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Flexibilization of Brazilian Good Manufacturing Practices requirements during COVID-19 outbreak in a comparative perspective

A flexibilização de requisitos brasileiros de Boas Práticas de Fabricação durante a pandemia da COVID-19 sob uma perspectiva comparada

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ABSTRACT

Introduction: The risk of drug shortages due to the COVID-19 pandemic required from national health authorities to take quick actions in order to avoid it and, at the same time, preserve the maintenance of a minimum standard of quality, safety and efficacy of medicines, as National Health Regulatory Agency (Anvisa) did by publishing RDC nº 392/2020. **Objective:** To carry out a comparative analysis between the exceptionalities listed in article 7 of RDC nº 392/2020 with the requirements of good manufacturing practices (GMP) exceptionally relaxed by foreign health authorities due to COVID-19, showing, whenever necessary, the impact of these requirements on the quality of medicines made available to the population. **Method:** A selective search was made for documents related to the temporary flexibility of GMP requirements for medicines and pharmaceutical ingredients during the COVID-19 pandemic at the electronic addresses on the internet of some health authorities. Such requirements were critically compared with those listed in article 7 of RDC nº 392/2020. **Results:** Exceptionalities were presented in a Table, detailing the topics and subtopics found in the analyzed documents of MHRA, EMA and Anvisa. More similarities were verified than differences between the flexible requirements, perhaps because RDC nº 392/2020 was prepared considering the documents referenced here from MHRA and EMA. **Conclusions:** Despite the mistakes pointed out and the criticisms made to RDC nº 392/2020, the merit of Anvisa cannot be diminished, as it was shown that regardless of the territory in which the regulatory agencies are located, there is considerable convergence among Brazilian expectations and those of the other health authorities consulted.

KEYWORDS: COVID-19; Anvisa; Good Manufacturing Practices; Medicines; Flexibilization

RESUMO

Introdução: O risco de desabastecimento de medicamentos em razão da pandemia da COVID-19 exigiu das autoridades sanitárias de alguns países medidas rápidas para tentar evitá-lo e, ao mesmo tempo, preservar a manutenção de um padrão mínimo de qualidade, segurança e eficácia dos medicamentos, como fez a Agência Nacional de Vigilância Sanitária (Anvisa), ao publicar a Resolução da Diretoria Colegiada (RDC) nº 392, de 26 de maio de 2020. **Objetivo:** Realizar análise comparativa entre as excepcionalidades elencadas no artigo 7º da RDC nº 392/2020 com os requisitos de boas práticas de fabricação (BPF) excepcionalmente flexibilizados por autoridades sanitárias estrangeiras em razão da COVID-19, evidenciando, sempre que necessário, o impacto desses requisitos para a qualidade dos medicamentos disponibilizados à população. **Método:** Foi feita a busca seletiva por documentos relacionados à flexibilização transitória de requisitos de BPF de medicamentos e de insumos farmacêuticos durante a pandemia da COVID-19 nos endereços eletrônicos existentes na *internet* de algumas autoridades sanitárias. Tais

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requisitos foram criticamente comparados com aqueles elencados no artigo 7º da RDC nº 392/2020. **Resultados:** As excepcionalidades foram discriminadas em tópicos e subtópicos encontrados nos documentos analisados da MHRA, EMA e Anvisa. Foram verificadas mais semelhanças do que diferenças entre os requisitos flexibilizados, talvez porque a RDC nº 392/2020 tenha sido elaborada considerando os documentos aqui referenciados da MHRA e EMA. **Conclusões:** Em que pese os equívocos apontados e as críticas realizadas à RDC nº 392/2020, o mérito da atuação da Anvisa em nada pode ser diminuído, pois foi evidenciado que, independentemente do território em que estejam localizadas as agências reguladoras, há considerável convergência das expectativas brasileiras com as das demais autoridades sanitárias consultadas.

PALAVRAS-CHAVE: COVID-19; Anvisa; Boas Práticas de Fabricação; Medicamentos; Flexibilização

INTRODUCTION

After reaching 118,000 cases in 114 different countries, COVID-19, identified in December 2019 in Wuhan, China, and caused by the new coronavirus (SARS-CoV-2), was labeled a pandemic by the World Health Organization (WHO).[1] This meant recognizing that the disease had spread throughout several continents in a sustained manner. The fast spread of the SARS-CoV-2 infection forced most governments in virtually all countries to implement measures to prevent or at least curb the spread of the disease and thus try to prevent the collapse of their health systems.

