable and clean really means in context of the law. Suitability and cleanliness were regularly controlled by inspection (detailed in the same bylaw §§57 – 63) but even the pharmacopoeia did not really help there.
One of the reasons for this may have been the shift of pharmaceutical production from apothecaries to pharmaceutical factories. The 9th edition of the Austrian pharmacopoeia explicitly states

> *„Bei der Herstellung von Arzneizubereitungen, für welche das Arzneibuch ein besonderes Verfahren vorschreibt, darf, wenn die Herstellung in fabriksmäßigem Maßstab erfolgt, von dieser Vorschrift abgewichen werden, sofern das erzielte Endprodukt den Anforderungen des Arzneibuchs entspricht* [13]".[IV]

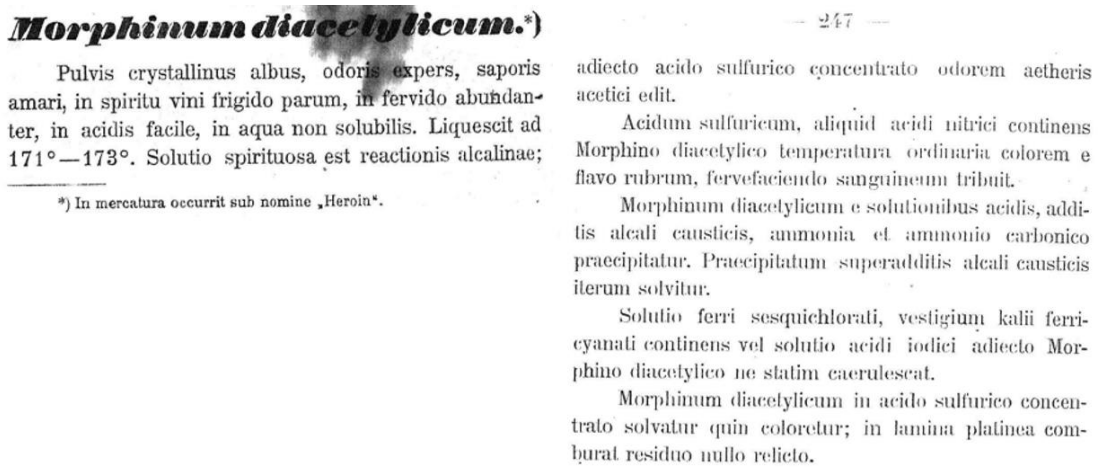
[IV] "*Production of pharmaceutical preparations where the pharmacopoeia defines a production process may, if the production is done on an industrial scale, be performed by a different process if the resulting product conforms to compendial criteria…* [13]", Author's translation

It is not that the 9th edition of the Austrian pharmacopoeia does absolutely not give any criteria for any equipment, examples range from stipulating that sieves have to be made from rust-free material [14] to elaborate drawings to define the apparatus for measuring dropping points [15].

And even if preparation of simple organic drug substances, like acetylsalicylic acid [16] are not mentioned in the pharmacopoeia, the substance itself, as well as the necessary reagents (acetylation mixture [17] and salicylic acid [18]) are part of the book.

It seems not like pharmacists were not trusted with complex and potentially lethal preparations, as can be attested by the injectabilia [19], where we also find some instructions what a suitable room for aseptical filling should look like (has an air look for a change of clothes into sterile clothing, is heated indirectly and ventilated with filtered air …) but we also find that such special rooms are only necessary when serially filling aseptic pharmaceuticals.

In general, it seems that it was assumed that inspectors would "…*know it when they see it*… [20]" and so impede use of unsuitable premises or equipment. For a person with a contemporary complexion regarding pharmaceutical production this reeks of almost lawlessness. One reason for this may be that the industrial production of pharmaceutical chemicals, that started around 1890 (with drugs like diacetylmorphine, barbital or acetylsalicylic acid) had not fully arrived in regulation.



Morphinum diacetylicum.*)

Pulvis crystallinus albus, odoris expers, saporis amari, in spiritu vini frigido parum, in fervido abundanter, in acidis facile, in aqua non solubilis. Liquescit ad 171°—173°. Solutio spirituosa est reactionis alcalinae;

*) In mercatura occurrit sub nomine „Heroin".

— 247 —

adiecto acido sulfurico concentrato odorem aetheris acetici edit.

Acidum sulfuricum, aliquid acidi nitrici continens Morphino diacetylico temperatura ordinaria colorem e flavo rubrum, fervefaciendo sanguineum tribuit.

Morphinum diacetylicum e solutionibus acidis, additis alcali causticis, ammonia et ammonio carbonico praecipitatur. Praecipitatum superadditis alcali causticis iterum solvitur.

Solutio ferri sesquichlorati, vestigium kalii ferricyanati continens vel solutio acidi iodici adiecto Morphino diacetylico ne statim caerulescat.

Morphinum diacetylicum in acido sulfurico concentrato solvatur quin coloretur; in lamina platinea comburat residuo nullo relicto.

Figure 1 Entry for diacetylmorphine in the 8th edition of the Austrian Pharmacopoeia [21]

1.2 Nobody thought anyone would die from that: Quality and the FDA

In other fields assumptions may be likened to barnacles, animals that slow down ships [22], but in the pharmaceutical industries assumptions are often more like jaguars: Animals that drop from trees to break necks when something unsuspectingly walks beneath their perch.

Someone once assumed that the sweet tasting chemical diethylene glycol, a good solvent for an early antibiotic (sulphanilamide), would be a suitable excipient to bring the drug into a liquid form. More than 100 lives were lost as diethylene glycol results in renal failure, especially in children [23].

Other people assumed that a mixing drum contained sulfathiazole and started a production run for some antimicrobial tablets utilising said drum. More than 300 people died from phenobarbital poisoning, as the assumption about the contents of the drum turned out to be wrong [24].

These two incidents in the first half of the 20th century were formative in developing regulation of drugs in the USA. The diethylene glycol incident happened 1937, it led directly to the passage of the 1938 Food, Drug, and Cosmetic Act [25] and, further down the road, it helped avert another disaster based on an unfounded assumption when thalidomide was not approved for marketing in the US [V] [26] because of the lack of substantial evidence of its safety [27], which was only possible due to the provision of said act.

The phenobarbital incident, which happened 1941, led directly to the first codification of current good manufacturing practices in the manufacture, processing, packaging and holding of drugs. After having published a proposed rule for public comment in February 1963 [28] the first GMP was published on the 20th of June 1963 [29].

[V] The Austrian counterpart to Frances Oldham Kelsey is Ingeborg Eichler [26]. The decisive role of 2 women in singlehandedly averting this tragedy in 2 countries seems to warrant further research

1.3 Connections across centuries: Common ground and differences between the Sanitätsnormativ and the first GMP

Both legislations presented here share common ground, addressing suitable ways to bring drugs to consumers without harming people by substandard production of medication. In some cases it is easy to see that the same problems were on the minds of legislators. Compare, for example, these two parts that both say “use competent personnel”:

“*…da es beſonders bei den Medicamentis chemicis gar oft auf gewiſſe wohlkündige Handgriffe ankommt, als werden die Apotheker ſolche und alle Composita nach maßgebiger Anleitung des Diſpenſatoriums zubereiten und dabei alle Vorſichtigkeit gebrauchen, auch da ihnen ein oder anderer Handgriff nicht vollkommen wiſſend wäre, ſich bei den Land - Fiſikern oder anderen geſchikten Medikern Rats erholen, keineswegs aber in Zubereitung der Azneien auf die Geſellen allein ſich verlaſſen*… [9 VI]“ (Sanitätsnormativ 1770, Part III, §5)	“*…Each critical step in the process, such as the selection, weighing, and measuring of components; the addition of active ingredients during the process; weighing and measuring during various stages of the processing, and the determination of the finished yield shall be performed by a competent, responsible individual…* [29]” (GMP 1963, §133.8 (a))

But almost 200 years of progress from 1770 to 1963 have to engender differences. A major one is easy to spot: Whereas the Sanitätsnormativ uses approximately 1250 words to regulate everything needed to run a pharmacy (and dedicates about 300 of them to the regulation of production in §5), the first instance of the GMP needs about double that amount (approx. 2550 words) to “only” regulate manufacturing of drugs.

[VI] “*As especially chemical preparations often depend on skilful handling of certain steps, apothecaries will diligently prepare these as well as all complex mixtures according to the relevant instructions of the dispensatory. If certain steps of an instruction are not totally familiar, instructions by a competent physician or other medic are to be sought. Apprentices should not be allowed to prepare such pharmaceuticals without supervision.* [9]“ Author’s translation

One reason for this seems simple to explain, the therapeutic armamentarium exploded due to the massive amount of knowledge discovered in the pharmaceutical sciences, starting with discoveries in inorganic chemistry and, via pharmacognosy and organic chemistry, arriving in a growing knowledge and use of the molecules of life like vitamins, hormones and antibiotics [30].

Both regulations also address contemporary concerns, a general focus on education during the time of Maria Theresia manifests in the stipulation of mandatory university studies for pharmacists in §1 of the Sanitätsnormativ and experiences like the phenobarbital incident are sure to be a major factor in mandating a reconciliation of matter in 133.8(f) of the first GMP.

1.4 So you think this is suitable? The need for validation

" ***Validation**, n. Act of enduring with validity*
***Validity**, **Validness**, n. State or quality of being valid; having strength, force, or power to convince; soundness; justness; efficacy; as, the validity of an argument*
(Law.) That quality of a thing which renders it maintainable in law or equity; as, the validity of a title to an estate [31] "

Zell's Popular Encyclopedia 1882

Regulation changes to stay current and relevant and this also happened to the current good manufacturing practices first released by the FDA in 1963. The regulations were expanded in 1971 "*…to clarify, strengthen, and make more specific the good manufacturing practice regulations for drugs…* [32]" and reorganised in 1975 to enable "*…establishing an orderly development of informative regulations for the Food and Drug Administration, furnishing ample room for expansion of such regulations in years ahead, and providing the public and affected industries with regulations that are easy to find, read, and understand...* [33]"

1978 saw a further change to the regulations, to "*…update present regulations in light of current technology for drug manufacturing and delineate requirements more specifically than do the present regulations. (…) in many instances the revisions are practices that have been considered implicit in the regulations (…) The regulations are being updated and made more explicit, and therefore less subject to varying interpretations, to assure that all members of the drug industry are made aware of the level of performance expected of them to be in compliance with the act…* [34]"

This preamble to a complete revision explicitly states two interesting things:

1) That there are implicit assumptions in regulations
2) That people tend to interpret regulations differently – and not always in a way that the regulator finds in compliance with the regulation.

One of the practice that was made explicit is the concept of "validation". There is no direct definition of validation in the regulation, but §211.165, concerning itself with testing and release for distribution, states, in clause (e):

"*The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with §211.194(a)(2).* [34]"

Thus, the issue of the GMP that gave us validation defined it as the establishing of the accuracy, sensitivity, specificity and reproducibility of a method.

Validation featured also in the comment section of the new regulations.

The proposed regulations were made public more than 2 years before the publication of the final rule and the publication itself spends 518 paragraphs (pages 45015 to 45076) on discussing comments and proposed changes. These 50 pages of discussion offer a window into the then prevalent thinking of the FDA, represented by the Commissioner.

What seems interesting in hindsight is the fact that a wonderfully short definition of validation, that was present in the explanations accompanying the proposed new rules, that saw "*…validation studies…*" as something that are "*…conducted to determine the variability of the manufacturing processes…* [35]" seems to have been totally lost in further developments.

A reason for the indirect definition inherent in §211.165 may be found in the aforementioned discussions, specifically in chapter VII of these, that deals in definitions. There the Commissioner states that he "*…believes that the length of part 210 would be unnecessarily increased by including in this part the definitions of terms that are well known or already defined in the act…* [34]" (§210.3 holds the definitions applicable to sections 210 and 211 of the regulations).

And the term "validation" may indeed be found in earlier GMP regulations:

The first identifiably instance in a regulation is in a 1972 subchapter about ophthalmic preparations that introduced the need for sterility of said preparations. As the discussion of the regulation conceded that requests for additional time to make the necessary changes for sterile production are reasonable, the Commissioner legislated, that "*…to provide time for validation of sterility tests (…) this ruling will be effective 12 months after the date of publication…* [36]"

The concept of validation seems clear enough that the Commissioner could use this word to state for which chores he would delay effectiveness of his new rule for 12 months, namely the validation of sterility test, but the concept is not so well-defined that it is routinely used for regulations.

