ARTICLE
https://doi.org/10.3395/2317-269X.00796

Prequalification of medicines: comparative analysis between WHO and Anvisa

A pré-qualificação de medicamentos: análise comparativa entre OMS e Anvisa

Marcus Vinicius Lima do Couto[I]

Fernando Medina[II]

Hudson Eduardo Souza da Costa[I]

Silvania Iacovino Dantas[III]

Jorge Antonio Zepeda Bermudez[III]

Norberto Rech[IV]

Jorge Carlos Santos da Costa[III,*]

[I] Instituto de Tecnologia em Imunobiológicos, Fundação Oswaldo Cruz (Bio-Manguinhos/Fiocruz), Rio de Janeiro, RJ, Brasil

[II] Instituto de Tecnologia em Fármacos, Fundação Oswaldo Cruz (Farmanguinhos/Fiocruz), Rio de Janeiro, RJ, Brasil

[III] Vice-Presidência de Produção e Inovação em Saúde, Fundação Oswaldo Cruz (VPPIS/Fiocruz), Rio de Janeiro, RJ, Brasil

[IV] Faculdade de Farmácia da Universidade Federal de Santa Catarina (UFSC), Florianópolis, SC, Brasil

*** E-mail:** jorge.costa@fiocruz.br

Received: Jun 9, 2016
Approved: May 10, 2017

ABSTRACT

The production of medicines with quality, safety and efficacy is essential to meet national and international requirements, aiming at subsidizing pharmaceutical care within the public health. Given the strategic role in which the public health industrial complex is inserted, compliance with Good Manufacturing Practices (GMP) of the World Health Organization (WHO) is essential to export its drugs via international organizations. The objectives of this article were to identify the main technical requirements recommended by WHO and enforced by the Brazilian Health Regulatory Agency (Anvisa), for compliance and recognition of GMP for medicinal products, and to compare them critically, to obtain the prequalification of medicines. This literature and documentary review promoted a comprehensive approach on national regulations and WHO guidelines. This work enabled to show a high degree of harmonization concerning the topics/subtopics compared between WHO and the national standards guides imposed by Anvisa about GMP, which demonstrates an integration of the national legislation in the international context, corroborating the alignment between Anvisa and WHO regarding compliance with GMP.

KEYWORDS: Good Manufacturing Practices; Quality Management; Official Pharmaceutical Laboratory; Prequalification; Sanitary Surveillance

RESUMO

A produção de medicamentos com qualidade, segurança e eficácia é fundamental para atender às demandas nacionais e internacionais, com o fito de subsidiar a assistência farmacêutica no âmbito da saúde pública. Diante do papel estratégico em que o complexo fabril público de saúde está inserido, o cumprimento das Boas Práticas de Fabricação (BPF) da Organização Mundial de Saúde (OMS) é essencial para a exportação de seus medicamentos via organismos internacionais. Os objetivos deste artigo foram identificar os principais requisitos técnicos recomendados pela OMS e exigidos pela Agência Nacional de Vigilância Sanitária (Anvisa), para o cumprimento e reconhecimento das BPF de medicamentos, e compará-los, de maneira crítica, em prol da obtenção da pré-qualificação de medicamentos. A metodologia empregada promoveu uma abordagem abrangente acerca das regulamentações nacionais e dos guias da OMS, por intermédio da seguinte técnica de coleta de dados: pesquisa bibliográfica e documental. O presente trabalho possibilitou evidenciar um alto grau de harmonização acerca dos tópicos/subtópicos comparados entre os guias da OMS e a normatização nacional imposta pela Anvisa em BPF, o que demonstra uma inserção da legislação nacional no contexto internacional, corroborando o alinhamento entre a Anvisa e OMS, no tocante ao cumprimento das BPF.

PALAVRAS-CHAVE: Boas Práticas de Fabricação; Gestão da Qualidade; Laboratório Farmacêutico Oficial; Pré-qualificação; Vigilância Sanitária

INTRODUCTION

Currently, the critical nature of final pharmaceutical products is regulated by their own mandatory legislation, in compliance with the Good Manufacturing Practices (GMP) guidelines, through inspection and control practices in pharmaceutical manufacturers. Therefore, pharmaceutical companies allocate a large part of their resources to ensure the quality of their production lines[1,2].

The quality of pharmaceuticals has been a concern of the World Health Organization (WHO) ever since its foundation. The World Health Assembly has adopted several resolutions and, more recently, the WHO 2001-2013 Medicines Strategy (Prequalification Program) has requested the organization to develop global standards, recommendations and instruments to ensure the quality of the medicines produced and marketed domestically or internationally[3,4,5].

These norms, standards and guidelines include guidance on: GMP, quality assurance for regulatory approval, prequalification of medicines and laboratories, certificate templates for quality-related activities, quality control testing, new specifications for inclusion in basic series tests and The International Pharmacopoeia, international reference standards for chemicals, and the International Nonproprietary Names (INN) program, which is used to identify each active substance or pharmaceutical ingredient (API) through a single, universally accessible name[5,6,7].

