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Good manufacturing practices of medicines and their determinants

As boas práticas de fabricação de medicamentos e suas determinantes

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ABSTRACT

Good Manufacturing Practices (GMP) ensure that drugs are consistently produced and controlled according to previously established quality standards. They are designed to manage and minimize the inherent risks involved in the manufacture of drugs in order to ensure the quality, efficacy and safety of the finished product. Since their inception as we know them today, several versions have taken place in Brazil and worldwide. This work proposes to analyze GMP, through the analysis of the content of Brazilian regulatory frameworks, identifying the determinants that can explain their evolution over the last decades. GMP were broken down into topics and subtopics and their versions present in the five regulatory frameworks studied were evaluated. It was possible to verify, in the evolution of drug manufacturing requirements, the interference of technological innovation and the influence of new practices related to quality, identifying the GMP transformation dynamics.

KEYWORDS: Good Manufacturing Practices; Health Care Coordination and Monitoring; Government Regulation; Pharmaceutical Technology; Drug Industry; Sanitary Surveillance

RESUMO

As Boas Práticas de Fabricação (BPF) garantem que os medicamentos sejam consistentemente produzidos e controlados de acordo com padrões de qualidade previamente estabelecidos. Têm por objetivo gerenciar e minimizar os riscos inerentes à fabricação de medicamentos com vista a garantir a qualidade, eficácia e segurança do produto acabado. Desde o seu surgimento da forma como conhecemos hoje, várias versões se sucederam no Brasil e no mundo. Esse trabalho se propõe a analisar as BPF, por meio da análise de conteúdo dos marcos regulatórios brasileiros, identificando as determinantes que podem explicar a sua evolução através das últimas décadas. As BPF foram decompostas em temas e subtemas e suas versões, presentes nos cinco marcos regulatórios estudados, foram avaliadas. Foi possível comprovar, na evolução dos requisitos de fabricação de medicamentos, a interferência da inovação tecnológica e a influência de novas práticas relacionadas à qualidade, identificando, dessa forma, a dinâmica de transformação das BPF.

PALAVRAS-CHAVE: Boas Práticas de Fabricação; Regulação e Fiscalização em Saúde; Regulamentação Governamental; Tecnologia Farmacêutica; Indústria Farmacêutica; Vigilância Sanitária

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INTRODUCTION

Good Manufacturing Practices (GMP) are the regulatory and technical instrument that guarantees that medicines are consistently produced and controlled according to previously established quality standards. They intend to manage and minimize the risks involved in the manufacture of medicines in order to ensure the quality, efficacy and safety of the finished products[1]. GMP were created by the World Health Organization (WHO) in 1967 to support the efforts of its member states in improving the quality of the medicines on the market[2]. The document approved in the XXI World Health Assembly named *Draft requirements for good manufacturing practices in the manufacture and quality control of drugs and pharmaceutical specialties* is the first official document to address the recommendation for the manufacture of medicines using the term GMP. Since then, several updates of this document have been produced by the WHO over the five following decades. The last one was in 2014[1].

The evolution of the rules for the manufacture of medicines is usually linked to disasters with great media attention involving the use of bad quality medicines that brought serious health problems to the users, and in some cases, caused the deaths of dozens of patients. To illustrate, we can mention the incident in 1941 involving sulfathiazole in the United States. Nearly 300 people were killed or injured due to the ingestion of pills tainted with phenobarbital. There is also the case of a failure during viral inactivation of a batch of polio vaccines in the 1950s, which led to the development of the disease in 60 people and in other 89 relatives, also in the United States[3]. Even today, fatal accidents due to the quality problems of medicines continue to occur around the world, including in Brazil[4]. In response to these tragedies, several actions were taken by the sanitary authorities of different countries towards adopting restrictive measures related to the manufacture of medicines[3]. However, it would be precipitate to affirm that the frequent changes in GMP are only and exclusively due to the tragedies involving quality problems medicines.