This may be seen in a further reorganization effort by the FDA. In 1974 the regulations concerning drugs for human use were updated. Although the changes were not substantive enough to warrant notice and public procedure, there was rewording. The word "validation" does not appear in the regulation, even if it would save a lot of text.

For example, §314.1 deals with applications and information requirements for new drugs. §314.1(8)(n) asks for "*…a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug…*", especially "*…The analytical controls used during the various stages of the manufacturing (…), including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. (…) Include the standards used for acceptance of each lot of the finished drug…* [37]"

If the indirect definition from §211.165 of 1978, that equates validation data for test methods to consist of data for "*…accuracy, sensitivity, specificity, and reproducibility…* [34]" is applied, then asking for validation data of the test methods employed would have made that paragraph significantly shorter.

That the FDA would do that sometimes (use the word "validation" before it was defined in the cGMP regulations) can be seen in the restatement of the cGMP in 1975. In §200.10, concerned with the use of contract facilities, subclause (d) states that "*…The Food and Drug Administration does not consider results of validation studies of analytical and assay methods and control procedures to be trade secrets that may be withheld from the drug manufacturer by the contracted extramural facility…* [33]"

Curiously, this seemingly full-fledged concept of validation studies is used only once more in this regulation, in a restatement of the need for validation studies of sterility testing methods for ophthalmic preparations, even if wider use of the concept would, again, have saved the need for extensive wording to describe expectations regarding the suitability documentation of methods.

And in another twist that shows the versatility, and lack of singular definition in this context, the word validation appears a third time in §207.35(4)(c), where it is stated that "*…although registration and drug listing are required to engage in the drug activities described in § 207.20, validation of registration and the assignment of a drug listing number do not, in themselves, establish that the holder of the registration is legally qualified to deal in such drugs...* [38]", meaning that even if the Commissioner provides the registrant with a validated form, showing that a drug establishment was registered, this in itself is not enough to commence operations.

This last use, then, conforms exactly to the law part of the definition given in Zell's Popular Encyclopedia 1882 as quoted at the beginning of this chapter, marking the concept of validation as used by the FDA in regulations in the 1970s as fluid and not defined until the end of the decade.

1.5 Killing a lot of people should be cost effective: Quality Management

> " ***Quality**, n. Property; attribute; that which belongs to a body or substance, or can be predicated of it; peculiar power, capacity, or virtue; distinguishing trait; moral characteristic, good or bad; as, a man of noble or base qualities – Comparative rank; condition in relation to others; character; as, a person of good quality – Assumed or asserted rank, part, standing, or position – Acquirement; accomplishment; acquisition; special qualification – Superior rank or distinction; elevation of birth, station, or character; as, a man of quality*
>
> *"To quality belongs the highest place" – Young*
>
> *The quality. Persons of high rank or station, in a collective sense, as distinguished from the commonally; as, the fashions were set by the quality.*
>
> *"He entertained the quality with his surprising wit" – Thackeray [39] "*
>
> Zell's Popular Encyclopedia 1882

According to the lore, the beginnings of quality management are to be found at the start of the twentieth century in the works of people like Taylor and Shewhart [40].

F.W. Taylor wrote "The Principles of Scientific Management", a book were he advocates management by measurement. The concept is also known as "Taylorism" and received a lot of critique under this name as a system that dehumanises workers [41]. This is not the place to weigh in on the discussion of how much Taylor thought of "common men" as lazy entities that had to be driven to performance, but reading the book with a mind set on quality management highlights passages like this:

> *"To explain briefly: owing to the fact that the workmen in all of our trades have been taught the details of their work by observation of those immediately around them, there are many different ways in common use for doing the same thing, (…) among the various methods and implements used in each element of each trade there is always one method and one implement which is quicker and better than any of the rest. And this one best method and best implement can only be discovered or developed through a scientific study (…) (T)he workman who is best suited to actually doing the work is incapable of fully understanding this science, without the guidance and help of those who are working with him or over him, either through lack of education or through insufficient mental capacity. In order that the work may be done in accordance with scientific laws, it is necessary that there shall be a far more equal division of the responsibility between the management and the workmen than exists under any of the ordinary types of management. Those in the management whose duty it is to develop this science should also guide and help the workman… [42]"*

It implies that Taylor would, at least, not find fault with giving continuing training based on codified instructions, with its practical effectiveness being periodically assessed [VII] [43], and it even implies that process performance qualification would be to his liking.

With W.A. Shewhart things are much clearer, his work "Economic Control of Quality of Manufactured Product" [44] gave us the phrase "Quality Control" and, according to his mentee E.W. Deming, the Shewhart cycle for constant evaluation:

Plan – Do – Study – Act

Shewhart and especially his disciple, Deming (and J. Juran [45]), are commonly seen as major proponents of quality management. Deming is known for his work promoting statistical process control in Japan [46], his writings make it clear that it was not only statistics and control charts, but also organisation and consumer research, that was on his mind when thinking about quality management. For example, he tells the German Industry in 1950 that not only statistical process control, but also "Statistical Administrators" and "Consumer Research" are needed to emulate the success of the US or Japan [47].
But I suspect a slightly different path has brought quality regulations and the necessity of validation into the canon of pharmaceutical regulation.

"Close Enough for Government Work" is a phrase that may have started out as meaning that something had especially high standards, but at latest after the second world war it had gotten a totally different meaning, demoting shoddy work done unenthusiastically [48].

This sometimes had devastating consequences, like delivery of shoddy infantry rifles that, in the worst case, would not only jam but explode, killing or maiming the soldier using them [49]. In light of these facts issuing of army standards for quality program requirements, like MIL-Q-9858, and making them mandatory for suppliers, is a logical step.

[VII] "*2.9 Besides the basic training on the theory and practice of Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programmes should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept.* [43]"

Eudralex Volume 4, Good Manufacturing Practices, Chapter 2 "Personnel", Version from 1998

Standardization in trade is a well-known thing, without standardization futures trading would only be possible for a few totally fungible commodities, like coinage, and even these commodities may have been a result of standardization [50] themselves.

Standardization in contracts resulted in the need for agreed qualities. A large variety of goods needed by the military was procured from private companies. The military needed these things to be usable, be it bullets or guns, shells or cruisers. For many of these things "usable" equates to "standardized", as it renders a rifle useless if the bullet does not fit and it renders a trained sailor less useful if one ship of a class works markedly differently than the next one of the same class.

In the second world war this gives us acceptable quality levels, that were controlled by resident government inspectors.

> "*End-of-line inspection with measuring instruments such as gauges was then performed for lots or batches according to standardized sampling plans. Lots with defect levels exceeding 'acceptable levels' were rejected [51].*"

But, with complex contracts – involving electronics, or necessitating design and development as well as production – this approach, based solely on statistical process control, was found lacking.

Especially for NASA, which was literally aiming to shoot for the moon, "Quality Provisions for Space System Contractors" were developed to ensure quality not only by measurement but also by management.

This gave us not only the need for quality program plans (reminiscent of quality manuals for ISO 9000 or EU GMP), failure mode, effect and criticality analysis or detailed inspection guidelines [52], it also gave us the need for a quality organisation that was independent of production and directly connected to top management.

It also made it much easier for contracting, standards made it possible for quality requirements to be easily included in contracts by reference, ensuring uniformity as well as completeness.

These US standards were extensive. When the British decided to create uniform standards for quality management [VIII] they decided to not adopt the US versions, as they feared that they would have little influence on amendments. Reflecting the experiences of the US with their standards, the British decided to make their standards simpler and make them general standards, usable by the military as well as by civilian institutions [53].

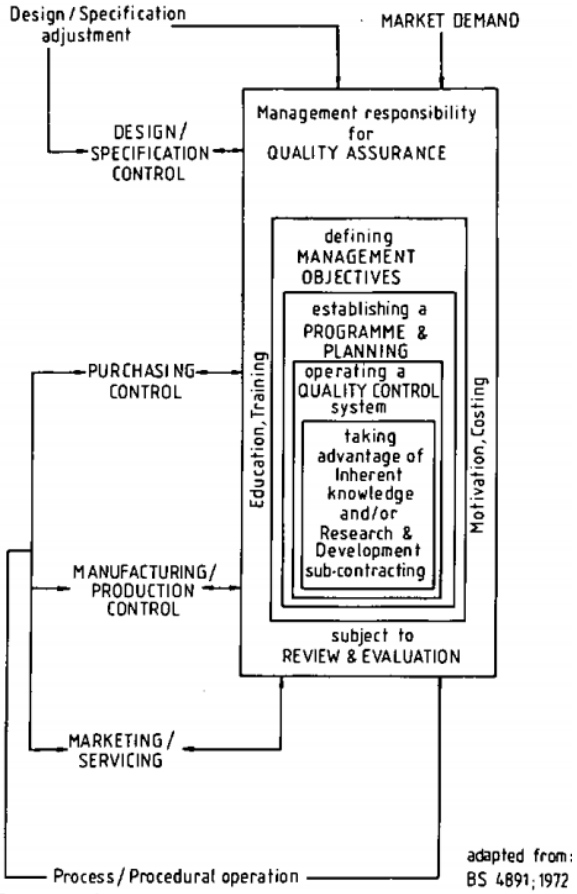


Figure 2. Some basic elements of quality assurance.

Figure 2: Basic Elements of QA according to BS 4891:1972

The British Standards Institute issued these military standards as guides to quality management (e.g. BS 4891:1972, a guide to quality assurance).

One of these standards, BS 5750:1979 (Quality Systems) was re-issued as ISO 9000 in 1987 [54].

It was not possible to find any sources for this conjecture, but in the authors opinion a move to quality management, as seen in the 1978 addition of the quality control unit in the US cGMP [IX], is much closer related to the demands of government procedures like NASAs NPC 200-2 [55] than to any perfection of quality management in the motor industries.

[VIII] The British military used six different standards for inspection of production – and other large, public enterprises like the post office also had distinct inspection standards [53]. A clear case for standardisation of standards.

[IX] "*§ 211.22 Responsibilities of quality control unit.*
(a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company. [34]"

On the one hand there is a relationship between pharmaceutical companies and FDA enforcement that is much more reminiscent of the relationship between weapon systems manufacturers and government inspectors, as this is a hierarchical relationship, with agents of the state (based on the state monopoly on violence) than between seemingly equal companies.

And on the other hand we have circumstantial evidence. If we compare the "3.2 Organization" part of NASAs NPC 200-2 from 1962 to the "§ 211.22 Responsibilities of quality control unit" in the FDAs 1978 cGMP revision, the independence and overall responsibility of the quality unit seem related:

"*…Personnel performing quality program functions shall have sufficient, well-defined responsibilities and the organizational freedom to recognize and assess quality problem and to initiate, recommend, and/or provide solutions…* [55]"	"*…There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, (…), and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated …* [34]"
NASA, NPC 200-2, 3.2 Organization	FDA, cGMP 1978, "§ 211.22 Responsibilities of quality control unit

Interesting to note here is that no quality unit independence from production is stipulated. Even today, cGMP does not mandate that the quality unit be independent of production, the FDA even states that in limited circumstances these functions could be performed by a single individual [56].

The European Union GMP, from its first instalment, differs here, stating that "*…the heads of Production and Quality Control must be independent from each other…* [57]".

This, seemingly, makes it closer to NPC 200-2 than the FDAs cGMP, as NPC 200-2 also wants the assigned personnel to have the ability to "*…**objectively** assess, document, and report findings…* [55]". And objective assessment seems harder, if not impossible, if one's own work is to be assessed [58].

1.6 Short Summary

Legislation concerning pharmaceutical production is enacted to protect the public.

> "*Unter den landesmütterlichen Beſorgniſſen, durch die Wir für das Beſte Unſerer Staaten wachen, verdient jene auf den Geſundheitſtand ein vorzügliches Augenmerk, und die in allen Ländern bereits aufgeſtellten diesfälligen Obrigkeiten und Beamten, die in den vorliegenden Geſchäften mit gutem Erfolg wirken, ſo wie die ohne allen Rükhalt angewandten, zu dem gemeinen Beſten zielen den Unkoſten geben von dieſer Unſerer landesmütterlichen Liebe die überzeugenden Proben* [59]."