All these elements should be used by national regulatory authorities, pharmaceutical companies and other stakeholders. The need to increase access to affordable quality medicines in many healthcare programs has created many challenges in the pharmaceutical sector. These challenges have to be faced in the reality of national regulatory authorities and their various degrees of ability to interpret and apply standards and guidelines, especially in the regulation and quality assurance of existing pharmaceuticals. Thus, WHO seeks to work to strengthen and promote international norms, standards and guidelines for the quality, safety and efficacy of medicines[5,7].

In this context, GMP, as an integral part of quality assurance, become even more relevant when the products are linked to the health area, as in the case of public drug production, given their direct influence on the quality of life of the population.

In Brazil, the existence of a public complex, of national scope, is a key characteristic of the local pharmaceutical industry. These facilities are primarily focused on manufacturing drugs for public health programs.

Given that Brazil is a middle-income country where the majority of the population finds pharmaceutical assistance in the public sector, Official Pharmaceutical Laboratories (LFO) play a unique role in the production of drugs. Together with the Ministry of Health (MS), they increase access to the essential drugs for this population through the Unified Health System (SUS), especially when it comes to basic healthcare[8,9,10,11].

Over time, some LFO have faced many obstacles to their activities. These obstacles were created by several factors that make it difficult for these laboratories to obtain the GMP certification granted by Anvisa. This problem has important effects not only on the institutions themselves, but also on the Brazilian health policy and, consequently, on the population.

Health regulations for GMP in Brazil

The current concept of health surveillance was framed in the 1980s. It says the State should safeguard consumer rights and promote good health conditions for the population[12]. Because of the importance of the pharmaceutical industry to the country's economy and health policy, it was necessary for the MS to institute and implement inspection and control measures for pharmaceutical manufacturers. Therefore, the Department of Health Surveillance (SVS) of the Ministry of Health mandated all pharmaceutical manufacturing facilities to comply with the GMP guidelines for the pharmaceutical industry, by means of Act SVS/MS n. 16, of March 6, 1995.

In 1999, through Law n. 9782 of January 26, 1999, the National Sanitary Surveillance System (SNVS) was defined and Anvisa was created. The agency is a special autonomous body linked to the MS with administrative independence, stability of its leaders and financial autonomy. Its institutional purpose is to promote the protection of the health of the population, through the health control of the production and marketing of products and services subject to health surveillance[13].

With the creation of Anvisa, surveillance actions followed by the implementation and enforcement of GMP became more significant. According to the current legislation, Anvisa's activities include the concession of the Good Manufacturing Practices Certificate (CBPF). In summary, Anvisa is responsible for the implementation and execution of the SNVS[13,14]. Anvisa is, therefore, responsible for regulating the production of medicines in Brazil. It is also responsible for publishing the resolutions that must be followed by pharmaceutical companies that operate in the country, including mandatory compliance with GMP standards[15].

The creation of Anvisa led to the need to review and update the current inspection-related legislation, in line with the GMP for medicines provided for in technical procedures issued by world-renowned organizations. The inspection of drug production facilities is an instrument to prove their accordance with standards that guarantee the quality of the products[15]. In this scenario, regulations began to be reviewed and some of them are no longer in force, such as Act n. 16, dated March 6, 1995, created by the MS, which was revoked by Resolution of the Collegiate Board of Directors (RDC) n. 134, of July 13, 2001, which was also revoked by RDC n. 210, of August 4, 2003. The latter was, in turn, revoked by Anvisa's RDC n. 17, of April 16, 2010.

The national health regulatory body should ensure that medicines available in the country are safe, of proven quality and efficacy. In order to promote compliance with these guidelines, drugs can only be marketed by the pharmaceutical industry after obtaining the CBPF granted by Anvisa[16].

Recommendations for WHO GMP

The provision of good quality essential drugs has been identified as one of the prerequisites for health care provision by WHO. Likewise, the effective functioning of national drug regulations and control systems has been identified as the primary means of ensuring medicine safety and quality.

GMP are key to a global quality assurance proposal. They also represent the technical standards behind the WHO certification system on the quality of pharmaceuticals involved in international trade[6,17].

The WHO GMP guidelines should be used as a standard to warrant the GMP status, which is one of the elements of the WHO certification system on the quality of pharmaceuticals placed on the international market through the evaluation of authorization requests and as the basis for the inspection of production facilities. They can also be used as training material for government drug manufacturing inspection teams, as well as to promote production, quality control and quality assurance in the industry[17].

WHO-published GMP are accepted worldwide, including for the release of drugs traded through alliances between countries. They are a relevant source of information for developing countries that lack official standards[18].

WHO is responsible for directing and coordinating health actions for UN agencies[18]. The export of medicines through UN agencies is only possible after obtaining the approval of the regulatory authority of the country – Anvisa, in Brazil. It is, however, only a prerequisite for domestic manufacturers to qualify their products[19].

Subsequently, after approval by the health regulator of each country, WHO shall thoroughly evaluate, through document analysis and inspections, all phases of production of medicines, from the production line to the distribution of the drug, with emphasis on unified standards of acceptable quality, safety and efficacy at a global level. Such an analysis is essential in order to obtain the prequalification of medicines, which enables manufacturers to provide medicines considered essential for member countries of the United Nations (UN), associated specialized agencies such as the Pan American Health Organization (PAHO) and the United Nations Children's Fund (Unicef), based on the need for pharmaceutical assistance[6,17,19,20].