In Brazil, the Minister of Health, authorized by Decree n. 7.616, of November 17, 2011,[2] issued Ordinance n. 188, on February 3, 2020, declaring a Public Health Emergency of National Concern (ESPIN).[3] A few days later, on February 7, Law n. 13.979, of February 6, 2020, was enacted to provide for "measures to deal with the Public Health Emergency of International Concern resulting from the coronavirus responsible for the 2019 outbreak".[4] This law, after having some of its provisions amended by Law n. 14.006, of May 28, 2020,[5] allowed the Brazilian Health Surveillance Agency (Anvisa) to grant "exceptional and temporary authorization for the import and distribution of any material, drug, equipment or supply subject to health surveillance without marketing authorization from Anvisa but considered essential in the fight against the coronavirus pandemic" (art. 3, § 7, IV).

Using the *a maiori, ad minus* logic (those who may more, all the more so may less), combined with the fact that the pandemic increases the risk of shortage of drugs and pharmaceutical supplies, on May 28, 2020, Anvisa published Joint Board Resolution (RDC) n. 392, of May 26, 2020,[6] which "determines the extraordinary and temporary criteria and procedures for the application of exceptions to specific requirements of Good Manufacturing Practices (GMP) and the Import of Drugs and Pharmaceuticals, due to the international public health emergency arising from the new coronavirus".

There are many reasons that can cause drug shortage during a pandemic, like temporary closure of manufacturing plants, travel restrictions with impact on exports, exports ban, increased demand for some drugs used to treat patients with COVID-19, and higher levels of inventories maintained by hospitals, citizens or government agencies. The risk of drug shortage has led some governments to impose restrictions on the amount that can be prescribed or purchased by citizens in drugstores.[7]

It is believed that, by publishing RDC n. 392/2020,[6] Anvisa sought to maintain a minimum standard of quality, safety, and stability of drugs whose supply may be directly affected by the pandemic, thus mitigating the possibility of drug shortage in Brazil. However, it is important to highlight that Anvisa was not the first to increase this flexibility, since other health agencies had already made similar decisions, like the United Kingdom health agency—Medicines and Healthcare Products Regulation Agency (MHRA)—and the European agency—European Medicines Agency (EMA).

In this sense, this study addresses some of the provisions of RDC n. 392/2020[6] and the GMP requirements that it temporarily loosened during the COVID-19 pandemic, and then tries to identify them in documents issued by other health agencies, namely those from the United Kingdom (MHRA), Australia (Therapeutic Goods Administration, TGA), the United States (Food and Drug Administration, FDA), and Europe (EMA). Based on the exceptions of immediate implementation listed in article 7 of RDC n. 392/2020,[6] we performed a comparative analysis to highlight the main regulatory differences and similarities between the GMP requirements that were exceptionally loosened because of COVID-19. Whenever necessary, we sought to show the impact of these requirements on the quality of the drugs made available to the population, whether imported or not.

METHOD

This study initially presents a contextualized analysis of the provisions of RDC n. 392/2020[6] so that the readers can have a brief but critical understanding of said regulation. Therefore, we also deemed necessary to have a brief discussion about the objective, scope, and types of exceptions provided for in the Resolution.

Then, using an exploratory method, we conducted a selective search for documents on the transient loosening of GMP requirements for drugs and pharmaceutical supplies during the COVID-19 pandemic on the websites of the following health agencies: Anvisa (http://portal.anvisa.gov.br), MHRA (https://www.gov.uk/government/collections/mhra-guidance-on-coronavirus-covid-19), EMA (https://www.ema.europa.eu/), FDA (https://fda.gov), and TGA (https://tga.gov.au). We chose the aforementioned agencies because of their global prominence and the fact that they are all in line with the guidelines set

by the Pharmaceutical Inspection Co-Operation Scheme (PIC/S), of which Anvisa is an applicant member. All these agencies are members of the PIC/S and, in the case of EMA, most of the health agencies of European Union (EU) countries are also members.