Legislation has to be adapted to stay current and relevant.

> "*The regulations are being updated and made more explicit, and therefore less subject to varying interpretations, to assure that all members of the drug industry are made aware of the level of performance expected of them to be in compliance with the act* [60]."

Pharmaceutical quality management, like all quality management, has been influenced by military procurement and still, partly, reflects the relationship between government inspector and production company.

The concept of validation explicitly entered cGMP in the 1970ies.

2 Development of Qualification

> " ***Qualification**, n. Act of qualifying or state of being qualified; adaptation – Any natural endowment or any acquirement which fits a person for a place, office or employment, or enables him to sustain any character with credit and success; legal power or requisite, – Act of limiting, or statue or condition of being limited; limitation; restriction; modification; abatement; diminution; as, speak one's mind without qualification of words* [61] "
>
> Zell's Popular Encyclopedia 1882

2.1 Introduction

The first EU GMP guide – then still being the EC GMP guide – defines qualification as *"…action of proving that any equipment works correctly and actually leads to the expected results…* [62]"

It is interesting to philosophize about the depth of this definition, because "…works correctly and actually leads to the expected results…" could be seen as redundant. But there can be cases where either part of that is not true, but the other part is, both cases highlighting missing understanding.
If a system works (runs a process) incorrectly and still yields the expected results – or if a system works correctly and leads to unexpected results – the knowledge about the system and the process is insufficient, system and process should be studied more. Repeating the simple words the authors teacher used to explain "qualification and validation" to class may help here:

> *"Your process should yield the results you want, consistently. Showing that this is the case is called validation.*
> *And every process runs on a system. Showing that the system is and does what you want is called qualification [63]."*

The phrase "qualification and validation" is something that is ubiquitous today, at least in the pharmaceutical industries (other industries may talk about verification and validation, addressing essentially the same problem [X] [64]).

[X] ISO 9000:2000 gives these definitions:
"*Verification: Confirmation, through the provision of objective evidence, that specified requirements have been fulfilled;*
Validation: Confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled;
Qualification Process: Process to demonstrate the ability to fulfil specified requirements [64]"

In research for this thesis Google Books [65] was used, as it allows to search for phrases in the literature and for cut-off at certain dates. Emergence of a phrase may, in this way, be traced. This was done for "qualification and validation" and it identified the earliest traces of use of this phrase beginning in the 1970 [XI] [66].
Common usage seems to have started with the 1990ies.

This fits the bits of legislative history mentioned in the introduction, it points to the fact that a law that asks for something to be done, be it genuinely new or only procedurally new, will engender thought on how these new things should be handled correctly to be compliant with expectations (maybe without wasting to much effort, too).

In the 1980ies definitions, like "*Verification of the operational characteristics prior to commissioning an environmental control system is defined as qualification of the system. The series of testing and verification* [XII] *procedures used to provide assurance of the system's proper and continuous operation is defined as validation* [67]." start to be seen.

The first legal definition comprising qualification and validation that could be found [XIII] [68] comes from the "EEC Guide to Good Manufacturing Practice for Medicinal Products 1989 [XIV]" and reads:

[XI] I used a search for the phrase "qualification and validation" in Google Books and tried to verify the search results. Some hits in the 1950ies and 1960ies were obvious mistakes like the inclusion of a technical report by the WHO showing phrases like "IQ, OQ, PQ) which obviously dates it much later. No hit could be verified (a possible use in a job advert in 1966 was not traceable for me) until use at a NASA hearing in 1974.

[XII] Shoutout to ISO 9000; see page 2 footnote X (The word verification is used in ISO 9000 but fell out of favour in GMP)

[XIII] The FDA „Guideline on General Principles of Process Validation" from May 1987 predates the EC GMP guide but the EC GMP guide claims to be law (based on directives 91/356/EEC and 91/412/EEC), whereas the FDA guideline does not ("*It does not create or confer rights for or on any person and does not operate to bind FDA or the public.* [68]") Funnily enough both documents explicitly allow different approaches if they can be shown to fulfil the same goals. Also noteable: The guideline gives definitions (e.g. it states "*The FDA defines process validation as follows*… [68]") that could not be found in the Federal Register and paints these as official definitions, but the guideline also states that "*[The regulation] does not create or confer rights for or on any person and does not operate to bind FDA or the public*… [68]".

[XIV] In the 1980ies the European Communities decided to reform pharmaceutical law and make compliance with the principles of Good Manufacturing Practices compulsory – but they ran into the problem of saying, exactly, what GMP is. So the "Working Party on Control of Medicinal Products and Inspections", a group set up by the Commission of the ECC in 1981, was tasked with developing the first GMP for the European Communities.

“QUALIFICATION

Action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification.

VALIDATION

Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification). [57]*”*

And such legal definitions help, as they constrain the room of possible measures and benchmarks that pharmaceutical inspection can apply to companies. They clarify what is asked for to guarantee a sufficiently high level of pharmaceutical quality, partly being set by wanting to not repeat mistakes of the past.

That there is a need for definitions in this field may be seen in the significant number/percentage of observations related to qualification and validation over time.

2 presentations of the Austrian agency for health and nutrition safety (AGES) [69] that indicated such need in 2008 and 2009 were identified:

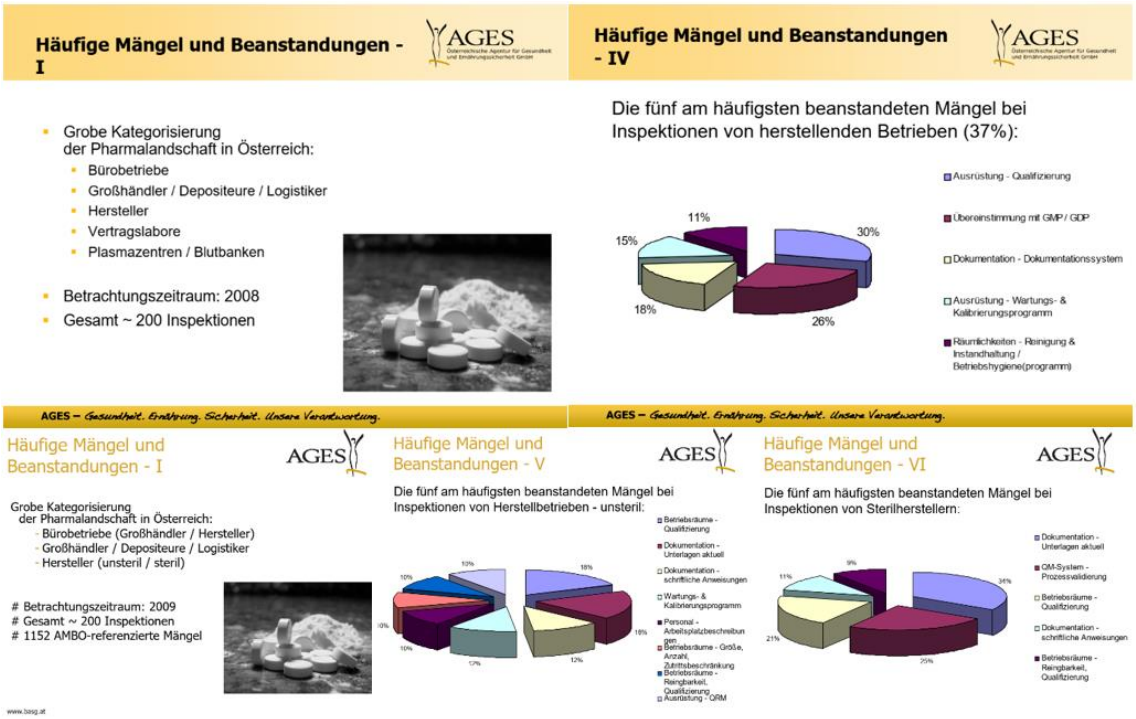


Figure 3 Presentation slides by Austrian pharmaceutical Enforcement, indicating qualification as a significant topic causing findings

The data from 2008 identifies 30% of all findings at production sites as having to do with equipment qualification, data from 2009 indicates findings related to qualification in up to 38% of the cases. A presentation on inspection by the FDA from June 2014 [70] does not have any graphics but mentions problems with qualification as one of the top 5 cGMP problem areas.

The pinnacle [XV] of legal definitions, helpful in seeing the extend of questions and answers pharmaceutical regulation today wants raised and answered by qualification and validation, when pharmaceuticals are to be produced safely, is Annex 15.

What makes Annex 15 part of the legal canon? Annex 15 in itself is part of the EU Guide to Good Manufacturing Practice and that, at the time of publication of the first Annex 15 (July 2001) [71], in itself was based on Directives 75/319/EEC and 81/851/EEC [72] and thus the definitions of Annex 15 are part of the legal canon of the European Communities.
As Directives have to be implemented in national law, in Austria a law from 1986, governing medicine production (Betriebsordnung), was changed in 2004 [73] to incorporate the relevant Directives and the European GMP directly in Austrian law, thus closing the loop between Austrian medical producers and Annex 15.

2.2 Annex 15

In its first iteration 2001 Annex 15 had 11 pages (including cover and glossary) and almost managed to describe qualification on one page [XVI], using less than 333 words, header and all.

And it states the basic principles of qualification, namely that designs should comply with GMP, that installed systems should comply with design and documentation and that the realised designs perform as needed for the tasks at hand – and that this compliance has to be documented.

What makes Annex 15 interesting in historical context is that there are 2 iterations of it, released in 2001 and 2015 [74]. By comparing the sectional differences, conclusions on the concerns of the authors may be drawn. As the authors of Annex 15 work, to a significant extend, in pharmaceutical inspection, such comparisons also shine a light on some of the challenges pharmaceutical inspectors face regularly enough to warrant definition.

[XV] Depending on inflection it may be described as “most detailed” or “most extensive”…

[XVI] 1,5 clauses had to move from page 5 to page 6, but better formatting would have been possible

2.3 Side-by-side comparison of the 2001 and 2015 versions of Annex 15 regarding qualification in the context of validation

Annex 15 starts with planning, performance and documentation of validation activities, in the case of the 2015 version quality risk management is explicitly mentioned. The section on qualification is titled “Qualification” in the 2001 version and “Qualification Stages for Equipment, Facilities, Utilities and Systems” in the 2015 version.

2.3.1 Introduction

2001-Version	**2015 Version**
[No Text]	“*(3.1) Qualification activities should consider all stages from initial development of the user requirements specification through to the end of use of the equipment, facility, utility or system. The main stages and some suggested criteria (although this depends on individual project circumstances and may be different) which could be included in each stage are indicated below:* [74]“

An introduction in the 2015 version defines qualification as a life-cycle activity, meaning it starts with conception of design and stops after obsolescence. A mitigation clause (“*although this depends on individual project circumstances and may be different* [74]”) consistent with the “different ways to a common goal”-approach of GMP (see footnote XIII on page 23) allows for a little bit of project-dependent variation.

2.3.2 User Requirement Specifications

User Requirement Specifications were only indirectly mentioned in the 2001 version, as comparing user requirements with planned design is what design qualification is all about.

2001-Version	**2015 Version**
[No Text]	"*(3.2) User requirements specification (URS) The specification for equipment, facilities, utilities or systems should be defined in a URS and/or a functional specification. The essential elements of quality need to be built in at this stage and any GMP risks mitigated to an acceptable level.* *The URS should be a point of reference throughout the validation life cycle.* [74]"

This clause in the 2015 version ensures that documentation is available that shows what a system was supposed to do at the start of a project.

2.3.3 Design Qualification

Design qualification was made mandatory with the 2015 version. Maybe inspectors happened to find themselves too often in situations where they had to explain that just because clause 9 of the 2001 version identifies itself as not mandatory - you did not have to do a DQ - it did not mean that clause 10 also was not mandatory and it has to be shown that design is compliant with GMP.

2001-Version	**2015 Version**
"*(9) The first element of the validation of new facilities, systems or equipment could be design qualification (DQ)* *(10) The compliance of the design with GMP should be demonstrated and documented* [71]"	"*(3.3) The next element in the qualification of equipment, facilities, utilities, or systems 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.* [74]"

Here inspection wants documentation on system suitability for GMP, this basically means answering the question “why do you think that this system can safely be used to produce these medicinal products?”.