Some authors attribute the increase of the surveillance (regulation) over a certain object, like GMP, to technological progress. Tenner[5] wrote about the iatrogenesis caused by new technologies and stated that technological progress imposes an ever greater surveillance on the same level of risk, since the use of more advanced technologies can produce better results but requires strict controls and criteria. Lucchese[6] exhaustively demonstrates the implications of technological progress in health regulatory system. According to him, with some exceptions (new technologies that simplify the need for control), technological innovations produce more intricate and powerful systems, with more components, which increases the probability of something wrong happening. Therefore, new technologies demand greater surveillance, knowledge of the human resources, ability and individual skill and experience[6].

In this sense, it is important to define the understanding and usage of the term technology. Among the several approaches and concepts about this term, the one that comes closer to the reality of manufacture of medicines is Blaumer's concept[7], which defines it as the set of physical objects and technical operations (mechanized or manual) used in the transformation of products in an industry. Based on this, Silva[8] proposed a new approach to the term to when it comes to technology management in manufacturing companies. The author addressed the concepts of macrotechnology, as the systemic concept inside an organization (structure, creativity, people, information, organization, among others), and microtechnology, as the set of interrelated technologies embedded in a process or product. Microtechnology consists, then, in Boundary Technologies (BT) included in a process or product that, in turn, is called Core Technology (CT). According to this approach, BT changes faster and more intensely than CT. For the author, most product improvements occur because of advances of BT and not CT. The characterization of the technologies used in the pharmaceutical industry may help us understand the evolution dynamics of GMP throughout the last decades.

Scientific studies about GMP of medicines and their relation with technological innovations, as well as other possible drivers, are very scarce. In this context, this paper aims to investigate the process of transformation of GMP and its driving forces, using Brazil as the evaluating site. The evolution of Brazilian GMP regulation and the international references on which it was based were systematically analyzed and the technological aspects involved and its impact in GMP were identified.

METHODS

To conduct qualitative research based on content analysis[9,10], the theoretical reference we adopted was the current version of GMP in Brazil, that is, RDC n. 17, of April 16, 2010[11]. It is considered one of the most important in the world[12] and its content is based on Annex IV of WHO Report n. 37 of 2003[13] and its other updates on the subject to date[14]. The RDC n. 17/2010 was compared with its predecessors (previous versions of Brazilian GMP regulations), that is, RDC n. 210, of August 4, 2003[15] (based on WHO Report n. 32 of 1992[16]), RDC n. 134, of July 13, 2001[17] (based on WHO Report n. 32 of 1992[16]) and SVS/MS Ordinance n. 16, of March 6, 1995[18] (based on WHO Report n. 25 of 1975[19]), as well as Decree n. 20,397, of January 14, 1946[20] and its respective complementation (DNS/MS Ordinance n. 1, of January 11, 1954)[21].

Among the techniques available to perform content analysis, we chose the thematic analysis, whose presence of certain topics denotes the reference values and the behavior models contained in the analyzed object. The content of RDC n. 17/2010[11] is very extensive. It contains more than 600 articles and several paragraphs and subsections. Because of the need to break down RDC n. 17/2010[11] into topics and the absence of references for this kind of work, the methodology we used was the same as that employed by the Food and Drug Administration (FDA) in its program of inspections and presented in the *Compliance Program Guidance Manual for FDA Staff: Drug Manufacturing Inspections. Program 7356.002 - 01*[22]. In this document, FDA divided GMP into

six systems, according to their format and content. They are: I) Quality; II) Facilities and Equipment; III) Materials; IV) Production; V) Packaging and Labeling; and VI) Laboratory Control.

With that in mind, in the present paper each system was defined as a topic that, in turn, was broken down into several subtopics that include all technical requirements of the theoretical reference. Chart 1 presents the subtopics of RDC n. 17/2010[11] and the information about the presence or absence of technical requirements in the previous versions of GMP we analyzed.

