Post-marketing sampling and testing programs for licensed medicinal products: a narrative review

Edvaldo Oliveira Neves[1, 2*], Paloma Michelle de Sales[2,3], Dâmaris Silveira[2]

¹Brazilian Health Regulatory Agency (ANVISA), Brasilia, DF, Brazil, ²Faculty of Health Sciences, University of Brasilia (UnB), Brasilia, DF, Brazil, ³Central Laboratory of Public Health of the Federal District (LACEN-DF), Brasilia, DF, Brazil

The globalization of the pharmaceutical market has enabled access to a considerable number of new medicinal products. Consequently, the circulation of substandard medicinal products has also increased. To minimize this problem, post-marketing quality sampling and testing programs are performed to monitor and confirm that the medicinal products available in the market meet appropriate quality requirements. In this review, the post-approval sampling and testing procedures of six regulatory authorities were compared with the goal of strengthening these market surveillance systems. Similarities were observed between the procedures adopted by different regulatory authorities. However, the agencies were not always transparent about the results of these monitoring procedures. A probable mismatch between the registration procedures and the quality requirements listed in official compendiums was observed, which resulted in dissonance and contradiction between the specifications approved by the regulatory authorities and those required in the pharmacopeias. Therefore, strengthening harmonization projects related to these activities can help minimize such difficulties.

Keywords: Medicines. Quality control. Post-marketing. Pharmaceutical products. Harmonization. Pharmacopeia.

INTRODUCTION

Unlike other available items in the market, medicinal products have a very apparent market dichotomy. These are objects of commercial importance and represent one of the sectors that move financial resources around the world, and their reach crosses international boundaries (Lybecker, 2006). It is estimated that the amount of money spent on medicinal products globally will reach more than USD 1.5 trillion by 2023 (IQVIA Institute, 2019). However, medicinal products are public assets that are necessary for the improvement of health policies, and are one of the most tightly regulated products in all countries (Lybecker, 2006).

Since the mid-1930s, many new medicinal products have entered the market. As a result, an outgrowth in the circulation of substandard (authorized medicinal products, but "out of specification") and counterfeit medicinal products (medicinal products deliberately misrepresented) has been observed (Ratanawijitrasin, Wondemagegnehu, 2002; WHO, 2017b). According to the World Health Organization (WHO), it is estimated that about 10% of the medicinal products in the market are substandard (WHO, 2017b). Data from the Promoting the Quality of Medicines (PQM), a United States Agency for International Development (USAID), and the U.S. Pharmacopeial Convention program showed that 5.6% samples of the 15,063 analyzed medicinal products failed the quality test between 2003 and 2013. Depending on the origin of the product, these numbers may be as high as 11.5% (Hajjou *et al.*, 2015). In 2018, an 18.7% prevalence of poor-quality medicinal products was reported in Africa. Although the economic burden of these products is unclear, the estimated impact can range from USD 10-200 billion, depending on the market size (Ozawa *et al.*, 2018).

*Correspondence: E. O. Neves. Agência Nacional de Vigilância Sanitária (ANVISA). Brasilia, DF, Brasil. SIA. Trecho 5, Área Especial 57. CEP: 71205-050. E-mail: edvaldo.neves@anvisa.gov.br
ORCID: https://orcid.org/0000-0002-1220-9675

Treating patients with substandard medicinal products can result in low bioavailability, suboptimal dosing, reduced efficacy, and thus increased mortality and morbidity. It will also lead to resistance to antibiotics, for example, which is one of the greatest threats to public health (Ratanawijitrasin, Wondemagegnehu, 2002; WHO, 2003; Newton, Green, Fernández, 2010; Priyanka, Jayshree, 2016; WHO, 2017a). Depletion of financial reserves of public health institutions, and the loss of confidence in health systems and health care workers are among the other concerning problems (Ratanawijitrasin, Wondemagegnehu, 2002; Newton, Green, Fernández, 2010; WHO, 2017a).