2.3.4 Factory Acceptance Test (FAT) / Site Acceptance Test (SAT)

Factory and site acceptance tests are far older than GMP [75] and will have been used as part of qualification before 2015 – especially for equipment where corrections are easy at the vendor's site, like large vessels.

2001-Version	**2015 Version**
[No Text]	"*(3.4) Equipment, especially if incorporating novel or complex technology, may be evaluated, if applicable, at the vendor prior to delivery.* *(3.5) Prior to installation, equipment should be confirmed to comply with the URS/functional specification at the vendor site, if applicable.* *(3.6) Where appropriate and justified, documentation review and some tests could be performed at the FAT or other stages without the need to repeat on site at IQ/OQ if it can be shown that the functionality is not affected by the transport and installation.* *(3.7) FAT may be supplemented by the execution of a SAT following the receipt of equipment at the manufacturing site.* [74]**"**

Adding it to the formal definitions makes it easy for inspection to accept the practice and at the same time reminds users that FAT and SAT have to be planned and documented like any other qualification activity.

2.3.5 Installation qualification (IQ)

The relationship of installation-, operational-, and performance qualification to site acceptance testing is easy to see. Annex 15 and the IQ/OQ/PQ-model can be seen as just structuring site acceptance testing (and leaving more place to add comments about which tests and documents would make the process easy to inspect).

2001-Version	**2015 Version**
"*(11) Installation qualification (IQ) should be performed on new or modified facilities, systems and equipment.*	"*(3.8) IQ should be performed on equipment, facilities, utilities, or systems.*
(12) IQ should include, but not be limited to the following:	*(3.9) IQ should include, but is not limited to the following:*
(a) installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;	*i. Verification of the correct installation of components, instrumentation, equipment, pipe work and services against the engineering drawings and specifications;*
(b) collection and collation of supplier operating and working instructions and maintenance requirements;	*ii. Verification of the correct installation against pre-defined criteria;*
(c) calibration requirements;	*iii. Collection and collation of supplier operating and working instructions and maintenance requirements;*
(d) verification of materials of construction [71]"	*iv. Calibration of instrumentation;*
	v. Verification of the materials of construction [74]"

Installation qualification will produce documented evidence that the system ordered is the system delivered. As design qualification has shown that the system designed should be the system that is needed, installation qualification closes this link between installed system and user requirement specifications further.

2.3.6 Operational qualification (OQ)

The boundaries between IQ and OQ are sometimes hard to define and version 2015 acknowledges that much more explicitly than the version from 2001 – as seen in the comparison of clause 13 and clause 3.10. The last sentence of clause 15 is recognised as redundant in the 2015 version, it replicates the requirement of clause 8 in the 2001 version that was extended into clause 2.10 in 2015.

2001-Version	**2015 Version**
"*(13) Operational qualification (OQ) should follow Installation qualification.* *(14) OQ should include, but not be limited to the following:* *(a) tests that have been developed from knowledge of processes, systems and equipment;* *(b) tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as "worst case" conditions.* *(15) The completion of a successful Operational qualification should allow the finalisation of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements. It should permit a formal "release" of the facilities, systems and equipment.* [71]"	"*(3.10) OQ normally follows IQ but depending on the complexity of the equipment, it may be performed as a combined Installation/Operation Qualification (IOQ).* *(3.11) OQ should include but is not limited to the following:* *i. Tests that have been developed from the knowledge of processes, systems and equipment to ensure the system is operating as designed;* *ii. Tests to confirm upper and lower operating limits, and /or "worst case" conditions.* *(3.12) The completion of a successful OQ should allow the finalisation of standard operating and cleaning procedures, operator training and preventative maintenance requirements.* [74]"

This section defines OQ; especially clause 15 respectively 3.12 should provide for an overview over the documents needed to operate a system according to GMP, making it easy for inspection to gather evidence of GMP compliant operations, or at least of the availability of the necessary documents.

2.3.7 Performance qualification (PQ)

Performance qualification is the boundary between describing how & proving that a system works as intended and proving that a process yields the desired product. The resulting problems in always defining a clear and consistent border between the steps of qualification is even seen by the 2001 version in that it allows a conjunction of PQ with OQ.

2001-Version	**2015 Version**
"*(13) Performance qualification (PQ) should follow successful completion of Installation qualification and Operational qualification.*	"*(3.10) PQ should normally follow the successful completion of IQ and OQ. However, it may in some cases be appropriate to perform it in conjunction with OQ or Process Validation.*
(14) PQ should include, but not be limited to the following:	*(3.11) PQ should include but is not limited to the following:*
(a) tests, using production materials, qualified substitutes or simulated product, that have been developed from knowledge of the process and the facilities, systems or equipment;	*i. Tests, using production materials, qualified substitutes or simulated product proven to have equivalent behaviour under normal operating conditions with worst case batch sizes. The frequency of sampling used to confirm process control should be justified;*
(b) tests to include a condition or set of conditions encompassing upper and lower operating limits.	*ii. Tests should cover the operating range of the intended process, unless documented evidence from the development phases confirming the operational ranges is available.* [74]**"**
(15) Although PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ. [71]**"**	

Defining phases for qualification has operational benefits, if done well it means that mistakes will be found and corrected before they influence tests down the line – thus speeding up the commissioning process.

For documentation this also leads to simplification, because any correction of the system during qualification has to be evaluated, especially to see if tests that were already done will have to be repeated. Corrections lead to documentation that also has to be reviewed, performance of additional tests that has to be checked etc., making it harder to gain the necessary overview to say if a part of a qualification should have

been seen as successful. Having freedom on where to shift the line between qualification steps a little bit means that formal release procedures can be optimised:

"*2.10 A formal release for the next stage in the qualification and validation process should be authorised by the relevant responsible personnel either as part of the validation report approval or as a separate summary document. Conditional approval to proceed to the next qualification stage can be given where certain acceptance criteria or deviations have not been fully addressed and there is a documented assessment that there is no significant impact on the next activity*. [74]"

2.3.8 Re-Qualification

Requalification as a separate entry was missing from the 2001 version, but it was enough to look into clause 45 to find a need for requalification, as facilities, systems and equipment were explicitly mentioned in the need for revalidation.

The addition in the 2015 version of an explicit entry directly after the chapter on qualification may hint on less than optimal implementation of requalification programs across the industry, at least in the view of pharmaceutical inspection.

2001-Version	**2015 Version**
[No Text], but under the header "Revalidation" states: "*(45) Facilities, systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation.* [71]"	"*(4.1) Equipment, facilities, utilities and systems should be evaluated at an appropriate frequency to confirm that they remain in a state of control.* *(4.2) Where re-qualification is necessary and performed at a specific time period, the period should be justified and the criteria for evaluation defined. Furthermore, the possibility of small changes over time should be assessed* [74]"

GMP mandates that production has to be in a state of control, the second law of thermodynamics states that entropy (a measure for "disorder") increases with time. Revalidation (including requalification) is necessary to reconcile these 2 facts.

2.3.9 Discussion of the changes

The 2015 version does not add any material changes to the process of qualification.

On the one hand it adds practices that were established long before the advent of GMP (FAT and SAT), on the other hand it acknowledges practices that had developed in application of the 2001 version (admixture of IQ, OQ and PQ relating to the fluidity of the concepts).

Further additions seem to be rooted in the need to clarify expectations. If the need for "*…product proven to have equivalent behaviour under normal operating conditions*… [74]" is added to the requirements for PQ then it seems legitimate to think that too often "any old, cheap stuff" was used in PQ, producing unreliable results and leading to production problems that ultimately endangered medicinal product safety. And if requalification necessitates an explicit mention it often will have been forgotten.

If the European Medicinal Agency leaves as much time between this edition of its guide to qualification and the next edition as it did with the last edition, then we will see version 3 of Annex 15 around 2030. Extrapolating from the changes to Annex 15 between 2001 and 2015 seems possible:

- There will not be much change in the system of qualification, certain details in recording and testing requirements will surely be added as every test that can be argued away by a company means less work and cheaper production for someone

- There will be additions to validation like the addition of continuous process verification. Whether AI or some other buzzword technologies will be included is to be seen and will depend on actual trends in implemented production methods, modern analytical methods allow for different approaches in describing processes and this will gradually result in novel validation techniques which will have to be regulated

- Any addition, deletion or alteration in Annex 15 will show current thinking of pharmaceutical inspection if the authorship of Annex 15 stays equivalent

- The deletion of "*retrospective validation* [71]"" between the 2001 and 2015 version seems not relevant for guesses about future changes, as the concept itself seems owned to a transitioning phase between a time before and a time after the legal definition of qualification and validation. The concept of retrospective validation itself did never sit easy with Annex 15 itself, as it seems radically opposed to the requirement "*All validation activities should be planned* [71]"".

3 Summary and Conclusions

This thesis compiled some of the historical context of pharmaceutical legislation in general and of qualification in particular.

It cited the worry of rulers and legislators for the well-being of their subjects as the fundamental reason for pharmaceutical legislation and established historical disasters in temporal context to steps of legislative development.

A focus on historical mishaps may lead to the conclusion that “all of these problems were in the past”. Thus, potentially, resulting in a wrong sense of security that “such things do not happen anymore".

In this context it seems timely to take note of this 1997 case of 2 newborn children that received potassium chloride in a lethal dose. This was the final result of a packaging error. The KCl was labelled as glucose – result of a packaging machine that had an unknown hidden pocket for vials, was used to consecutively pack glucose and KCl and whose operating personnel did err in reconciliation of materials [76].

How much damage can be done if wanton disregard of pharmaceutical regulation is applied may be seen in a case from 2012, were 793 patients were infected with fungal meningitis that led to the death of 64 [77].

The need for pharmaceutical legislation, and its enforcement, thus is established and also, with these two examples, shown as contemporary relevant.

Safety of patients is a reason for pharmaceutical legislation, but needs of pharmaceutical producers are the reason to watch and analyse legal developments. This article [78] details the experienced reaction of a conference chairperson, reporting that many attendants were unaware of changes to Annex 15, even though they were published months in advance.

Being surprised (or blindsided, as the article headline calls it) by regulation always implies the possibility of resource waste. If task resulting from new legislation – changes to standard operating procedures, preparation of risk analyses, qualification of measuring equipment etc. – could have been done, or at least been planned, in a more leisurely way, then better work may have resulted.

It would even have been possible to try to influence legislation, draft legislation was posted specifically to invite comments, to enable stakeholders to have due influence on the process. So if bad regulation could be influenced – or even be averted – by commenting on it, maybe even by participating in a dialog with regulators, then awareness of regulation seems essential to ensure efficient production.

In the concrete example the changes to the Annex 15 transport validation regulation[74] read like emphasis, not real change.

And any such proposal by regulators (that seems to clarify regulatory expectations) could, and in the authors opinion should, also lead to reflection of established practices in light of regulatory concern, as displayed by the proposed regulation.

The only alternative available to heeding regulatory concerns seems regulatory enforcement. Timely compliance, enabled by watching developing regulation, appears to be a better way to avoid the damages, reputational as well as otherwise, of a warning letter, a product recall or a suspension of licences.

By looking at how much can go wrong when pharmaceutical production goes wrong, how legislation reacts to that and how that process nowadays enables a wide range of stakeholders to influence it by commenting, it also becomes clear that the system may even need these comments to fulfil another aspect pharmaceutical legislation addresses.

The need of pharmaceutical legislation seems to be “ensuring the access of subjects to safe medication”.

GMP itself focuses on the “safe medication” parts, but price has to be seen as an important influence on the “access” part. A safe medicine that is not affordable will not help any patient. This creates contention, in that an infinite amount of regulatory requirements would need an infinite amount of work (in production as well as in enforcement) and thus necessitate an infinite price tag.

So a balance has to be found – and introducing the practical perspective into the process has to come from the people involved in the practical process.

And, last but not least, in the authors opinion, it helps to know a little bit of historical context when following daily requirements of GMP. Knowing that all the rules are based in a simple and intelligible desire to ensure access to safe and efficacious medicinal products for patients seems easier than blindly following rules that are because authority says so.

In short this work purports to show how a conscientious person would produce pharmaceuticals, how these ways developed, when followed in a legislative context, and how this may be harnessed to streamline pharmaceutical production a bit.