The inexistence of documents on the temporary flexibility of GMP requirements on these websites was considered enough for us to ignore the respective health agency in this study. In cases where one or more documents on the exceptional waiver to comply with or postpone the fulfillment of a certain GMP requirement were found on the researched websites, we read them thoroughly and then compared them under a regulatory perspective with the reference framework of the exceptions of immediate implementation listed in article 7 of RDC n. 392/2020.[6]

The exceptions of RDC n. 392/2020[6] were organized in topics of GMP and respective subtopics, and summarized in a Chart indicating their existence or non-existence in the documents. While reading the foreign documents, when we found an authorization for the relaxation of any requirement that does not exist in article 7 of RDC n. 392/2020,[6] this was also inserted in the comparison Chart. Since maintenance, qualification, and calibration activities may be applicable to several operations (like production, quality control laboratories, warehousing, among others), these were included in a topic called "Engineering", regardless of the area responsible for their execution or management.

Finally, we pointed out the main regulatory differences and similarities regarding the exceptionally flexible GMP requirements and discussed them critically and in depth, highlighting, whenever necessary, the impact of these requirements on the quality of drugs available to the population, whether imported or not.

RESULTS AND DISCUSSION

Context of RDC n. 392/2020

Before moving on to the comparative analysis of the topics and subtopics summarized in the Chart, we believe it is important to comment on the objective, scope, and types of exceptions provided for in RDC n. 392/2020[6] to provide some context.

In relation to the objective of RDC n. 392/2020[6] (art. 1), we consider the reference to "international public health emergency arising from the new coronavirus" to be mistaken. The reference was recognized by the WHO on January 30 this year.[8] This criticism is levelled at the textual coherence of the Resolution, because sometimes it considers the emergency situation declared by the WHO and sometimes it refers to that recognized by the Brazilian Ministry of Health, of national concern. That is the case of article 14, which determines that "the effectiveness of this Resolution and the exceptions it authorizes shall automatically cease as soon as the Ministry of Health recognizes the end of the Public Health Emergency of National Concern declared by Ordinance n. 188/GM/MS, on February 4, 2020".

With regard to scope, according to article 2 of RDC n. 392/2020,[6] it includes companies that manufacture and import drugs and pharmaceutical supplies located in the Brazilian territory. Since there was no specific mention to active pharmaceutical ingredients, it is understood that manufacturers and importers of pharmaceutical fillers can also benefit from the flexibility authorized by this Resolution, as long as the criteria are met. Section II of Chapter I, by limiting the scope of RDC n. 392/2020[6] to the Brazilian territory, although Brazil is a major importer of drugs and, mainly, of pharmaceutical supplies, Anvisa denied the RDC exceptions to foreign manufacturers of

Chart. Comparison of the requirements of Good Manufacturing Practices eased by the following health agencies: Brazil's National Health Surveillance Agency, European Medicines Agency and Medicines and Healthcare Products Regulation Agency due to the COVID-19 pandemic.

Topics and subtopics	Anvisa	EMA	MHRA
Quality Assurance			
Suspension of on-site audits for requalification of suppliers	Yes	Yes	Yes
Authorization not to carry out/postpone investigation of "minor" deviations	Yes	Yes	Yes
Postponement of CAPA implementation related to minor deviations	No	Yes	No
Time-based document review	Yes	Yes	Yes
Suspension of internal audits	Yes	Yes	Yes
Suspension of on-site training to update on GMPs	Yes	Yes	Yes
Permission to validate production processes concurrently	No	Yes	No
Possibility of using facilities or equipment with limited prospective qualification	No	Yes	No
Exceptional drug release	Yes	Yes	Yes
Exceptional permission to transport drugs in quarantine	Yes	Yes	Yes
Approval of GxP[a] documents not managed by validated computer systems	No	No	Yes
Postponement of stability study tests	No	Yes	No
Engineering			
Suspension of calibration, qualification, and preventive maintenance activities	Yes	Yes	Yes[b]
Quality Control			
Reduction of tests performed in the reanalyses of raw materials	No	No	Yes
Permission to outsource quality control tests to a laboratory other than the one declared in the marketing authorization	Yes	Yes	No
Exemption/postponement of quality control analysis in national territory of imported medicines	Yes	Yes	Yes
Exemption of sterility tests in national territory on imported medicines	Yes	No	Yes