The WHO Prequalification Program

The WHO Prequalification of Medicines Programme, established in 2001, aims to assess the quality, safety and efficacy of medicines in order to optimize the use of resources and improve public health indicators in regions lacking basic pharmaceutical assistance, i.e. essential medicines, and populations affected by neglected diseases. It is the only global drug quality assurance program[3,21].

The prequalification process consists of a scientifically rigorous and transparent assessment, which includes the analysis of process-related information (dossier) submitted by pharmaceutical manufacturers and through on-site inspections of their production facilities, with due production monitoring and performance evaluation. This information, together with other criteria, is used by the UN and other procurement agencies to make purchasing decisions regarding medicines, vaccines, diagnostic kits and/or API[5,6,7,21]. This WHO activity, in close collaboration with national regulatory agencies and partner organizations, aims to prioritize access to essential drugs[5,21].

Any drug manufacturer may express interest in having its products and production facilities evaluated by the WHO Prequalification of Medicines Programme. Every manufacturer must submit a dossier with extensive information on the submitted product, in order to enable the evaluation teams to analyze its quality, safety and efficacy. The documentation must be accompanied by a cover letter, a sample of the product, as well as the Site Master File (SMF) of the facilities manufacturing the drug[5,20].

At regular intervals, the WHO website publishes an invitation to the interested manufacturers asking them to participate voluntarily in this procedure. Only the products included in the invitation and in the expression of interest are eligible for prequalification[5,20]. According to WHO, the manufacturer should provide a comprehensive set of data on the quality, safety and efficacy of the product under assessment[6,7,20,22,23]. This includes, for example, information about: General considerations/Company organization; Personnel; Facilities; Packaging and packing; Production; Quality control; Stability; Clinical trials; Distribution and trade; Regulatory documents.

After screening all the documentation, if the process is accepted for evaluation, the applicant organization will be informed by letter with the reference number of the dossier. The letter will serve as an agreement between WHO and the applicant for participation in the prequalification and as a commitment to comply with the provisions of the prequalification procedure[6,7,20].

Each applicant may request a hearing or a meeting with WHO experts involved in the evaluation of this applicant's dossiers to clarify some selected issues. WHO can provide technical assistance to applicants regarding the information on the appropriate product to be submitted, as well as the production and control requirements. Evaluation teams include WHO staff and experts from national regulatory authorities around the world[6,7,20].

WHO will, in a timely manner, plan and coordinate the conduction of inspections at the manufacturing sites of the finished pharmaceutical product or API, and at the clinical testing units or contracted research organizations[5,7,20,21].

A public inspection report reflects the inspection that was carried out and provides a summary of the remarks and findings made during the inspection. However, it excludes confidential information as well as all individual remarks that were reported in the full inspection report. It also indicates the date, length and scope of inspection[6,20].

Manufacturers of prequalified pharmaceutical products will be re-inspected at regular intervals, as established by WHO, usually once every three years. Every five years from the date of prequalification or when requested to do so by the WHO Prequalification of Medicines Programme, the holder of a prequalified product must present data and information about the product for WHO evaluation[6,20].

Some companies currently offer advisory, consultancy and training services in pre-audits to assess compliance with WHO GMP recommendations (*Mock Inspection*), as well as in assisting in the preparation of the action plan, follow-up actions with the definition of responsibilities and deadlines[23].

The stages of WHO prequalification of medicines are illustrated in Figure 1.

Thus, this study aims to evaluate the insertion of Anvisa's GMP in the international scenario through a comparative analysis of the Brazilian legislation and the main technical requirements to obtain the WHO prequalification. Likewise, this paper intends to contribute to a broad reflection and serve as a source of information for the production of medicines in Brazil, thus supporting the qualification of the national pharmaceutical manufacturing complex, with emphasis on the LFO and in line with the specific regulatory requirements of Anvisa's recommendations.

METHOD

The methodology adopted in this paper is classified as exploratory in its purpose, since it provided a comprehensive approach to the main Brazilian GMP regulations in the field of medicines and WHO guidelines, which demanded a review of specific literature to support the intended analysis. The methodology was based on document and bibliographical research, done mainly through searches carried out in the main databases and specialized websites, like Biblioteca Virtual em Saúde (http://bvsms.saude.gov.br), Anvisa (http://portal.anvisa.gov.br), Periódicos Capes (http://www.periodicos.capes.gov.br/), WHO (http://www.who.int/en/) and Google Scholar (https://scholar.google.com/). In order to trace and list the main technical requirements for the project, the aforementioned documents were, a priori, read in a selective manner. We considered what is essential for compliance with Anvisa's regulations and chose the WHO GMP guidelines as references. These are key to international recognition and certification prior to the WHO prequalification. These requirements were individualized and summarized in orderly and dedicated tables according to the content addressed.