4 Supplementary Texts

I could find neither the “Sanitätsnormativ 1770” nor the first published instance of the cGMP online as a text. Both are available as rendition of scans with automated optical character recognition-generated text overlay. I copied these automatically generated texts and visually compared them to the scans to remove mistakes made by the automated optical character recognition algorithm. To enable further research, the texts are reproduced here.

4.1 III. Inſtrutzion für die Apotheker (Sanitätsnormativ 1770)

“*III. Inſtrutzion für die Apotheker.*

§. 1. Da an der Zubereitung der Arzneien alles gelegen iſt, als ſolle eine Apotheke zu führen Niemand erlaubet werden, der nicht gleichfalls auf einer erbländiſchen Univerſität, der eine mediziniſche Fakultät einverleibet iſt, ordentlich examiniret werden, und das Zeugniß ſeiner Fähigkeit erhalten. Zu dieſem Examen kann ſich jeder Apotheker - Jung ſtellen, nach dem er die überall üblichen Jahre der Lehre oder ſeines Tyrocinii erſtreket hat.

§. 2. Die ſo geſtaltig angenommenen Apotheker haben ihre beſtändige Rükſicht auf einen gottgefälligen Lebenswandel zu richten, von der Sanitätkommiſſion ihre Abhängigkeit und Subordinazion zu erkennen, und ſich nach den vorgeſchriebenen Diſpenſatorien und Tarordnungen, in Zukunft aber nach der Vorſchrift des eheſtens zum Vorſchein kommenden Codicis Pharmacopoei, zu achten.
Dieſen Sazungen haben ſich die Apotheker allerdings zu fügen, und ſolche nicht in dem Mindeſten zu überſchreiten; maſſen die Landes- Regierungen und Sanitätkommiſſionen an gewieſen ſind, in Uebertretungfällen, ſie mögen von ihnen, Apothekern ſelbſt, oder ihren Bedienten begangen werden, mit einer empfindlichen Geld- oder auch anderen arbitrariſchen Leibesſtrafe fürzugehen.

§. 3. Außer in dem Falle der äußerſten Not, wo der Beiſtand des Medikers nicht zu erholen iſt, ſind den Apothekern alle in- und äußerlichen Kurarten und die eigenmächtige Diſpenſazion der Arzneien unter ſcharfer Ahndung verboten; die Medizinen ſind in genüglicher Quantität und Güte nach Vorſchrift geſagter Diſpenſatorien in Bereitſchaft zu halten, in Folge deren auch die jährlich unverſehens vornemenden Biſitazionen gerichtet werden ſollen.

§. 4. Mit allen der Sanitätkommiſſion unterworfenen Perſonen ſollen ſie im guten Verneunen ſtehen, den Dienſtboten der Kranken eine genügliche Auskunft und Nachricht über den Gebrauch der Medizinen erteilen, ihnen beſcheidentlich begegnen, und ſie ſo geſchwind als möglich abfertigen, hienächſt aber die Proviſoren, Geſellen und Jungen in guter Ordnung halten, und dieſen nicht eher ihren Lehrbrief erteilen, als nachdem ſie in der erlernten Kunſt die erforderlichen Kenntniſſe und Erfahrenheiten ſich beigeleget haben.

§. 5. Die Ingredientia Medicamentorum und Simplicia aus allen dreien Reichen müſſen, ſobald man ſelbe zur Korrupzion ſich zu neigen verſpüret, weggeſchaffet, ſo wie jene, welche an ſich ſelbſt mit der Zeit ihre Kraft verlieren, alle Jahre friſch und in hinreichender Menge und Güte angeſchaffet, zu rechter Zeit eingeſammelt, mit allem Fleiße aus getroknet und gereiniget, und in ſauberen Gefäßen aufbehalten, die alten und verdorbenen Präparate aber, welche nicht durch chemiſche Handgriffe wiederum verbeſſert werden können, ausgeſondert und an ihrer Statt friſche verfertiget werden; und da es beſonders bei den Medicamentis chemicis gar oft auf gewiſſe wohlkündige Handgriffe ankommt, als werden die Apotheker ſolche und alle Composita nach maßgebiger Anleitung des Diſpenſatoriums zubereiten und dabei alle Vorſichtigkeit gebrauchen, auch da ihnen ein oder anderer Handgriff nicht vollkommen wiſſend wäre, ſich bei den Land - Fiſikern oder anderen geſchikten Medikern Rats erholen, keineswegs aber in Zubereitung der Azneien auf die Geſellen allein ſich verlaſſen, ſondern bei Zuſammenſezung und Verfertigung der Rezepte mit allem Fleiße darob fein, damit dieſelbe vorgeſchriebenermaſſen gemacht, und nichts davon vernachläſſiget, weder eine andere Spezies eingemenget werden möge. - Vorzüglich iſt unter ſchwerer Strafe zu ſorgen, daß die Gefäße, Tiegel, Mörſer und dergleichen, worin die Arzneien zubereitet werden, wohl gereiniget und jenes Unheil vermieden werde, welches hierinfalls durch den Einfluß ſchädlicher Materien entſtehet, und oft mit den Arzneien die empfindlichſten Folgen nach ſich gezogen hat. - Im Falle ein oder anderes vorgeſchriebenes Ingrediens wicht vorhanden wäre, ſo haben ſie ſolches dem betreffenden Mediker des Endes, auf daß er ſelbſt an deſſen Statt ein an deres von gleicher Wirkung anordnen könne, zu melden, die Rezepte hingegen fürnemlich, wenn darin Ingredienzien von ſtarker Operazion befindlich wären, keinesdings dem Lehrjungen, um nicht etwa durch Unbehutſamkeit oder andere Fehler dem Kranken zu ſchaden, zur Verfertigung anzuvertrauen.

§. 6. Die Apotheker ſowol als Materialiſten ſollen in Betreff des Opii, Mercurii sublimati und anderer Korroſiven, Venenatorum und ſtarken Brecharzneien gute Vorſicht nemen, und nichts von dergleichen angreifenden und ſchädlichen Materialien, wie auch keine composita Medicamenta ohne Verſchreibung oder Zenſur des Medikers hindangeben und verkaufen. Jedoch bleibet ihnen frei, gelinde Laxantia und Lenitiva, als Manam, Cassiam, Tamarinden, Folia sennae, deren Syrupos und dergleichen, in gemäßigter Doſis für ſich ſelbſt hindan zu geben. - Wenn derlei ſtarke, beſonders abtreibende oder giftige Medikamente von unbekannten Menſchen oder verdächtigen Weibs Perſonen begehret würden, ſo ſollen die Apotheker oder andere, die ſolche Dinge feil haben, ſolches gehörig anzeigen, und ohne Gutheißen eines Medikers nicht verabfolgen laſſen, auch überhaupt die Venenosa nicht anders, als an Perſonen guten Rufs und Namens, und auf derſelben eigenhändigen Schein hindangeben. Abtreibende Arzneien ſind ſogar den Hebammen ohne Bewilligung des Medikers nicht zu verabfolgen, und in dieſem Stüke eine ununterbrochene Beſcheidenheit und Aufmerkſamkeit zu gebrauchen.

§. 7. Da bei dem Verkaufe des Arſeniks vielfältige Gefahren unterlaufen, ſo wird den Apothekern alles Ernſtes geboten, den ihren Offizinen nötigen Vorrat dieſes giftigen Materials allzeit wohlverſchloſſen aufzubewahren und keines zu verkaufen, damit etwa nicht durch Geſchirre, ſo dazu gebrauchet wurden, ſchädliche Folgen entſtehen; gleichwie aber dasſelbe dennoch in deun menſchlichen Gebrauche zu manchen Künſten und Zubereitungen unentbehrlich, ſo ſolle es keinem andern zu verkaufen erlaubet ſein, als einer einzigen Perſon und in einem einzigen Gewölbe in den Städten, und dieſes zwar nur einem ſolchen Manne, der von dem Ortsmagiſtrate ausgewählet und für beſcheiden und ſicher anerkennet wird. Auch dieſem wird hiemit zur geſezmäßigen Richtſchnur vorgeſchrieben, daß er ein eigenes Buch halte, in welches alle diejenigen, die einiges Arsenicum ankaufen, den Empfang, die Quantität desſelben, den Tag und ihren Namen einſchreiben müſſen, dabei aber wohl zu beobachten kommt, daß ſolch giftiges Materiale Niemanden als bekannten ſicheren Perſonen gegeben werde; ſollte ſich aber darum Jemand einfinden, der dem Verkäufer nicht ſattſam bekannt wäre, ſo iſt ihm keines zu verabfolgen, wenn er nicht zwei dem Verkäufer bekannte Zeugen mitbringet, die nebſt dem Käufer ihre Namen in das verſtandene Buch ein ſchreiben und beſtätigen müſſen, daß der oder diejenige, welche einiges Arsenicum verlanget, die angeblich ſichere Perſon ſei.

§. 8. In den kleineren Städten auf dem Lande, falls keine Apotheke ſein ſolle, haben die Mediker vorzuſorgen, daß die nötigſten Mittel beigeſchaffet werden und bei Handen ſeien.

§. 9. Zu Zeiten einreißender Krankheiten ſolle bei Tag und Nacht, wo es möglich, ein geſchikter Geſell oder tauglicher Jung in der Apotheke zugegen ſein, welcher den notleidenden Kranken die erforderlichen Arzneien ſchleunigſt, um ſelbe durch Aufenthalt nicht in Gefahr des Lebens zu ſezen, abzureichen hat. In großen Apotheken hingegen, wo mehr als ein Geſell vorhanden, ſoll allemal einer davon die Woche haben, in welcher er gar nicht aus dem Hauſe und der Apotheke gehe, ſondern zu allen Zeiten bei Tag und Nacht bereit ſei. Mit einem Worte: eine der wichtigſten Pflichten der Apotheker beſtehet in dem, daß ſie ſich in der regelmäßigen Beförderung der Arzeimittel nichts zur Laſt legen laſſen.

§. 10. Was die Materialiſten, Gewürzkrämer Deſtillanten, Brantweinbrenner, Wurzelkrämer und dergleichen betrifft, da ſollen dieſe Arzneien, welche allein in die Apotheken gehören, nicht zubereiten oder nach der Hand verkaufen, am allers wenigſten aber ſich des Kurirens anmaſſen, ſondern lediglich ſich ihres Gewerbes halten, und im Widrigen gewärtigen, daß gegen die diesfälligen Uebertreter nebſt der Konfiskazion ihrer Medikamente, auch noch mit einer beſonderen Geld- oder, bei nicht verfangender Verbeſſerung, empfindlicher Leibesſtrafe für geſchritten werde. Es wird daher allen den Marktſchreiern und dergleichen Wurzelkrämern, Okuliſten und Operateurs das Feilhaben der Arzneien in öffentlichen Gewölbern und Privathäuſern gänzlich verboten, und wird dieſes Verbot auch auf die im Lande her umziehenden Waſſer- und Olitätenkrämer erweitert, welchen nicht anders, als nach den in den Erblanden beſtehenden Geihandels-Generalien ihre Wäſſer und Oele zu verkaufen erlaubet iſt, mit der allgemeinen Hauptregel, daß alles das, was von ihnen feilgeboten wird, in die Reihe der Simplicium allerdings gehöre. [59]“

4.2 First Drug cGMP 1963

“*PART 133 - DRUGS; CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURE, PROCESSING, PACKING, OR HOLDING*

In the FEDERAL REGISTER of February 14, 1963 (28 F.R. 1459), proposed regulations to establish criteria for current good manufacturing practice in the processing, packing, and holding of drugs were published. Extensive comments were received, and on the basis of these comments and other relevant information, the Commissioner of Food and Drugs has determined that the following regulations should issue. Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sees. 501 (a)(2)(B), 701(a); 52 Stat. 1050 as amended 76 Stat. 780, 781; 1055; 21 U.S.C.A. 351(a) (2) (B), 371 (a)), and the authority delegated to him by the Secretary of Health, Education, and Welfare (25 FR. 8625): It is ordered, That these regulations be adopted as set forth below:

DEFINITIONS

Sec. 133.1 Definitions.

FINISHED PHARMACEUTICALS; MANUFACTURING PRACTICE

133.2 Current good manufacturing practice.
133.3 Buildings.
133.4 Equipment.
133.5 Personnel.
133.6 Components.
133.7 Master formula and batch-production records.
133.8 Production and control procedures.
133.9 Product containers.
133.10 Packaging and labeling.
133.11 Laboratory controls.
133.12 Distribution records.
133.13 Stability.
133.14 Complaint files.