Anvisa: National Health Surveillance Agency; CAPA: Corrective and Preventive Action; EMA: European Medicines Agency; MHRA: Medicines and Healthcare Products Regulation Agency; GMPs: Good Manufacturing Practices.
[a] Initials in English used to indicate good practices in general, like good manufacturing practices and good laboratory practices; b Does not include flexibility related to qualifications.
Source: Prepared by the authors, 2020.

drugs or pharmaceutical supplies exported to Brazil. This could hinder the supply of some drugs and pharmaceutical supplies during the pandemic, which we believe is directly opposed to the intention of the Resolution. Still in this regard, it could be asked whether the adoption of these exceptions by foreign companies and exporters of drugs and pharmaceutical supplies to Brazil could not be subjected to the screening of the Brazilian agency for case-by-case evaluation, considering that article 9 of said RDC established that "the exceptions not covered in Section II must be electronically submitted for Anvisa's evaluation [and favorable opinion]." We understand that this would not be possible because that article is located in Section III of Chapter II, which implies the necessary reference to Section II of the same Chapter and not to Section II of Chapter I. If that was the agency's intention, it should have it done in an express and unambiguous way, which clearly did not happen.

By defining the exceptions in the sole paragraph of article 1, RDC n. 392/2020[6] divided them into two categories as to their form of application: those of immediate implementation after notification to Anvisa (art. 6, I) and those of implementation subject to the evaluation and favorable opinion of the agency (art. 6, II). The former are listed in the items of article 7 of that Resolution, whereas the latter comprise all the exceptions not listed in this article, according to the interpretation of article 9 of said RDC. Regarding the exceptions of immediate implementation, the head provision of article 7 could lead to the understanding that meeting the conditions of article 3 (implementation via formally documented risk management, having due control of the effects of non-compliance, and, of course, provided they are due to reasons proven to be related to the COVID-19 pandemic) would be enough for immediate implementation as soon as the notification is made. We dare to disagree with this understanding because, in our opinion, it lacks a systematic assessment of the provisions of the RDC under study. As necessary as complying with the provisions of article 3 of RDC n. 392/2020[6] is respecting what is imposed by article 5, which determines that the petitioning of these exceptions of immediate implementation (as well as those of implementation conditioned to the approval and favorable opinion by Anvisa) is only allowed "in cases where the companies involved in the manufacture of the drug or pharmaceutical supply hold a valid Good Practice Certification issued by Anvisa". Notifications that are not compliant with the aforementioned articles and the immediate implementation of some of the requirements provided for in article 7 of the RDC mean that the company failed to act with loyalty and good faith before the Administration (art. 4, II, Federal Law n. 9.784, of January 29, 1999)[9] and is therefore subject to the penalties provided for in article 10, XXXIV and XXXV of Law n. 6.437, of August 20, 1977.[10]

The previous understanding of the requirements for the immediate implementation of the exceptions listed in the items of article 7 of RDC n. 392/2020[6] is important because these exceptions, synthesized in topics and subtopics in the Chart, were the references for the comparative analysis of flexible GMP requirements adopted by some health agencies discussed below.

GMP requirements for medicines and pharmaceutical supplies from a comparative perspective

During the exploratory research, we found no documents on more flexible GMP requirements for medicines or pharmaceutical supplies on the websites of the health agencies of Australia (TGA) and the United States (FDA). With regard to GMP, TGA provided guidance on how national[11] and international[12] inspections should be conducted during the pandemic. The FDA, in turn, spoke about hygiene and sanitization measures that companies should reinforce or adopt to guarantee the quality and safety of drugs, especially biopharmaceuticals, in case any employee is infected.[13] Since these documents do not directly address the object of the present study, they were not considered for analysis purposes.

The Chart summarizes the topics and subtopics found in the documents analyzed from MHRA, EMA, and Anvisa. The exceptions of immediate implementation detailed in RDC n. 392/2020[6] were considered as a reference in its preparation. It is worth mentioning that all these health agencies establish the need for companies to justify their decisions formally and adequately regarding the flexibility to be adopted, with a serious risk assessment of this decision for the drug that will be made available to the population.