The main documents adopted as references for the proposed work were: "WHO - Quality Assurance of Pharmaceuticals. A Compendium of Guidelines and related materials, volume 2/2007", and "WHO - Expert Committee on Specifications for Pharmaceutical Preparations - Technical Report Series (TRS) n. 961/2011".

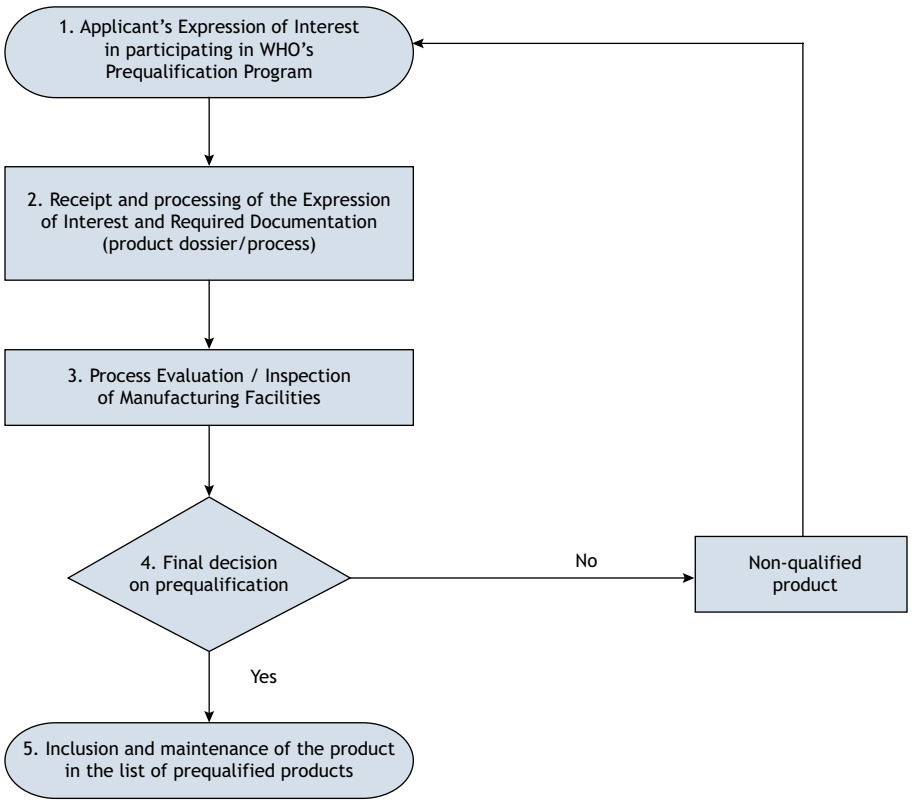

Figure 1. Flowchart with the stages of WHO prequalification of medicines.

This guide specifically outlines the procedures for the prequalification of pharmaceutical products in Annex 10, according to WHO GMP principles and guidelines, referred to in Annex 2 of the Technical Report Series n. 986/2014.

The defined requirements of the proposed analysis were divided into topics and subtopics for comparison purposes, in accordance with WHO guidelines and principles and their degree of compliance with Anvisa.

The comparative regulatory analysis of the categorized topics of equivalent subjects was carried out consecutively. Subsequently, the results of the comparative analysis were catalogued according to the main technical requirements of the GMP, starting with the construction of synthetic charts and the subsequent discussion about the context. Finally, the main obstacles, recommendations and perspectives capable of subsidizing LFO were identified to help these LFO in the creation of an action plan aiming at WHO prequalification.

RESULTS

As mentioned in the methodology, the information was collected from official WHO publications, thus emphasizing its role in establishing the guiding principles of health policies worldwide.

After analyzing the information listed in the aforementioned references, we noticed that the documents refer to other specific complementary guides, also published by WHO, considering their respective updates. These include detailed focus on certain relevant topics in the scope of GMP. Based on them, we listed the topics addressed in the research process (Chart 1).

When addressing the national legislation related to GMP, RDC n. 17, of April 16, 2010, which regulates Anvisa's GMP for medicines, can be highlighted as the official regulation. Additionally, special complementary guides issued by the agency itself, of a non-compulsory nature, are considered of fundamental importance, albeit for guidance purposes only. However, due to the contents and formats of these guidelines and the experience acquired through the monitoring of health inspections carried out by the regulatory sector over the years, Anvisa has the power and autonomy to request any additional information necessary for the understanding of documentary analysis that could directly impact the compliance of GMP by drug manufacturers and, therefore, the quality of the drugs produced.

Among the specific complementary guides adopted by Anvisa, Chart 2 shows those consulted for the study in question.

According to WHO, considering the compliance with the GMP and the consequent prequalification of the medicines, some topics and subtopics should be checked and evaluated for their level of demand and compliance.

For the topic of "Quality Management in the Pharmaceutical Industry: Philosophy and Essential Elements", the following subtopics were defined based on our sources of consultation (Chart 1): Quality assurance; Good Manufacturing Practices for Medicines (GMP); Sanitation and hygiene; Qualification and validation; Complaints; Product recollection; Production and analysis contract; Self-inspection and quality audits; Personnel; Training; Personal hygiene; Facilities; Equipment; Materials; Documentation; Good Production Practices and Good Quality Control Practices.