The classification of "partially" was used in cases where the requirements, albeit present, were insufficiently described. The same classification was used in the cases where the item was in the Inspection Guide (Annex III) and not in the text of the GMP regulations (Annex I). The inspection guide is an instrument that works as a checklist, in which each item is classified as "Essential", "Necessary", "Recommendable" or "Informative" and is found in three versions of the GMP (Ordinance n. 16/1995 [18], RDC n. 134/2001[17] and RDC n. 210/2003[15]). In order to give greater freedom to the sanitary authority at the moment of its elaboration, the guide was often more detailed than the text of the GMP itself.

Another relevant methodological consideration concerns the possible insertion of the same subtopic into different topics. For example, the subtopic of Qualification of Equipment that, due to its characteristics, could be placed under the topics of "Production", "Packaging and Labeling" and "Laboratory Control". In these cases, the subtopics of this nature were placed under "Quality", thus avoiding duplicity. The presence of these elements was only considered when they were included in all pertinent areas set forth in the adopted reference (RDC n. 17/2010[11]). Otherwise, the subtopic was classified as partially.

RESULTS AND DISCUSSION

In Chart 1, the subtopics personnel, air system – sterile and general construction requirements seem to shape the elaboration of rules for the manufacturing of medicines ever since the beginning, because they are present in all previous versions of GMP and regulations related, even those that are partial or underdeveloped. The presence of requirements related to these subtopics denotes the concern with aspects related to the hygiene, cleanliness and the possibility of microbiological contamination in medicines, mainly, the sterile ones.

In addition to the aforementioned subtopics, the concern with the possibility of cross contamination is present since the first GMP related regulation, which addressed the manufacturing of medicines in Brazil in the 1940s. The inclusion of requirements related to this subtopic (segregation of areas for production; use of equipment and tools dedicated to the manufacturing of certain products; campaign production; use of airlocks with different air pressures; reduction to the minimum of the contamination risk caused by recirculation or re-entry of untreated or insufficiently treated air etc.) suggests a possible influence of the tragedy occurred in the United States in the same decade (1941), in which 300 people were poisoned after consuming sulfathiazole pills contaminated with phenobarbital.

One can notice that in each new Brazilian GMP version and regulations related, regardless of tragedies, there are requirements intended to eliminate or mitigate the possibility of cross contamination of specific products. The first document to set forth rules for the manufacturing of medicines in Brazil, Decree n. 20.397/1946[20], already included specific requirements (segregation of areas for production, as well as the use of dedicated material and equipment) for the production of anti-tetanic serum, anti-carbuncle or BCG vaccines.

When considering that each one of the mentioned products can be defined as a new technology, the relation of its appearance with the changes in GMP becomes clear. With the discovery and spread of the use of several antibiotics in the 1940s and 1950s, technology driving force, once more, was present when examining the requirements for manufacturing addressed in the DNS/MS Ordinance n. 1/1954[21], which complements Decree n. 20.397/46 [20] (from the technical point of view) and has the following text:

BRAZILIAN SERVICE OF MEDICINE INSPECTION in conformity with Art. 13, letter C, of Decree n. 21.339, of June 20, 1946, and considering the development that has been happening in the Brazilian pharmaceutical industry concerning the manufacturing of antibiotics, DECIDES: [...] [21] (Bolding is ours)

This standard determined that the manufacturing of antibiotics had to be done under some requirements for biological products already published in Decree n. 20.397/1946[20]. Thus, the antibiotics had to be manufactured in specific places, in addition to meeting the other requirements of manufacturing pertinent to any other pharmaceutical product.

Ordinance n. 16/1995[18], in its Annex I, based on the GMP guidelines of WHO of 1975[19], also brings specific requirements related to the manufacturing of antibiotics and express concern with the possibility of cross contamination of these products. In Annex III (Inspection Guide) of the same regulation, this concern was specifically directed to penicillin and cephalosporin, emphasizing the need for dedicated areas for the manufacturing of these products.