While Anvisa and the EMA issued only one document regarding GMP requirements that could be managed differently during the COVID-19[6,14] pandemic, MRHA issued five documents to address each topic separately.[15, 16,17,18,19] The flexible requirements are summarized in the Chart.

Although the GMP requirements loosened by RDC n. 392/2020[6] have been the reference for the Chart, we noticed there are other requirements loosened by the EMA or MHRA that were not expressly addressed by the RDC, like fewer reanalyses of raw materials, postponement of tests of stability studies, postponement of the implementation of corrective and preventive actions (CAPA) related to minor deviations identified before the pandemic, among others. The absence of such requirements in RDC n. 392/2020[6] does not mean that Anvisa prohibits their implementation, but, for this to happen, the company must file a petition with the agency and await its favorable opinion. If that does not occur within eight business days, the implementation is automatically authorized (articles 9 and 10). Considering the silence of this RDC about how to count deadlines, we understand that the rule provided for in article 13 of RDC n. 204, of July 6, 2005[20] is applicable. It establishes that, "for the purposes of counting deadlines, the start day is excluded and the expiration day is included".

One of the requirements that was made more flexible concerns on-site audits of suppliers, which, in the case of RDC n. 392/2020,[6] was considered in art. 7, I. This provision seems perfectly normal, given the limitations imposed by the governments on the transit and travel of people to try to stop the pandemic of COVID-19. We understand that the list of this item is not exhaustive, but exemplary, to guide companies as to what

can be done. For example: a remote audit could be conducted on a supplier of a certain pharmaceutical supply as an alternative to the periodic on-site monitoring audit (organized according to the company's justifiable criteria, which may take into account the criticality of the supply for the quality, safety or efficacy of the drug, relationship track record, knowledge of the company about the supply, among others), as long as there is already a track record that demonstrates positive results in previous on-site audits and GMP compliance. On the other hand, we must be careful about remote audits replacing first audits of new suppliers, since in these cases little is known about their quality assurance system, their facilities etc. Furthermore, initiating the receipt of a certain active pharmaceutical ingredient from a new supplier may require prior authorization from the General Management of Medicines (GGMED), as established in Annex I, item 1 of RDC n. 73, of April 7, 2016,[21] which we understand has not been temporarily lifted by RDC n. 392/2020.[6]

Like in Brazil, the EMA[14] and MHRA[15] also provide for remote supplier audits or evaluation of satisfactory results of prior inspections conducted by European health agencies. A distinction between Anvisa and these two health agencies is that, unlike the Brazilian agency, they do not consider the possibility of using audit reports carried out by service providers (art. 7, I, "b," RDC n. 392/2020).[6] At this point, the conservative stance of the EMA and MHRA seems to have been more appropriate than that of Anvisa, since choosing a good service provider that knows how to evaluate good practices can be as difficult as choosing a pharmaceutical supplier. After all, the audit must be done not to evidence regulatory compliance only, but to actually assess the supplier in its entirety so that negative impacts on drugs are as small as possible.

The EMA[14] considered that some temporary changes in certain aspects of the quality system could be adopted by companies to allow the rearrangement of their workforce to produce medicines considered crucial during the pandemic. This understanding is shared by the MHRA.[17] Among the changes considered by the EMA are the extension of the document review period due to time issues, the postponement of internal audits to verify compliance with GMPs and periodic on-site update training, the investigation of deviations classified as minor, and the postponement of maintenance, requalification, revalidation, and recalibration activities.[14] A similar approach was adopted by Anvisa, although it has not limited this greater flexibility to periodic qualifications, validations, and calibrations, as the EMA did by adding the "re" prefix before each of these words. Even though this slight distinction may seem irrelevant, it has a considerable impact on manufacturing routines. According to the EMA, the postponement of such activities would only be possible if there was already some "experience" with the instruments, equipment or systems, whereas in Brazil this is not a requirement, which raises some concern. Since this exception of immediate implementation and the actions provided for in the paragraphs of article 7, II, of RDC n. 392/2020[6] are not exhaustive or cumulative, but, in our opinion, exemplary, companies could, at their "justified" criterion, unduly postpone the execution of these activities as soon as notified to Anvisa.