For the "Validation" topic, the following subtopics were listed according to their references (Chart 1): Relation between validation and qualification; Validation; Qualification; Calibration and verification; Validation Master Plan; Qualification and validation protocol; Qualification and validation reports; Stages of qualification; Change control; Personnel; Validation of heating, ventilation and air-conditioning systems; Validation of water systems for pharmaceutical use; Cleaning validation; Validation of analytical methods; Validation of computerized systems; Qualification of systems and equipment and Validation of non-sterile processes.

Regarding the "Water for pharmaceutical use" topic and its respective references, according to Chart 1, we proposed a division into the following subtopics: General requirements for water systems for pharmaceutical use; Water quality specifications; Methods of water purification; Water storage and distribution systems; Operational considerations and Water system inspection.

On the topic of "Good Manufacturing Practices for heating, ventilation, and air-conditioning for non-sterile pharmaceutical forms", the following subtopics were selected, using specific

Chart 1. Fundamental principles of WHO GMP for pharmaceuticals.

Tópicos
Quality Management in the Medicine Industry: Philosophy and Key Elements (*) - ("*Quality Assurance of Pharmaceuticals. A Compendium of Guidelines and related materials*, volume 2/2007 - Chapter 1") an Annex 2 of Technical Report Series n. 986/2014.
Validation (*) - ("*Quality Assurance of Pharmaceuticals. A Compendium of Guidelines and related materials*, volume 2/2007 -Chapter 1"), Annex 2 of the *Technical Report Series* n. 986/2014, Annex 4 (Exhibits 1 a 7) of the *Technical Report Series* n. 937/2006 and Annex 3 (Exhibit 7) of the *Technical Report Series* n. 992/2015.
Pharmaceutical Water (*) - ("*Quality Assurance of Pharmaceuticals. A Compendium of Guidelines and related materials*, volume 2/2007 - Chapter 1") and Annex 2 of the *Technical Report Series* n. 970/2012.
Good Manufacturing Practices for Heating, Ventilation and Air-Conditioning for non-sterile dosage forms - ("*Quality Assurance of Pharmaceuticals. A Compendium of Guidelines and relatedmaterials*, volume 2/2007 - Chapter 1") and Annex 5 of the *Technical Report Series* n. 961/2011.

*The highlighted topics correspond to Titles II, V and VI of RDC n. 17/2010 of Anvisa, respectively.

Chart 2. Supplementary GMP-specific guidelines for medicines issued by Anvisa.

Content	Issuance
Guides related to Quality Assurance[25]	2006
Computer System Validation Guide[26]	2010
Quality Guide for Water Purification Systems for Pharmaceutical Use[27]	2013
Quality Guide for Air Treatment Systems and Environmental Monitoring in the Pharmaceutical Industry[28]	2013

literature also described in Chart 1: Protection; Particle control; Protection of the environment; Design of systems and components for heating, ventilation and air-conditioning (HVAC); Commissioning, qualification and maintenance; and Facilities.

Since the focus of the study was on the production of non-sterile drugs, we did not deal with the WHO study references corresponding to Titles III and IV of Anvisa's RDC n. 17/2010, which deal with Sterile Products and Biological Products, respectively.

Comparative Analysis - WHO Recommendations x Anvisa Requirements

The recommendations related to the subtopics of each highlighted topic were analyzed in view of the guidelines and principles referenced in the WHO guidelines, as outlined in Chart 1. Thus, such topics and their respective subtopics, with their technical requirements, were defined as essential. Based on them, we proposed the comparative analysis to verify the convergence or divergence of the official legislation or Anvisa guiding documents in comparison with the WHO recommendations.

In this context, Anvisa elaborates specific complementary guides, with comprehensive content on several aspects, such as guides related to Quality Assurance, Validation of Computerized Systems, Water Purification Systems for Pharmaceutical Use and Air Treatment Systems and Environmental Monitoring in the Pharmaceutical Industry, as already highlighted in Chart 2. This created a guiding framework without legal force, but increasingly required from the regulated sector. This presentation allows easy visualization of the topics and subtopics addressed in the research and allows some flexibility in the way of internalizing the proposed activities, due to their complementary nature, as long as they are technically justifiable, due to their impact on the quality of medicines.

The present comparative analysis highlighted the mention of the supplementary specific guidelines of GMP for medicines issued by Anvisa, since certain WHO recommendations, albeit not present in the national health regulations in GMP medicines – RDC n. 17/2010, are found in these guides. In other cases, the WHO recommendations, although present in official legislation, are presented in more detail in the scope of these guidelines.

Such guidelines, either related to official legislation or suggested by the guides, are considered fundamental to the objectives of the work and seek to guarantee the essential principles of quality, safety and efficacy in medicine production.

Quality management in the pharmaceutical industry: philosophy and essential elements

According to WHO, quality management should involve the entire organization. In contract situations, it inspires trust in suppliers, and the concepts of quality assurance, GMP and quality control are intertwined and of paramount importance for the production and control of pharmaceuticals[6].