Authority: §§ 133.1 to 133.14 issued under secs. 501, 701; 52 Stat. 1050 as amended 76 Stat. 780, 781; 1055; 21 U.S.C.A. 351, 371.

Definitions.

§ 133.1 Definitions.

(a) As used in this Part 133, "act" means the Federal Food, Drug, and Cosmetic Act, sections 201-902, 52 Stat. 1052 (21 U.S.C. 321-392), with all amendments thereto.

(b) The definitions and interpretations contained in section 201 of the Federal Food, Drug, and Cosmetic Act shall be applicable to such terms when used in the regulations in this Part 133.

FINISHED PHARMACEUTICALS; MANUFACTURING PRACTICE

§ 133.2 Current good manufacturing practice.

The criteria in §§ 133.3-133.13, inclusive, shall apply in determining whether the methods used in, or the facilities or controls used for, the manufacture, processing, packing, or holding of a drug conform to or are operated or administered in conformity with current good manufacturing practice to assure that a drug meets the requirements of the act as to safety, and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess, as required by section 501(a) (2) (B) of the act. The regulations in this Part 133 permit the use of precision automatic mechanical or electronic equipment in the production of drugs when adequate inspection and checking procedures are used to assure proper performance.

§ 133.3 Buildings.

Buildings in which drugs are manufactured, processed, packaged, labeled, or held shall be maintained in a clean and orderly manner and shall be of suitable size, construction, and location in relation to surroundings to facilitate maintenance and operation for their intended purpose. The buildings shall:

(a) Provide adequate space for the orderly placement of equipment and materials used in any of the following operations for which it is employed, to minimize any risk of mix-ups between different drugs, their components, packaging, or labeling:

(1) The receipt, sampling, and storage of components.
(2) Any manufacturing and processing operations performed on the drug.
(3) Any packaging and labeling operations.
(4) Storage of containers, packaging materials, labeling, and finished products.
(5) Control and production-laboratory operations.

(b) Provide adequate lighting and ventilation, and when necessary for the intended production or control purposes, adequate screening, filtering, dust, humidity, temperature, and bacteriological controls, as for example, to prevent contamination of products by extraneous adulterants; to prevent the dissemination of micro-organisms from one area to another; to facilitate the sterilization of special work areas, such as those used for production of parenteral preparations; to provide suitable housing for any animals; and to avoid other conditions unfavorable to the safety and integrity of the product.

(c) Provide for adequate washing, cleaning, toilet, and locker facilities.

§ 133.4 Equipment.

Equipment used for the manufacture, processing, packaging, labeling, holding, or control of drugs shall be maintained in a clean and orderly manner and shall be of suitable design, size, construction, and location in relation to surroundings to facilitate maintenance and operation for its intended purpose. The equipment shall:

(a) Be so constructed that any surfaces that come into contact with drugs are suitable, in that they are not reactive, additive, or absorptive to an extent that significantly affects the identity, strength, quality, or purity of the drug or its components.
(b) Be so constructed that any substances required for the operation of the equipment, such as lubricants or coolants, may be employed without hazard of becoming additive to drug products.
(c) Be constructed to facilitate adjustment, cleaning, and maintenance as necessary to assure the reliability of control procedures, to assure uniformity of production, and to assure the exclusion from drugs of contaminants, including those from previous and current manufacturing operations.
(d) Be of suitable size and accuracy for use in any intended measuring, mixing, or weighing operations.

§ 133.5 Personnel.

The key personnel involved in the manufacture and control of the drug shall have a background of appropriate education or appropriate experience or combination thereof for assuming responsibility to assure that the drug has the safety, identity, strength, quality, and purity that it purports to possess.

§ 133.6 Components.

Components used in the manufacture and processing of drugs, regardless of whether they appear in the finished product, shall be identified, stored, examined, tested, inventoried, handled, and otherwise controlled in a manner to assure that they conform to appropriate standards of identity, -strength, quality, and purity, and are free of contaminants at time of use, and to provide that appropriate records are maintained of their origin, receipt, examination, testing, disposition, and use in drug manufacture or processing.

§ 133.7 Master-formula and batch-production records.

(a) For each drug product, master-formula records shall be prepared, endorsed, and dated by a competent and responsible individual and shall be independently checked, reconciled, endorsed, and dated by a second competent and responsible individual. The record shall include:

(1) The name of the product, a description of its dosage form, and a specimen or copy of the label and each other portion of the labeling contained in a retail package of the drug.
(2) The weight or measure of each ingredient per dosage unit or per unit of weight or measure of the finished drug, and a statement of the total weight or measure of any dosage unit.
(3) A complete batch formula for each batch size to be produced from the master-formula record, including a complete list of ingredients designated by names or codes sufficiently specific to indicate any special quality characteristic; an accurate statement of the weight or measure of each ingredient, regardless of whether it appears in the finished product, except that reasonable variations may be permitted in the amount of components necessary in the preparation in dosage form, provided that the variations are stated in the master formula; an appropriate statement concerning any calculated excess of an ingredient; appropriate statements of theoretical weight or measure at various stages of processing; and a statement of the theoretical yield.
(4) A description of the containers, closures, packaging, and finishing materials.
(5) Manufacturing and control instructions, procedures, specifications, special notations, and precautions to be followed.

(b) A separate batch-production and control record shall be prepared for each batch of drug produced and shall be retained for at least 2 years after distribution has been completed. The batch-production and control record shall include:

(1) An accurate reproduction of the appropriate master-formula record, checked and endorsed by a competent, responsible individual.

(2) Records of each step in the manufacturing, processing, packaging, labeling, and controlling of the batch, including dates, specific identification of each batch of components used, weights or measures of components and products in course of processing, in-process and laboratory-control results, and the endorsements of the individual actively performing or the individual actively supervising or checking each step in the operation.
(3) A batch number that permits determination of all laboratory-control procedures and results on the batch and all lot or control numbers appearing on the labels of drugs from the batch.

§ 133.8 Production and control procedures.

Production and control procedures shall include all reasonable precautions, including the following, to assure that the drugs produced have the identity, strength, quality, and purity they purport to possess.

(a) Each critical step in the process, such as the selection, weighing, and measuring of components; the addition of active ingredients during the process; weighing and measuring during various stages of the processing, and the determination of the finished yield shall be performed by a competent, responsible individual and checked by a second competent, responsible individual, or if such steps in the processing are controlled by precision automatic mechanical or electronic equipment their proper performance is adequately checked by one or more competent, responsible individuals.
(b) All containers and equipment used in producing a batch of drugs shall be clearly labeled at all times to identify fully and accurately their contents, the stage of processing, and the batch, and shall be stored and handled in a manner adequate to prevent mixups with other drugs.
(c) Equipment, utensils, and containers shall be thoroughly cleaned and previous identification removed between batches and in continuous batch operations at suitable intervals, to prevent contamination and mixups.
(d) Appropriate procedures to minimize the hazard of contamination with micro-organisms in the production of parenteral drugs, ophthalmic solutions, and any other drugs purporting to be sterile.
(e) To assure the uniformity and integrity of products, there shall be adequate in-process controls, such as checking the weights and disintegration time of tablets, checking fill of liquids, and checking .the adequacy of mixing, the homogeneity of suspensions, and the clarity of solutions.
(f) Competent and responsible personnel shall check actual against theoretical yield of a batch of drug, and in the event of any significant unexplained discrepancies, key personnel shall prevent distribution of the batch in question and other associated batches of drugs that may have been involved in a mixup with it.

§ 133.9 Product containers.

Suitable specifications, test methods, cleaning procedures, and, when indicated, sterilization procedures shall be used to assure that containers, closures, and other component parts of drug packages are-suitable for their intended use, in that they are not reactive, additive, or absorptive to an extent that significantly affects the identity, strength, quality, or purity of the drug, and furnish adequate protection against its deterioration or contamination.

§ 133.10 Packaging and labeling.

Packaging and labeling operations shall be adequately controlled to assure that only those drugs that have met the specifications established in the master-formula records shall be distributed; to prevent mixups between drugs during the packaging and labeling operations; to assure that correct labeling is employed for the drug; and to identify finished products with lot or control numbers that permit determination of the history of the manufacture and control of the batch of drug. Packaging and labeling operations shall:

(a) Be performed with adequate physical segregation of such operations from operations on any other drugs to avoid mixups.
(b) Provide that each type of labeling used shall be stored in a manner that avoids mixups between labelings and shall be carefully checked for identity and conformity to the labeling specified in the batch-production records.
(c) Provide adequate control of the quantities of labeling issued for use with the drug. (Competent, responsible personnel shall reconcile any discrepancy between the quantity of drug finished and the quantity of labeling issued. In the event of any significant unexplained discrepancy, key personnel shall prevent distribution of the batch in question and other associated batches of drugs that may have been involved in a mixup.)
(d) Provide for an inspection of the facilities to be used prior to labeling a drug to assure that all the previously used labeling and other drugs have been removed.
(e) Provide for adequate examination or laboratory testing of adequately representative samples of finished products after packaging and labeling to safeguard against any error in the finishing operations, and to prevent distribution of any batch until all specified tests have been met.

§ 133.11 Laboratory controls.

Laboratory controls shall include the establishment of adequate specifications and test procedures to assure that components, drug preparations in the course of processing, and finished products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(a) The establishment of master records containing appropriate specifications for each component used in drug production and a description of the test procedures used to check them, including provision for testing adequately representative samples. Such records shall also provide for appropriate retesting of materials subject to deterioration.
(b) The establishment of appropriate specifications, when needed, for drug preparations in the course of processing, and a description of the test procedures to check them, including provision for testing adequately representative samples.
(c) The establishment of appropriate finished-product specifications and a description of laboratory test procedures to check them, including provision for testing adequately representative samples.
(d) Adequate provision for checking the identity and strength for all active ingredients of drugs, for assuring the sterility of articles purporting to be sterile, and the freedom from pyrogens of articles that should be tested for freedom from pyrogens.
(e) Adequate provision to check the reliability, accuracy, and precision of any laboratory test procedures used.
(f) A reserve sample of at least twice the quantity of drug required to conduct all the tests performed on the batch of drug shall be retained at least 2 years after distribution has been completed.
(g) Provision for complete records of all data concerning laboratory tests performed, including the dates and endorsements of individuals making the tests, and provision for specifically relating the tests to each batch of drug to which they apply. Such records shall be retained for at least 2 years after distribution has been completed.

§ 133.12 Distribution records.

Complete records shall be maintained of the distribution of each batch of drug in a manner that will facilitate its recall if necessary. Such records shall be retained for at least 2 years after distribution has been completed, and shall include the name and address of the consignee, the date and quantity shipped, and the lot or control numbers identifying the batch of drug.

§ 133.13 Stability.

Adequate provision shall be made for testing the stability of components, drug preparations in the course of processing, when needed, and finished drugs. Such stability tests shall:

(a) Make adequate provision for determining the reliability and specificity of stability test methods employed.
(b) Make adequate provision to determine the stability of products in the containers in which they are marketed to assure, among other things, that the container is suitable, in that it is not reactive, additive, or adsorptive to an extent that significantly affects the identity, strength, quality, or purity of the drug.
(c) Provide for stability studies of any solutions prepared as directed in the drug labeling at time of dispensing.
(d) Provide for suitable expiration dates to appear in the labeling of the drug when needed to assure that the drug meets appropriate standards of identity, strength, quality, and purity at time of use.

§ 133.14 Complaint files.

Records shall be maintained of all written or verbal complaints for each product. Complaints shall be evaluated by competent and responsible personnel and, where indicated, appropriate action taken. The record shall indicate the evaluation and action.

Effective date: This order shall become effective on date of publication.

(Secs. 501, 701, 52 Stat. 1050 as amended 76 Stat. 780, 781; 1055 21 U.S.C.A. 351, 371)

It is recognized that some modification of these regulations is indicated in connection with their application to the manufacture of chemicals and other raw materials used as components of finished drugs and in connection with their application to the production of such drugs as medicated feeds for administration to animals, in which current practice involves less rigid conditions. Proposed regulations dealing with these areas will be published at a later date.