The text of paragraphs of article 7, II, of RDC n. 392/2020[6] is virtually the same as that prepared by the MHRA,[17] with the exception of item "b" of RDC n. 392/2020,[6] which does not exist in the British text. This paragraph considers as an action for the postponement of maintenance activity the analysis of the average time between failures of the instrument, equipment or system. However, it is known that timely and suitable preventive maintenance avoids the need for corrective maintenance (repair), which, in turn, impairs the existence and recording of this data. Still in relation to the postponement of calibration and maintenance activities, the MHRA considered several other possibilities of carrying out these activities before admitting any postponement. In other words, companies must demonstrate that it's impossible for their own personnel or for third parties to do it, even if remotely or assisting the company's personnel. Only after these steps have been taken will the postponement of activities now under discussion be allowed, upon careful evaluation. It is important to highlight that, if the objective of making these (and other) GMP requirements more flexible is to avoid drug shortage during the pandemic, an evaluation that does not consider all the relevant data for its postponement can lead to hasty conclusions and, consequently, to failure or break in equipment, instruments or systems, which can also hinder drug production.

Regarding the regulatory flexibility applicable to imported drugs, the EMA expressed concern about those that are required to treat patients with COVID-19.[14] Among them, the possibility of postponing or not carrying out quality control tests by countries outside the EU. In this case, there must be a plausible justification and the drug must be received in Europe in "quarantined" conditions, submitted to all tests declared in the drug marketing authorization, and, at the end, the person responsible for its certification and subsequent release (called *qualified person*) must decide about it. The European agency also considered the possibility of postponing or not carrying out some tests to release imported drugs in Europe, as long as they are critical for the treatment of patients with COVID-19, there is imminent risk of their shortage, the tests declared in the marketing authorization have been conducted by the manufacturer outside the EU, and they prove to meet the specifications. This exception must be reported in advance to the local health authority of the member country and is subject to compliance with certain requirements: a) certification of the manufacturing company by an EU member or by some health authority with which there is mutual recognition; b) history of tests performed by the manufacturer outside the EU that demonstrate results that are consistent with those performed by the European importer; c) carrying out, in European territory, at least the identity test in the form declared in the drug marketing authorization; d) in the case of biological drugs, specific analyses, especially tests that demonstrate viral inactivation, must continue to be carried out by the importer (or by a contracted laboratory, when this is declared in the marketing authorization) before the batch is released. The decision to release a batch before all analyses in Europe are completed

must be recorded as a deviation in the company's quality system, along with all the documentation and rationale that led to that decision. The EMA also stresses that the tests that had to be postponed must be done after the batch is released and the local health authority in the member country must be informed immediately if any result does not match the specifications.

As long as the laboratories responsible for the microbiological or biological tests declared in the marketing authorization cannot work because of the lockdown imposed by the public administration or because of quarantine imposed on the team after confirmed/suspected cases of COVID-19, Anvisa allows the outsourcing without any change to the organizational unit responsible for the marketing authorization of drugs and pharmaceutical supplies (art. 7, III, RDC n. 392/2020).[6] After reading this provision, we can conclude that this permission is granted both for imported drugs and for drugs manufactured in Brazil. This wording seeks to temporarily and implicitly suspend the provisions of article 28, paragraph 2, of RDC n. 234, of June 20, 2018,[22] which provides that "cases of outsourcing of production stages and quality control analyses must comply with the provisions of the current legislation for the marketing authorization and post-marketing authorization of drugs and biological products regarding the conditions of the manufacturing site and the quality control site". As for the need to outsource physical-chemical tests of drugs manufactured in Brazil in the face of the same impediments considered for microbiological and biological tests, we believe it is necessary for the company to file the petition and wait for the agency's reply. Its immediate implementation is not allowed, since there is no such provision in the wording of RDC n. 392/2020.[6]

The previous understanding regarding physical-chemical tests does not apply to other quality control tests that must be carried out on drugs imported into the country, including the sterility test, in the case of sterile drugs. RDC n. 392/2020[6] tried to provide for this in items IV and V of article 7. Diligently reading these provisions enables us to conclude that they are incomplete, since their wording does not allow us to discern whether the agency intended to exempt the importer from carrying out all tests on imported drugs or if its intention was to allow the outsourcing of these tests in the same manner as item III of the same article for biological and microbiological tests. We dare to assume, without stating it, that the agency intended to exempt importers from laboratory tests that must be carried out in the Brazilian territory, as determined by article 9 of RDC n. 10, of March 21, 2011.[23] However, drug importers must be cautious if they want exemption from these mandatory tests, since the actions mentioned in the paragraphs of the aforementioned provisions were already covered by items I, IV, and V of article 10 of RDC n. 10/2011.[23] Considering that the actions mentioned in items IV of article 7 of RDC n. 392/2020[6] are not exhaustive, it is understood that the other items of article 10 of RDC n. 10/2011[23] must also be considered in the evaluation of formal company risk.