Through critical analysis of the topic of "Quality Management in the drug industry: philosophy and essential elements", we verified there is no disagreement between the guidelines required by Anvisa regarding the technical requirements of the subtopics addressed here, relating them to WHO recommendations.

Considering that these requirements are part of GMP procedures, the evaluation suggests that the concepts in this field are applicable in general, demonstrating Anvisa's assimilation of the ideas propagated in the world scenario by WHO.

There is, therefore, a clear demonstration of how all subtopics are essential for the national regulatory body and are in line with the WHO recommendations on GMP for medicines, especially those that plan to become prequalified or, in other words, of proven quality, safety and effectiveness, to be made available to international organizations. Briefly, the topic in question, covering the technical requirements for each subtopic linked, is determined by Anvisa through Resolution RDC n. 17, of April 16, 2010, in its Title II.

In this context, the similarity between the existing content of the WHO guidelines and RDC n. 17/2010 demonstrates the harmony between the approaches of Anvisa and WHO. This is in line with the trend of incorporation of international guidelines within the scope of the official national legislation regarding Quality Management in the pharmaceutical industry: philosophy and essential elements.

Validation

Anvisa establishes guidelines that aim to eliminate errors and mitigate risks that may impact drug production activities. These guidelines are known as GMP for medicines. These guidelines have some essential components, such as validation tests and tests conducted by study protocols, which, after trials, provide content for conclusive reports that must be maintained and modified by another validation study in cases where significant changes occur and in the periodic revalidations, which aim to maintain the reproducibility of the processes at all times.

The analysis enabled us to evaluate the importance of the topic, demonstrating consensus on the fundamental concepts of validation disseminated internationally by WHO, as a primary requirement for the implementation and recognition of compliance with GMP for medicines.

The recommendations of WHO are officially recognized by Anvisa in the technical requirements related to the subtopics that make up the topic addressed in RDC n. 17/2010 – Title V and in RE n. 899, of May 29, 2003, which specifically addresses the Guide for Validation of Analytical Methods, and, in a complementary and detailed manner, for guideline purposes in the Guides related to Quality Assurance[25], topics such as: Clean Validation, Validation of Non-Sterile Productive Processes and the Guide to Validation of Computerized Systems[26].

Finally, the individual comparative study of each subtopic and its respective requirements allowed us to draw a more reliable picture of the degree of compliance of the stakeholders. This, in turn, enabled us to diagnose the alignment of Anvisa requirements to WHO guidelines. This seems to demonstrate that the adoption of a regulation for GMP involves validation activities carried out by the national regulatory body.

Water for pharmaceutical use

In order to obtain water at the desired quality level, it is necessary to consider the quality of the water available and the desired water quality. One must then consider the possible treatment techniques, their restrictions, and the use of complementary treatment systems.

In this scenario, in 2013 Anvisa published a Quality Guide for Water Purification Systems for Pharmaceutical Use[27], which describes the minimum requirements of water systems for pharmaceutical use.

It is also worth highlighting that, since it is a complementary document, as an alternative to the criteria presented, different procedures may be adopted, provided that they are technically justifiable, with a favorable opinion from the regulatory body.

This fact shows that the guidelines referenced in Anvisa's guides on GMP technical requirements applied to the technologies used in water purification for pharmaceutical use are constantly updated in order to seek improvements and reduce the risk of contamination of chemical, biological or microbiological nature.

Thus, the analysis of the specific documentation has shown that the topic in question also has a high degree of convergence with the WHO recommendations. We emphasize Technical Report Series (TRS) n. 970, Annex 2 of 2012, and health legislation in force proposed by Anvisa - RDC n. 17/2010, in its Title VI: Water for pharmaceutical use, since both references recommend adherence to topics such as: Water quality specifications, Water purification methods, Purification systems, Water storage and distribution and Operational considerations. Anvisa does not address procedures related to the topic of water system inspections in detail.

However, despite this slight divergence regarding the requirements of the subtopic mentioned above, Anvisa's regulations, as well as its guidelines, have demonstrated to be in line with the WHO minimum requirements for the production of medicines, since they include all items deemed essential, in their entirety, regarding the impact on the quality, safety and efficacy of the drugs produced, which is considered fundamental by WHO.

This can be evidenced by describing the technical requirements of subtopic VIII - self-inspection and quality audits of the topic "Quality Management in the Pharmaceutical Industry: Philosophy and Essential Elements", which emphasize, for example, the need to establish procedures for critical utilities (e.g. water systems for pharmaceutical use) that are relevant to the GMP.

Thus, Anvisa seems to be clearly seeking to promote the harmonious understanding of the topic in health regulation, in accordance with the thinking of WHO, since the content of the documents prepared by the regulatory sector is based on the international recommendations of WHO, making it in line with global trends in GMP.

Good Manufacturing Practices for heating, ventilation and air-conditioning (HVAC) for non-sterile pharmaceutical forms

Without adequate validation of clean room environments, Anvisa believes the quality of the products can be questioned. Validation, certification and monitoring of clean room environments will vary and depend on the classification of these areas. For this reason, it is important to have an adequate design to validate and/or monitor these environments.