In the Inspection Guide of the later versions of GMP (RDC n. 134/2001[17]and RDC n. 210/2003[15]), the need for manufacture in segregated areas that, until then, was in force only for penicillin and cephalosporin, was extended to biological products (living microorganisms), other antibiotics, hormones, highly active products (thalidomide, prostaglandins, immunosuppressant drugs and some psychoactive substances), cytotoxic and cytostatic substances. RDC n. 210/2003[15] even demanded that penicillin and cephalosporin be manufactured in buildings apart from the other products.

The introduction of new technologies represented by the new classes of products drove the sanitary regulation to act according to the "Precautionary Principle"[23], establishing that the manufacture of these products would have to be done in

Chart 1. Content present in RDC nº 17/2010 regarding the other regulatory frameworks related to Good Manufacturing Practices

Topics and subtopics	Decree n. 20.397/1946	Ordinance n. 16/1995	RDC n. 134/2001	RDC n. 210/2003	RDC n. 17/2010
Quality					
Change Control	Absent	Absent	Partially	Partially	Present
Periodic review of the product	Absent	Absent	Absent	Absent	Present
Supplier Qualification	Absent	Absent	Partially	Partially	Present
Self-inspection	Absent	Partially	Present	Present	Present
Recall	Absent	Partially	Present	Present	Present
Complaint/returned products	Absent	Present	Present	Present	Present
Treatment of nonconformities/CAPA	Absent	Absent	Present	Present	Present
Organizational structure	Absent	Absent	Present	Present	Present
Training	Absent	Partially	Present	Present	Present
Personnel (responsibilities/knowledge and abilities/ health of personnel)	Partially	Partially	Partially	Partially	Present
Document management	Absent	Absent	Present	Present	Present
Batch release	Absent	Absent	Partially	Partially	Present
Reprocessing	Absent	Absent	Present	Present	Present
Validation/ Validation Master Plan	Absent	Absent	Present	Present	Present
Computer systems/validation	Absent	Absent	Partially	Partially	Present
Cross contamination and mix-up	Partially	Present	Present	Present	Present
Research & development	Absent	Absent	Present	Present	Present
Facilities and equipment					
Preventive maintenance	Absent	Partially	Present	Present	Present
Qualification of Equipment	Absent	Absent	Present	Present	Present
Water system	Absent	Partially	Partially	Partially	Present
Air system - sterile	Partially	Present	Present	Present	Present
Air system - not sterile	Absent	Partially	Present	Present	Present
General requirements for construction	Partially	Present	Present	Present	Present
Materials					
Receipt - identification test (of each container)	Absent	Absent	Present	Present	Present
Storage (electronic quarantine)	Absent	Absent	Partially	Present	Present
Physical segregation of material - storage	Absent	Present	Present	Present	Present
Retest	Absent	Absent	Absent	Absent	Present
Management of stock (adoption of codes and batch numbers)	Absent	Partially	Present	Present	Present
Supply management (FEFO)	Absent	Partially	Present	Present	Present
Production					
Blow/fill/seal technology	Absent	Absent	Absent	Absent	Present
Isolators	Absent	Absent	Present	Present	Present
Aseptic production - Clean Areas	Absent	Absent	Present	Present	Present
Validation of sterilizing filtration	Absent	Absent	Absent	Absent	Present
Clean Validation	Absent	Absent	Present	Present	Present
Media Fill	Absent	Absent	Present	Present	Present
Sterilization validation	Absent	Absent	Present	Present	Present
Packaging and labeling					
Reconciliation	Absent	Present	Present	Present	Present
Line Release	Absent	Partially	Present	Present	Present
Line electronic controls	Absent	Absent	Present	Present	Present
Laboratory Control					
Analytical method validation	Absent	Partially	Present	Present	Present
Results out of the specifications	Absent	Absent	Absent	Absent	Present
Stability study	Absent	Present	Present	Present	Present

Source: Own development.

segregated areas. Only after the assimilation of the technical knowledge about these technologies over time was the reversion of these restrictive measures possible. In that point, those measures demanded that several products were manufactured in dedicated areas. With the publication of RDC n. 17/2010[11], the requirements for manufacturing in dedicated areas were rationalized. In this resolution, segregation of manufacture was restricted to penicillin, cephalosporin, carbapenems, in addition to low therapeutic index substances, cytotoxic substances and certain hormone classes.