About the sterilization test of drugs manufactured in Brazil, it is learned from the wording of item VI of article 7 of RDC n. 392/2020[6] that Anvisa intended to postpone, and not exempt, the performance of such test. This postponement does not apply to aseptically packaged drugs, but only to terminally sterilized drugs, regardless of the type of sterilization applied (radiation, heat etc.) The EMA[14] and MHRA[15] adopted similar flexibility for imported drugs, with nothing said about those manufactured in Europe or in the UK.

Equally worthy of comparison is the provision to postpone the investigation (but not the marketing authorization) of deviations classified as minor (art. 7, VIII, RDC n. 392/2020).[6] This classification is made according to the internal procedures of the companies, considering the impact they may have on the final quality of the drug. This flexibility was also considered by the EMA[14] and MHRA.[15] The latter, in turn, allowed more flexible investigation only after the impact has been assessed by the company's Quality Assurance. This does not mean exempting it from documenting the deviations so that any observed trend is immediately investigated and addressed.

We notice that the flexible requirements discussed above bear more similarities than differences. We dare to attribute this to the fact that RDC n. 392/2020 was prepared considering the documents referenced here from the EMA and MHRA. This conclusion is based both on the publication timeline and on the similarities between the provisions.

CONCLUSIONS

The development and marketing of any drug entail many risks that must be mitigated whenever identified. Identifying these risks requires deep knowledge of the technology used in the manufacture and of how the drug acts when taken by people. GMPs require that many studies be done and documented to show that the activities of each stage of drug production are under control, so that the risks to the population are prevented or, at least, reduced to scientifically acceptable criteria. However, we must admit that knowledge is limited. Although damage is purportedly avoided, this is not always true, as shown by various tragedies occurred throughout history.[24] In fact, these tragedies encouraged the improvement of the regulatory framework that exists today, which leads to the conclusion that, behind any good practice requirement there is always a good reason that warrants its existence. That is why increasing the flexibility of any regulatory requirement demands a lot of responsibility from both companies and health agencies. Both must seek to ensure the quality of the drugs available to the population.

The comparison of RDC n. 392/2020[6] with the documents on more flexible GMPs from the EMA[14] and MHRA[15,16,17,18,19] shows that—regardless of the territory in which the regulatory agencies are located—there is considerable convergence of regulatory expectations. After examining the documents mentioned in this article, we could notice the European agency's concern about drugs considered critical for the treatment of COVID-19 patients, unlike the other two agencies we compared to it (MHRA and Anvisa), which did not present the same delimitation.

Considering that the knowledge about this disease is still new and being acquired during the pandemic, we understand that it is difficult to limit the flexibility of some GMP regulatory requirements to a few drugs, because the impact of the pandemic on the manufacturing chain and logistics of drugs to treat, cure or diagnose other diseases is also unpredictable and should therefore be considered too.

The considerations or even the criticisms made in this article to some provisions of RDC n. 392/2020[6] in no way diminish the merit of Anvisa's initiative. We must all understand that, in times like these, when little is known about the disease, as is the case of COVID-19, the speed with which some decisions must be made and regulations be issued can result in some understandable mistakes. What cannot happen is the misuse of these mistakes by companies to justify non-compliance with GMP requirements, because it is their responsibility to assess the impact that the requirements can have on the drugs, whose quality, safety, and efficacy cannot be compromised under any circumstances.

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Authors' Contribution

Cassano AO – Conception, planning (study design), acquisition, analysis, interpretation of data, and writing of the paper. Areda CA – Analysis, interpretation of data, and writing of the paper. The authors approved the final draft of the paper.

Conflict of Interest

The authors report that there is no potential conflict of interest with peers and institutions, nor political or financial conflicts in this study.