In the view of WHO, GMP recommendations dictate that quality control is paramount at every stage of the process, so it is of the utmost importance that a qualification plan for the air treatment system be established, planned and implemented at the beginning of the process, when control is possible in a more comprehensive way at a lower cost, according to the guidelines of Anvisa.

In short, the comparative analysis addressed this topic in a broad fashion and demonstrated that the criteria required by Anvisa, mainly through the Quality Guide for Air Treatment and Environmental Monitoring Systems in the Pharmaceutical Industry of 2013[28], on GMP for HVAC systems, are as comprehensive and rigorous as the WHO principles and guidelines concerning the same topic. This corroborates the agency's priority objective, the production of quality, safety and efficacy products for the population's consumption.

The study proved the agreement between the content of the requirements made by Anvisa for the aforementioned subtopics and the WHO recommendations.

DISCUSSION

Over the last few years, Anvisa has made efforts to adapt health regulations for medicines and to meet certain recommendations in GMP in the face of global regulatory trends.

This can be seen in the elaboration of specific guidelines (Chart 2) that complement the resolutions about the impact on GMP, with emphasis on DRC n. 17/2010, which deals specifically with the GMP of medicines. These documents, as already highlighted, although not compulsory, are highly detailed and often more demanding than the WHO recommendations. Documents like the Guide to Validation of Computerized Systems have been increasingly used as instruments to assess compliance with GMP, in accordance with the prerogatives of the regulatory body, and their content is based on international references, the Brazilian official legislation, and Anvisa's experience in health surveillance.

Given the above, it becomes evident that all the requirements for impact on the quality of medicines, alluding to the subtopics of the topics covered in the quality assurance research regarding the requirements of Anvisa's GMP health regulation, are standardized and converge to the understanding proposed by WHO.

Therefore, we can see that the Brazilian health regulations for medicines associated with the guidelines set out in the specific supplementary guides with an impact approach in GMP, compared to the WHO principles and guidelines, do not represent an obstacle to obtaining recognition of compliance with GMP.

Therefore, the lack of a suitable and dedicated structure for the requisition, evaluation and consolidation of all the documents that must be in the dossiers of products applying to the WHO Prequalification of Essential Medicines Programme is a major obstacle to the success of this proposal.

Furthermore, we point out that such noncompliance may be worsened by the lack of specific guidelines for professionals working in this segment within an LFO. These guidelines should emphasize how to perform the activities so as to fulfill all the requirements and thus obtain the prequalification. This could be achieved, for example, with the elaboration of a "Handbook or Guide to Procedures for Prequalification of Medicines with WHO".

The elaboration of such technical guidelines, with periodic updating and collaboration of the LFO and Anvisa, could be interesting, as it would help in the training of the players involved, to identify obstacles, as well as in the resolution of issues.

Such guidance would be extremely relevant given the lack of publications and dissemination of the necessary procedures for prequalification of medicines by WHO. These guidelines could contain specific knowledge, encourage reflection and suggest the adoption of actions on this topic, in response to the demand for medicines with internationally recognized quality, safety and efficacy for the world's population currently without basic pharmaceutical assistance.

CONCLUSIONS

Quality assurance of pharmaceuticals is a major public health challenge, particularly in the light of the growing health problems in regions lacking pharmaceutical assistance.

The present study made it possible to show a high degree of harmonization between the topics/subtopics of the WHO guidelines and the Brazilian standards determined by Anvisa in GMP. This demonstrates the insertion of Brazil's legislation in the international context and corroborates the alignment between Anvisa and WHO, with regard to compliance with GMP.

Therefore, we can conclude that the national regulatory body obtaining and maintaining the GMP certification, as well as managing and conducting the necessary procedures for the prequalification of medicines, according to WHO-TRS Guide n. 961/2011, with emphasis on Annex 10 and some supplementary guidance, is the main instrument for achieving prequalification, i.e. international recognition of GMP compliance by WHO.