Dated: June 12, 1963.
GEO. P. LARRIK,
Commissioner of Food and Drugs.
[F.R. Doc. 63-6336; Filed, June 19, 1963; 8:45 a.m.] [29]“

5 Abbreviations

AGES ..... Agentur für Gesundheit und Ernährungssicherheit
approx. ..... approximately
BCE ..... before current epoch
BS..... British Standards
(c)GMP ..... (current) Good Manufacturing Practice
DQ ..... Design Qualification
EC ..... European Communities
EEC ..... European Economic Community
EU ..... European Union
FAT..... Factory Acceptance Test
FDA ..... U.S. Food and Drug Administration
IOQ..... combined Installation/Operation Qualification
IQ..... Installation Qualification
ISO ..... International Organization for Standardization
NASA..... National Aeronautics and Space Administration
OQ..... Operational Qualification
PQ ..... Performance Qualification
SAT ..... Site Acceptance Test
URS..... User Requirement Specification
US(A)..... United States (of America)
WHO..... World Health Organisation

6 Literature, Notes and Sources

[1] Commission Directive 2003/94/EC, Article 2(6); 14.10.2003, Official Journal of the European Union; Brussels

[2] Part 133-Drugs; Current Good Manufacturing Practice in Manufacture, Processing, Packing, Or Holding, § 133.2;
Federal Register Volume 28, Number 32, 14.02.1963, page 1459 – 1461; The National Archives of the United States; Washington

[3] EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 1, Manufacture of Sterile Medicinal Products (corrected version), 25.11.2008 (rev.), European Commission Enterprise And Industry Directorate-General, Consumer goods, Pharmaceuticals, Brussels; 4.1 (particles) and 19 (microbial)

[4] ICH guideline Q3D (R1) on elemental impurities; 28.03.2019, European Medicines Agency, Committee for Human Medicinal Products, Amsterdam

[5] Validation of Cleaning Processes (7/93) – GUIDE TO INSPECTIONS VALIDATION OF CLEANING PROCESSES, page 6/8
Download from https://www.fda.gov/validation-cleaning-processes-793 16.7.2020

[6] EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 15, Qualification and Validation, 5.2.2; 30.03.2015, European Commission Directorate-General For Health And Food Safety, Medicinal Products – Quality, Safety and Efficacy; Brussels

[7] J. C. de Roode, T. Lefèvre, M. D. Hunter, “Self-Medication in Animals”, Science 340 (2013), 6129: 150-151;
DOI: 10.1126/science.1235824

[8] R. Eisler, “Chrysotherapy: a synoptic review”; Inflammation Research 52 (2003), 487–501;
DOI 10.1007/s00011-003-1208-2

[9] M. Macher, “Dr. Macher’s Handbuch der kais. kön. Sanitäts-Gesetze und Verordnungen mit besonderer Beziehung auf die innerösterreichischen Provinzen“, 1. Band (Graz: J.F. Dirnböck, 1846)

[10] „*Daher die Klagen vieler Apotheker, ‚daß sie nach manchen Vorschriften ... nicht arbeiten können und die Prozesse mißlingen*“, author’s translation
K. Ganzinger „Über einige Neuerungen in den Pharmakopöen seit dem Ende des 18. Jahrhunderts“, Geschichtsbeilage der Deutschen Apotheker-Zeitung zugleich Mitteilungsblatt der Internationalen Gesellschaft für Geschichte der Pharmazie e. V. 13 (1961), 4: 25-28

[11] „… hatte der Kandidat ein Examen aus Botanik, Arzneimittellehre und Chemie abzulegen und vor einer aus Mitgliedern der medizinischen Fakultät bestehenden Kommission einige chemisch-pharmazeutische Operationen praktisch durchzuführen….“
K. Ganzinger, „Das österreichische Sanitätsnormativ von 1770 und die Pharmazie“, Veröffentlichungen der Internationalen Gesellschaft für Geschichte der Pharmazie eV, edited by H. Hügel, W-H. Hein, editors (Stuttgart: Wissenschaftliche Verlagsgesellschaft mbH, 1973) Neue Folge Vol. 40, 53–69

[12] „Die Betriebsräume, Einrichtungsgegenstände, Behältnisse und Geräte müssen in Ordnung und in gebrauchsfähigem Zustand sowie rein gehalten werden“
Verordnung des Bundesministers für soziale Verwaltung im Einvernehmen mit dem Bundesminister für Land- und Forstwirtschaft vom 4. Juli 1934, betreffend den Betrieb von Apotheken (Apothekenbetriebsordnung), §3, 04.08.1934, Bundesgesetzblatt für den Bundesstaat Österreich 171/1934, Wien

[13] Österreichisches Arzneibuch (Pharmacopoea Austriaca Editio Nona), 9. Ausgabe (Wien: Österreichische Staatsdruckerei, 1960), 1. Band page 8

[14] Ibid., page 9

[15] Ibid., page 43

[16] Ibid., page 153

[17] Ibid., page 1669

[18] Ibid., 2. Band, page 223

[19] Ibid., 1. Band page 869

[20] S. Potter, Justice, opinion of, in Jacobellis v. Ohio (1964),
downloaded from https://en.wikipedia.org/wiki/I_know_it_when_I_see_it 17.05.2021

[21] Pharmacopea Austriaca Editio Octava, Viennæ cæs. reg. aulæ et imperii typographia, Wien, 1906, page 246

[22] R.B. Tucker, „Six Innovation Leadership Skills Everybody Needs To Master“, Forbes, 14.02.2017,
downloaded from https://www.forbes.com/sites/robertbtucker/2017/02/09/six-innovation-leadership-skills-everybody-needs-to-master/#48d7c0386e5b 19.01.2021

[23] C. Ballentine “Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident”, FDA Consumer magazine (1981), June
downloaded from https://www.fda.gov/files/about%20fda/published/The-Sulfanilamide-Disaster.pdf 19.01.2021

[24] J.P. Swan, “The 1941 sulfathiazole disaster and the birth of good manufacturing practices”, PDA Journal of Pharmaceutical Science and Technology 53 (1999), 3:148-53

[25] C. Ballentine “Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident”, FDA Consumer magazine (1981), June

[26] No authorship, “In memoriam Frau Hofrat Dr. Ingeborg Eichler”, Österreichische Pharmakologische Gesellschaft (2008)
downloaded from https://www.aphar.at/pdfs/Nachruf-Ingeborg-Eichler.pdf 19.01.2021

[27] FDA virtual exhibit “Frances Oldham Kelsey: Medical reviewer famous for averting a public health tragedy”, collection of FDA History Exhibits (online)
downloaded from https://www.fda.gov/about-fda/virtual-exhibits-fda-history/frances-oldham-kelsey-medical-reviewer-famous-averting-public-health-tragedy 19.01.2021

[28] Part 133-Drugs; Current Good Manufacturing Practice in Manufacture, Processing, Packing, Or Holding,
Federal Register Volume 28, Number 32, 14.02.1963, page 1459 – 1461; The National Archives of the United States; Washington

[29] Part 133-Drugs; Current Good Manufacturing Practice in Manufacture, Processing, Packing, Or Holding,
Federal Register Volume 28, Number 120, 20.06.1963, page 6385 – 6387; The National Archives of the United States; Washington

[30] K. Ganzinger, „Geschichte der Pharmazie im Spiegel der österreichischen Pharmakopöen von Maria Theresia bis 1855“, Österreichische Apothekerzeitung 26 (1972) 49: 861-868

[31] L. Colange, “Zell’s Popular Encyclopedia. A complete Dictionary of the English Language with a Pronouncing Vocabulary and a Gazetteer of the World”, (Philadelphia: T. Ellwood Zell, 1882), Vol. IV Poti – Z, page 2436
downloaded from https://books.google.at/books?id=ukQxAQAAMAAJ 17.05.2021

[32] Part 133-Drugs; Current Good Manufacturing Practice in Manufacture, Processing, Packing, Or Holding,
Federal Register Volume 36, Number 10, 15.01.1971, page 601 – 605; The National Archives of the United States; Washington

[33] Title 21-Food and Drugs, Chapter I-Food and Drug Administration, Department of Health, Education, and Welfare [Recodification Docket No. 9] Subchapter C-Drugs: General Reorganization and Republication,
Federal Register Volume 40, Number 60, 27.03.1975, page 13996 – 14049; The National Archives of the United States; Washington
(pages 14025 – 14028 for Part 211-Current Good Manufacturing Practice for Finished Pharmaceuticals)

[34] “*SUMMARY: This document amends the FDA regulations that set forth current good manufacturing practice (CGMP) for human and veterinary drug products. The amendments update present regulations in light of current technology for drug manufacturing and delineate requirements more specifically than do the present regulations. Although some of the provisions in these amendments represent requirements not specifically included in the existing CGMP regulations, in many instances the revisions are practices that have been considered implicit in the regulations or are at least considered by most manufacturers to be desirable requirements for their own operations.*
(…) The regulations are being updated and made more explicit, and therefore less subject to varying interpretations, to assure that all members of the drug industry are

made aware of the level of performance expected of them to be in compliance with the act."
Title 21-Food and Drugs, Chapter I-Food and Drug Administration, Department of Health, Education, and Welfare [Docket No. 75N-0339] Human and Veterinary Drugs, Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding, Federal Register Volume 43, Number 190, 28.09.1978, page 45014 – 45087; The National Archives of the United States; Washington
(pages 45077 – 45087 for Part 211-Current Good Manufacturing Practice for Finished Pharmaceuticals)

[35] Department of Health, Education, and Welfare, Food and Drug Administration [21 CFR Parts 201,207,210, 211,229] [Docket No. 75N-0339] Human and Veterinary Drugs, Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding,
Federal Register Volume 41, Number 31, 13.02.1976, page 6877 – 6894; The National Archives of the United States; Washington

[36] Title 21-Food and Drugs, Chapter I-Food and Drug Administration, Department of Health, Education, and Welfare, Subchapter C-Drugs, Ophthalmic Preparations, Ophthalmic Ointments; Sterility Requirements,
Federal Register Volume 37, Number 209, 28.10.1972, page 23105 – 23110; The National Archives of the United States; Washington

[37] Part 314-New Drug Applications, Federal Register Volume 39, Number 62, 29.03.1974, page 11718 – 11732; The National Archives of the United States; Washington

[38] Federal Register Volume 40, Number 60, 27.03.1975, page 13996 – 14049; The National Archives of the United States; Washington, see pages 13997, 13998 and 14023

[39] Zell's Popular Encyclopedia, Vol. IV Poti – Z, page 2020

[40] K. Eby, "A Quality Principle: Everything You Need to Know about Total Quality Management", 21.06.2021,
downloaded from https://www.smartsheet.com/total-quality-management 04.02.2021: Author was not able to find a paper that really stated that, but both contributions (Shewhart as well as Taylor) regularly cropped up when reading about the development of quality management

[41] S.J. Ralston, "Doing versus Thinking: John Dewey's Critique of Scientific Management", SSRN (2013)
downloaded from https://ssrn.com/abstract=2255687 04.02.2021

[42] F.W. Taylor, "The Principles of Scientific Management", (New York, London: Harper & Brothers, 1919, Copyright 1911)

[43] The Rules Governing Medicinal Products in the European Union, EudraLex, Volume 4, Pharmaceutical Legislation, Medicinal products for human and veterinary use, Good manufacturing practices, 1998, Office for Official Publications of the European Communities, Luxembourg

[44] W.A. Shewhart, Bell Telephone Laboratories, Inc., “Economic Control of Quality of Manufactured Product”, Seventh Printing, (Toronto, New York, London: D. van Nostrand Company, Inc. no date given for printing – preface dated April 1923)
Part III (chapters 10-12) is named “Basis for Specification of Quality Control” and part VII (chapters 22-25) is named “Quality Control in Practice”

[45] M. Best, D. Neuhauser, “Walter A Shewhart, 1924, and the Hawthorne factory”, Quality and Safety in Health Care 15 (2006) 1:142-143

[46] W.E. Deming, “Statistical Control of Quality in Japan”, Conference Paper, International Conference on Quality, Tokyo (1969)
downloaded from https://deming.org/wp-content/uploads/2020/06/Statistical-Control-of-Quality-in-Japan-1969.pdf 04.02.2021

[47] W.E. Deming, „Die Verantwortung der Betriebsführung für die Anwendung statistischer Methoden in der deutschen Industrie" Weltwirtschaftliches Archiv, Zeitschrift des Instituts für Weltwirtschaft an der Universität Kiel, Herausgeber F. Baade 71 (1953) 2: 234 - 250

[48] W.L. Papp, “It’s Close Enough for Government Work – The Antithesis of Quality Attracts Quality”, Air Force Civil Engineer 8 (1967) 2: 30 - 31
downloaded from https://books.google.at/books?id=3twscEauJcMC 18.05.2021

[49] R.D. Hinrichs, “Rifle development, standardization, and procurement in the United States military 1950-1967”, graduate thesis, Iowa State University (2009), see, for example, page 19/20 or page 69, downloaded from https://lib.dr.iastate.edu/cgi/viewcontent.cgi?article=1538&context=etd 04.02.2021

[50] D. Graebner, “Debt, the first 5000 Years”, First Edition (New York: Melville House Publishing, 2011); page 26

[51] P. Gibbon, L. Henriksen, „On the Pre-history of ISO 9000: The Making of a Neo-liberal Standard.“ in “Governing Through Standards :Origins, Drivers and Limitations” edited by S. Ponte, P. Gibbon, J. Vestergaard (London, Palgrave Macmillan 2011) 130-158; page 135

[52] Office of Manned Space Flight “Reliability Program Evaluation Procedures (SP-6002)” and Office of Manned Space Flight “Quality Program Evaluation Procedures (SP-6003)”, September 1963, National Aeronautics and Space Administration, Washington, D.C.