The influence of the technological innovation in GMP is also present in subtopics related to validation exercises, which appeared only in RDC n. 134/2001[17]. The appearance of new analytical methodologies assisted by new equipment, such as high performance liquid chromatographs, introduced in the routine of pharmaceutical analysis in the 1990s, allowed the adoption of practices related to the validation of analytical method, cleaning and process. Likewise, the technological development was decisive in the insertion of subtopics as computer systems, qualification of equipment and research & development.

Other subtopics, such as isolators (present since 2001, in RDC n. 134/2001[17]) and technologies of blow/fill/seal (present in RDC n. 17/2010[11]), clearly illustrate the influence of technological innovation in the manufacturing of medicines. Agalloco et al. reported in 2002[24] a significant increase in the use of advanced technologies related to aseptic filling of sterile products, which includes isolators, restricted access barrier systems (RABS) and blow/fill/seal equipment. These technologies are closed and tight systems that minimize microbiological contamination caused most of the times by the human factor during the steps of filling and closing of injectable products.

Finally, subtopics like receipt and storage reaffirm the role of technological innovations in the evolution of the GMP version in question. The emergence of Near Infra-red (NIR) spectroscopy and supply and material management software enabled, respectively, the identification of each volume of raw material, mainly in industries of Large Volume Parenteral (LVP) solutions, and the storage in chaotic system, optimizing the use of spaces in warehouses and making it safer to manage material. A similar breakthrough occurred in packaging lines that began to have several different sensors in order to achieve electronic controls and to fix possible human and mechanical errors throughout the packaging process. For this reason, RDC n. 210/2003[15] included the subtopic of electronic controls in line and demanded the use of technological apparatuses in the packaging lines (barcode scanners, photographs, presence sensors, among others) in order to inspect 100% of the production, replacing or complementing the control of the process.

Therefore, it becomes useful to use the model proposed by Silva[8] of characterization of product and process technologies (microtechnologies) of the manufacturing industry, in order to understand the dynamics of the evolution of GMP. When considering that the CT comprises the manufacturing process itself in a pharmaceutical dosage form (for example, injectable products), once it distinguishes itself from any other process for its specific use purposes, properties and characteristics, it is verified that the use of new BT causes changes in the properties and characteristics of the process and adds safety or another desirable attribute, in addition to adding value to the process and to the product. Moreover, we observed that the appearance of BT happens faster than CT. Figure 1 illustrates this methodological application in the manufacturing process of injectable products. Each one of the BT presented is a consequence of the improvement of other BT used until then in the manufacturing of a CT, in this case, the manufacturing process of injectable products. Thus, for example, the automatic review replaces the manual review of vials/ampoules, the use of isolators adds greater safety than the aseptic filling under laminar flow and the sterilizing filtration is an important alternative to heat sterilization of thermolabile medicine.