REFERENCES

1. Mazzucato M, Penna, C. The Brazilian innovation system: a mission-oriented policy proposal. Brasília, DF: Centro de Gestão e Estudos Estratégicos; 2016. (Temas estratégicos para o desenvolvimento do Brasil).
2. Moretto, R.H. Garantia da qualidade coordena Boas Práticas de Fabricação nas indústrias. Rev Control Contamin. 2002;5(36):12-23.
3. World Health Organization. Prequalification of medicines programme. Geneva: World Health Organization; 2013[acesso 11 nov 2013]. Disponível em: http://apps.who.int/prequal/default.htm
4. World Health Organization. Prequalification of medicines by WHO. Geneva: World Health Organization; 2013[acesso 11 dez 2013]. Disponível em: http://www.who.int/mediacentre/factsheets/fs278/en
5. Hoen EF, Hogerzeil HV, Quick JD, Sillo HB. A quiet revolution in global public health: The World Health Organization's Prequalification of Medicines Programme. J Public Health Policy. 2014;35(2):137-6. https://doi.org/10.1057/jphp.2013.53
6. World Health Organization. WHO good manufacturing practices for pharmaceutical products: main principles and essential elements: annex 2. Geneva: World Health Organization; 2014. (Technical report series, Vol 986).
7. Moore T, Lee D, Konduri N, Kasonde L. Assuring the quality of essential medicines procured with Donor Funds. Washington: The World Bank; 2011[acesso 11 fev 2017]. (HNP discussion paper, Vol 70853). Disponível em: https://openknowledge.worldbank.org/handle/10986/1357https://openknowledge.worldbank.org/handle/10986/1357
8. Bermudez JAZ. Acesso a medicamentos e políticas públicas. J Economistas. 2012;(270):10-1.
9. Bermudez JAZ. Acesso a insumos em saúde: desafios para o Terceiro Mundo. Cad Saúde Pública. 2007;23(4):744-5. http://dx.doi.org/10.1590/S0102-311X2007000400001
10. Bermudez JAZ, Egléubia A, Labra ME. A produção pública de medicamentos no Brasil: uma visão geral. Cad Saúde Pública. 2006;22:109-18. http://dx.doi.org/10.1590/S0102-311X2006001100012
11. Bermudez JAZ, Possas CA. Análisis crítico de la política de medicamentos em el Brasil. Bol Oficina Sanit Panam. 1995;119(3):270-7.
12. Eduardo MPB, Miranda ICS. Vigilância sanitária. São Paulo: Instituto para o Desenvolvimento da Saúde; 1998, (Saúde & Cidadania, Volo 8).
13. Brasil. Lei N° 9.782, de 26 de janeiro de 1999. Define o Sistema Nacional de Vigilância Sanitária, cria a Agência Nacional de Vigilância Sanitária, e dá outras providências. Diário Oficial União. 27 jan 1999.
14. Agência Nacional de Vigilância Sanitária – Anvisa. Resolução RDC N° 17, de 16 de abril de 2010. Estabelecer os requisitos mínimos a serem serguidos na fabricação de medicamentos para padronizar a verificação do cumprimento das Boas Práticas de Fabricação de Medicamentos (BPF) de uso humano durante as inspeções sanitárias. Diário Oficial União. 29 abr 2010.

15. Agência Nacional de Vigilância Sanitária – Anvisa. Política vigente para a regulamentação de medicamentos no Brasil. Brasília, DF: Agência Nacional de Vigilância Sanitária; 2004[acesso 11 fev 2017]. Disponível em: http://bvsms.saude.gov.br/bvs/publicacoes/anvisa/manual_politica_medicamentos.pdf
16. Fiocchi CC, Miguel PAM. As dificuldades para a implantação da qualidade baseado nas Boas Práticas de Fabricação (BPF) em uma empresa de médio porte do setor farmacêutico: um estudo exploratório. In: 23o. Encontro Nacional de Engenharia de Produção; 21-24 out 2003; Ouro Preto, MG. p. 1-8.
17. World Health Organization - WHO. Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. 2nd ed. Vol. 2, Good manufacturing practices and Inspection. Geneva: World Health Organization; 2007.
18. Benedetti RLC. Contribuição dos sistemas de qualidade: proposta de modelo de gestão da qualidade para Bio-Manguinhos/Fiocruz [dissertação]. Rio de Janeiro: Escola Nacional de Saúde Pública Sérgio Arouca; 2008.
19. Pinheiro R. OMS aprova qualidade de vacinas brasileiras, mas faz algumas recomendações. JusBrasil. 2008[acesso 11 fev 2017]. Disponível em: http://agencia-brasil.jusbrasil.com.br/noticias/147614/
20. World Health Organization - WHO. Procedure for prequalification of pharmaceutical products: annex 10. Geneva: World Health Organization; 2011. (Technical report series, Vol 961).
21. Bassat Q, Tanner M, Guerin PJ, Stricker K, Hamed K. Combating poor-quality anti-malarial medicines: a call to action. Malar J. 2016;15:302. https://doi.org/10.1186/s12936-016-1357-8
22. Health Organization – WHO. Procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies: annex 8. Geneva: World Health Organization; 2003. (Technical report series, Vol 908).
23. The Food & Drug Letter, editors. Inspection readiness. Falls Church: Washington Business Information; 2013. (The executive briefing series).
24. Agência Nacional de Vigilância Sanitária – Anvisa. Guias relacionados à Garantia da Qualidade: revisão periódica do produto. Brasília, DF: Agência Nacional de Vigilância Sanitária; 2006.
25. Agência Nacional de Vigilância Sanitária – Anvisa. Guia de validação de sistemas computadorizados. Brasília, DF: Agência Nacional de Vigilância Sanitária; 2010.
26. Agência Nacional de Vigilância Sanitária – Anvisa. Guia de qualidade para sistemas de purificação de água para uso farmacêutico. Brasília, DF: Agência Nacional de Vigilância Sanitária; 2013.
27. Agência Nacional de Vigilância Sanitária – Anvisa. Guia da qualidade para sistemas de tratamento de ar e monitoramento ambiental na indústria farmacêutica. Brasília, DF: Agência Nacional de Vigilância Sanitária; 2013.

Conflict of Interest

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