[53] P. Gibbon, L. Henriksen, „On the Pre-history of ISO 9000: The Making of a Neo-liberal Standard.“; page 139-141

[54] Ibid., page 155

[55] NASA Quality Publication NPC 200-2 “Quality Program Provisions for Space System Contractors”, April 1962, National Aeronautics and Space Administration, Washington, D.C.

[56] "*Under a quality system, it is normally expected that the product and process development units, the manufacturing units, and the QU will remain independent. In very limited circumstances, a single individual can perform both production and quality functions. That person is still accountable for implementing all the controls and reviewing the results of manufacture to ensure that product quality standards have been met. Under such circumstances, it is recommended that another qualified individual, not involved in the production operation, conduct an additional, periodic review of QU activities.*"
Guidance for Industry; Quality Systems Approach to Pharmaceutical CGMP Regulations, September 2006, U.S. Department of Health and Human Services ,Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Veterinary Medicine (CVM), Office of Regulatory Affairs (ORA), Rockville, Maryland, page 6

[57] The Rules Governing Medicinal Products in the European Community, Volume IV, Guide to good manufacturing practice for medicinal products, 1989, Office for Official Publications of the European Communities, Luxembourg, item 2.3, page 22

[58] D.A. Davis et.al., "Accuracy of Physician Self-assessment Compared With Observed Measures of Competence. A Systematic Review" Journal of the American Medical Association, 289 (06.09.2006) 9: 1094-1102

[59] M. Macher, "Dr. Macher's Handbuch der kais. kön. Sanitäts-Gesetze und Verordnungen mit besonderer Beziehung auf die innerösterreichischen Provinzen", 1. Band (Graz: J.F. Dirnböck, 1846), page 111, opening paragraph of the "Sanitätsnormativ 1770"

[60] Title 21-Food and Drugs, Chapter I-Food and Drug Administration, Department of Health, Education, and Welfare [Docket No. 75N-0339] Human and Veterinary Drugs, Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding, Federal Register Volume 43, Number 190, 28.09.1978, page 45014 – 45087; The National Archives of the United States; Washington, page 45014

[61] Zell's Popular Encyclopedia, Vol. IV Poti – Z, page 2020

[62] The Rules Governing Medicinal Products in the European Community, Volume IV, Guide to good manufacturing practice for medicinal products, 1989, Office for Official Publications of the European Communities, Luxembourg, page 12

[63] R. Bliem, FH Studiengang Bioengineering mit Schwerpunkt biotechnologisches Qualitätsmanagement, lecture 2006, author's personal notes

[64] International Standard ISO 9000 Quality management systems - Fundamentals and vocabulary, 15.12.2000, ISO copyright office, Geneva, page 15-16

[65] https://books.google.at/

[66] Google book search:

„The report“ WHO, supposedly 1950:
https://books.google.at/books?id=HMPtjT69ITgC

The whole search for up to 01.01.1950:

https://www.google.com/search?q=%22qualification+and+validation%22&sxsrf=ALeKk00Ot1MREooY_8v9jOZ8zSfgAxrsOQ%3A1616599906539&source=lnt&tbs=cdr%3A1%2Ccd_min%3A%2Ccd_max%3A1%2F1%2F1950&tbm=bks (1 hit, 24.03.2021)

The whole search for 01.01.1950 – 31.12.1960:

https://www.google.com/search?q=%22qualification+and+validation%22&sxsrf=ALeKk03KcEV-Pc3RToOXnIF_gswtnWVp1Q%3A1616599889967&source=lnt&tbs=cdr%3A1%2Ccd_min%3A1950%2Ccd_max%3A1960&tbm=bks (8 hits, 24.03.2021)

The whole search for 01.01.1961 – 31.12.1970:

https://www.google.com/search?q=%22qualification+and+validation%22&sxsrf=ALeKk00JQaJIkLZoUw-57569XeAwSoqQyA%3A1616600590844&source=lnt&tbs=cdr%3A1%2Ccd_min%3A1%2F1%2F1961%2Ccd_max%3A12%2F31%2F1970&tbm=bks (6 hits, 24.03.2021)

Food, Drug cosmetic law reporter, supposedly 1963:

https://books.google.at/books?id=6X5PAQAAIAAJ it shows the phrase “description of loading configuration”,
which was searched for in the pages of the journal, as available on JSTOR:
https://www.jstor.org/action/doBasicSearch?Query=description+of+loading+configuration+AND+jid%3A%28j50021284+OR+j50021283+OR+j50021244%29 and could only be found in a symposium report from 1982.

The whole search for 01.01.1971 – 31.12.1980:

https://www.google.com/search?q=%22qualification+and+validation%22&sxsrf=ALeKk00pZkqnndcO7K2XMvGFaAKn_7z3Mg%3A1616601308729&source=lnt&tbs=cdr%3A1%2Ccd_min%3A1%2F1%2F1971%2Ccd_max%3A12%2F31%2F1980&tbm=bks (3 hits, 24.03.2021)

The whole search for 01.01.1981 – 31.12.1990:

https://www.google.com/search?q=%22qualification+and+validation%22&biw=1745&bih=800&sxsrf=ALeKk03dzMUgmzMXb-L1RNw3B1rmPzk2uQ%3A1616602522859&source=lnt&tbs=cdr%3A1%2Ccd_min%3A1%2F1%2F1981%2Ccd_max%3A12%2F31%2F1990&tbm=bks (36 hits, 24.03.2021)

The whole search for 01.01.1991 – 31.12.2000:

https://www.google.com/search?q=%22qualification+and+validation%22&biw=1745&bih=800&sxsrf=ALeKk02OxA5yYI84Wt8s4fqDu8fkZdV3JA%3A1616602603011&source=lnt&tbs=cdr%3A1%2Ccd_min%3A1%2F1%2F1991%2Ccd_max%3A12%2F31%2F2000&tbm=bks (~55 hits, 24.03.2021)

The whole search for 01.01.2001 – 31.12.2010:

https://www.google.com/search?q=%22qualification+and+validation%22&biw=1745&bih=800&sxsrf=ALeKk03hwahiXxZSdqbhNDR0TGBFPalpsA%3A1616602703176&source=lnt&tbs=cdr%3A1%2Ccd_min%3A1%2F1%2F2001%2Ccd_max%3A12%2F31%2F2010&tbm=bks (~77 hits, 24.03.2021)

The whole search for 01.01.2011 – 31.12.2020:

https://www.google.com/search?q=%22qualification+and+validation%22&biw=1745&bih=800&sxsrf=ALeKk02RiOKlh8yS7fYz3mMtUKgldzeDVw%3A1616602912466&source=lnt&tbs=cdr%3A1%2Ccd_min%3A1%2F1%2F2011%2Ccd_max%3A12%2F31%2F2020&tbm=bks (17 hits, 24.03.2021)

The declining number of hits may be explained in the declining popularity of Google Books.

[67] Pharmaceutical Dosage Forms, Parenteral Medications Band 2 page 338 https://books.google.at/books?id=WhRtAAAAMAAJ&q=%22qualification+and+validation%22&dq=%22qualification+and+validation%22&hl=de&sa=X&ved=2ahUKEwiJseacmuDvAhWKyYUKHTgwDAM4FBDoATACegQIBhAC

[68] Center for Drugs and Biologics, Center for Devices and Radiological Health, "Guideline on General Principles of Process Validation", May 1987, Food and Drug Administration, Rockville, Maryland

[69] A. Kraßnigg, "GM/DP-Inspektionen",no date given, downloaded from https://www.basg.gv.at/uploads/cal_docs/090603_Inspektionen_Uebersicht.pdf, 12.04.2021, and
R. Schwarz, "AGES Gespräche, Inspektion pharmazeutischer Betriebe", 10.11.2010, downloaded from https://www.basg.gv.at/uploads/cal_docs/101110_Inspektion_pharmazeutischer_Betriebe.pdf, 12.04.2021

[70] U.M. Inokon, "Approaches to GMP inspection CDER Small Business - Regulatory Education for Industry(REdI)", June 2014, downloaded from https://www.fda.gov/media/89231/download 12.04.2021, page 54

[71] Final Version of Annex 15 to the EU Guide to Good Manufacturing Practice, July 2001, European Commission Enterprise Directorate-General, Single market, regulatory environment, industries under vertical legislation, Pharmaceuticals and cosmetics, Brussels

[72] The Rules Governing Medicinal Products in the European Union, EudraLex, Volume 4, Pharmaceutical Legislation, Medicinal products for human and veterinary use, Good manufacturing practices, 1998, Office for Official Publications of the European Communities, Luxembourg

[73] 479. Verordnung der Bundesministerin für Gesundheit und Frauen betreffend Betriebe, die Arzneimittel herstellen, kontrollieren oder in Verkehr bringen (Arzneimittelbetriebsordnung 2005 - AMBO 2005), 14.12.2004, Bundesgesetzblatt für die Republik Österreich II 479/2004, Wien

[74] EudraLex Volume 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Annex 15: Qualification and Validation, 30.03.2015, European Commission Directorate-General for Health and Food Safety, Medicinal Products – Quality, Safety and Efficacy, Brussels

[75] See page 243 for „tests, factory“ and „tests after installation, shipboard“ for a 1920 naval version of FAT and SAT;
General Specifications for Machinery for Vessels of the United States Navy covering Work under Cognizance of U.S. Bureau of Steam Engineering, 1920, Government Printing Office, Washington, downloaded from https://books.google.at/books?id=goJQAAAAYAAJ 18.05.2021

[76] J. Uehlecke, „Zucker und Kaliumchlorid aus selber Maschine“, taz. die tageszeitung, 19.01.1999, downloaded from https://taz.de/Archiv-Suche/!1306206&SuchRahmen=Print/ 11.04.2021

[77] Food and Drug Administration, Office of Criminal Investigations, “January 31, 2018: New England Compounding Center Pharmacist Sentenced for Role in Nationwide Fungal Meningitis Outbreak”, 31.01.2019; U.S. Department of Justice Press Release, District of Massachusetts
downloaded from https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/press-releases/january-31-2018-new-england-compounding-center-pharmacist-sentenced-role-nationwide-fungal 21.04.2021

[78] Kevin, “BioLife Solutions : Pharma Industry Blindsided By October 1, 2015 Deadline for New EU Requirements On Transportation Qualification And Validation”, 22.02.2016, BioLife Solutions Inc., downloaded from https://www.marketscreener.com/quote/stock/BIOLIFE-SOLUTIONS-INC-16113710/news/BioLife-Solutions-nbsp-Pharma-Industry-Blindsided-By-October-1-2015-Deadline-for-New-EU-Requireme-21895230/ 18.05.2021

Für Dipl.-Ing. Honorarprofessor Dr.nat.techn. Rudolf Bliem
(in ewigem Dank dafür mich für QM begeistert zu haben)
und Regina Scheiber