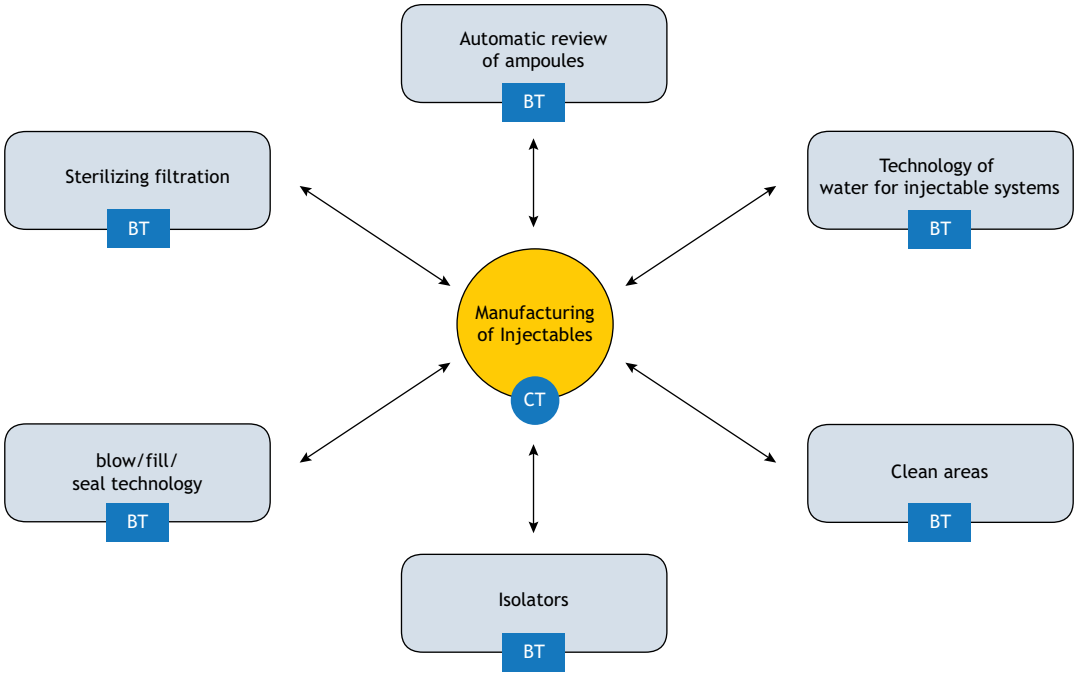
The situations described so far disclose one of the determinants of GMP, forcing its evolution and pointing to some of its characteristics. However, it is important to observe that the influence of technological innovations occurs in an antagonistic manner, depending on the technology in question. If on the one hand, the emergence of new BT adds safety to the manufacture of medicines and, therefore, makes GMP more permissive, on the other hand, when it comes to new CT involving new products (cephalosporins, carbapenems, cytotoxic substances, biological products obtained through recombinant DNA techniques etc.), or even new processes (manufacturing process of new pharmaceutical forms or new therapeutic systems), this seems to demand a more severe and precautious approach by the GMP.

The other subtopics that deserve to be highlighted in the study are tools of Quality Assurance or procedures/activities related to the topic of Quality, applied and improved throughout the years by the pharmaceutical industry. In these cases, the analysis of the presence of these subtopics must be expanded not only to the pharmaceutical universe, but also to the evolution of quality concepts and practices.

With the emergence of characteristic elements of the so-called "Quality Assurance", one of the moments of the Age of the Quality[25], practices focused on the continuous improvement of processes widely spread amongst various productive sectors. When analyzing some instruments of Quality, like ISO 9001[26], one quickly identifies the presence of requirements related to the subtopics of supply qualification, self-inspection, treatment of nonconformities/CAPA, organizational structure, document documentation/management and batch release[27]. These Quality practices seem to have been assimilated by the pharmaceutical industry in the second half of the century, following the movement of quality led by Japanese companies after the 1960s.

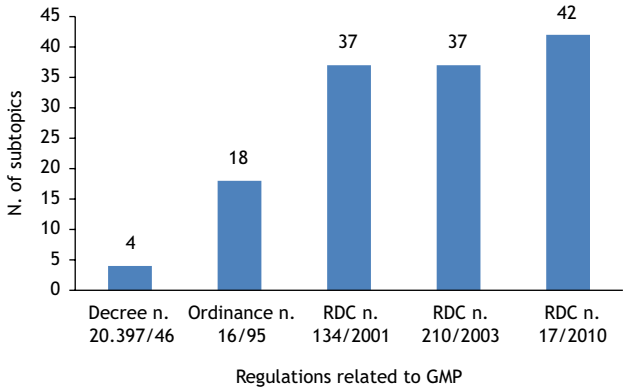
Thus, another possible determinant of GMP arises, showing that advances related to the theme Quality decisively influence the need for updates in GMP.

The evolution of the demands present in the GMP versions and regulations related analyzed is illustrated in Figure 2, which



Source: Adapted of Silva[a]

Figure 1. Microtechnology: Set of technologies of injectable manufacturing processes.



Source: Own development

Figure 2. Quantity of subtopics present in regulations GMP related.

shows the GMP dynamics imposed by the emergence of new technologies and by the evolution of the practices related to Quality. With the exception of RDC n. 210/2003[15], which did not increase the number of subtopics compared to its previous version, in all the other cases, there was an increase in the number of subtopics, highlighting the dynamism of GMP.

Based on the latest version of GMP published by WHO in 2014[1], it is expected that the update of the RDC n. 17/2010[11] surpasses the 42 subtopics identified today. New recommendations must be incorporated, like the implementation of risk management tools, in which the risks to the medicine quality are assessed, controlled, communicated and reviewed by a systematic process. Demands concerning the need to perform periodic reviews of products and the introduction of the concept of Quality Unit must also be present in the next version of Brazilian GMP[1]. However, considering the update speed of GMP in Brazil, it is impossible to predict when the new GMP will be published and represent, in fact, the up to date version of the GMP of WHO. Chart 2 shows the chronology of Brazilian GMP updates in relation to WHO.

Chart 2. Relation between Brazilian and WHO GMP Regulations

GMP - Brazil	GMP - WHO	Gap
		Brazil X WHO WHOWHO
Ordinance n. 16	*Technical Report Series (TRS) n. 567*	20
1995	1975	
RDC n. 134	*Technical Report Series (TRS) n. 823*	9
2001	1992	
RDC n. 210	*Technical Report Series (TRS) n. 823*	11
2003	1992	
RDC n. 17	*Technical Report Series (TRS) n. 908*	7
2010	2003	
No update so far	*Technical Report Series (TRS) n. 961*	-
	2011	
No update so far	*Technical Report Series (TRS) n. 986*	-
	2014	

Source: Own development

The delay of the Brazilian GMP versions compared to WHO GMP shows a variation of 20 years (Ordinance n. 16/95[18]X TRS 567/75[19]) to seven years (RDC n. 17/2010[10] X TRS 986/908/2003 X TRS[1]), which denotes a certain slowness in the Brazilian regulation process, making it difficult to predict the next update.

CONCLUSIONS

The division of GMP in components represented by topics and subtopics enabled the production of this paper in a more logical and systematic manner. Furthermore, it allowed a better visualization of the evolution of the requirements of GMP throughout its five previous versions.

Despite placed under secondary optics, amid serious tragedies that mark the history of medicine manufacturing in Brazil and in the world, the technological development and the evolution of the Quality related practices and concepts play a leading role in the evolution of GMP, both directly and indirectly. The analysis made under scientific accuracy raises no doubt that the technological innovation, already argued by a number of authors, in fact directly influences GMP. The emergence of some requirements for GMP clearly illustrates that. Yet, regarding Quality, its practices and concepts have been evolving over the centuries and, therefore, it is natural that its advances are incorporated to the production of goods and services, also to the manufacture of medicines. This component is intrinsically related to the human factor, since many of its practices aim to minimize or eliminate the risk of flaws caused by human interference in the manufacturing process.

We expect that this study enable the next GMP updates to be more than simple answers to established practices in the market, result of the incorporation of new knowledge or technologies, but a more pro-active action by the sanitary authorities aiming at the quality of the marketed medicines.

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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.