WHO has expressed that countries have to develop regulations and procedures to ensure the safety, efficacy, and quality of medicinal products by controlling and monitoring their circulation in their markets (WHO, 2003). One of these procedures is the sampling and laboratory testing of medicinal products rightfully introduced to the market (WHO, 2016). However, several countries with limited resources have difficulty implementing an effective regulatory system (Ratanawijitrasin, Wondemagegnehu, 2002; WHO, 2003; Rägo, Santoso, 2008). Only about 20% of the countries in the world have well-developed and operational regulation of pharmaceutical products (WHO, 2003; Weyer, 2016).

As a result, regulatory harmonization projects have been an important tool to enhance the quality control programs of marketed medicinal products. (Rägo, Santoso, 2008). These actions reinforce the development of guidelines related to quality and market supervision, development of quality standards, and strengthening of good laboratory practices. Among others initiatives, the international performance of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), the WHO/ Essential Medicines and Pharmaceutical Policies (WHO/ EMP), the Organization for Economic Co-operation and Development (OECD/Health Division), and the International Regulators Consortium Initiative, are examples that can be highlighted (EMA, 2016a). Harmonization initiatives from European Directorate for the Quality of Medicines and HealthCare (EDQM),

the Southern African Development Community (SADC), and the Pan American Network for Drug Regulatory Harmonization (PANDRH) are implemented regionally (EMA, 2016a).

In addition to the harmonization projects cited above, it is also possible to highlight the regular interactions between regulatory authorities (RAs) through clusters. These are regulatory and scientific information exchanges aimed at leveraging the most successful examples of collaboration, best practices, and to identify opportunities to increase efficiency. This approach addresses a broad range of scientific and regulatory topics, including post-market actions. Examples are the clusters between the FDA and EMA, which over the years have also had the participation from other RAs (Teixeira, Kweder, Saint-Raymond, 2019).

This review focuses on the procedures used by different RAs to evaluate human medicinal products after marketing authorization, and to identify areas that require considerable attention during harmonization. Consequently, this can contribute towards strengthening the health systems. Therefore, this review is focused on the monitoring of human medicinal products submitted and approved in the marketing authorization applications. Since falsified, unlicensed medicinal products are not covered by the regulations cited in this review, these products must be dealt with separately.

MATERIAL AND METHODS

Five government entities were selected for comparison. Two international reference RAs, the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), a national RA with highly centralized procedures and a regional RA with decentralized procedures (Van Norman, 2016). Three RAs with a short regulatory history and limited economic or regulatory capacity: the Brazilian Health Regulatory Agency (ANVISA, Brazil); the National Authority of Medicines and Health Products (INFARMED I.P., Portugal); and National Food and Drug Surveillance Institute (INVIMA, Colombia). While ANVISA and INFARMED have their own pharmacopeia, INVIMA does not have an official

compendium (WHO, 2018b). ANVISA and INVIMA are regional reference RAs in Latin American. INFARMED is a European RA that has followed the European Union (EU) directives.

In addition to these, the WHO guidelines were also analyzed. The post-marketing quality control program guidelines and data were obtained from RAs websites and relevant legislation.

The procedures adopted by different regulatory authorities were compared by analyzing the following: existence of an institutionalized program of sampling and testing medicinal products; similarity in selection criteria for medicinal products to be surveyed; similarity in analytical processes performed during regulatory activity; convergence between approved and official specifications; and transparency of these criteria, procedures, and analytical data.

RESULTS AND DISCUSSION

The regulatory system related to quality assurance of medicinal products involves a wide and varied network of interconnected elements with different levels of complexity. It starts with the technical and scientific evaluation of product development, which is the technical basis for the marketing authorization or licensing. The next phase is the assessment of whether the company's operations are compliant with good manufacturing practices (GMP). The final step is the market surveillance and conduction of surveys to ensure the quality of medicinal products by sampling and testing (EU, 2001).

The analyses performed by the laboratories specified in the general pharmaceutical legislation are essential to ensure compliance with the quality parameters throughout their life-cycle (WHO, 2010).

Therefore, laboratory testing of medicinal products is an integral part of the post-marketing surveillance. It supports the RAs with the inspection services and serves as a basis for subsequent administrative or legal actions (WHO, 2010; FDA, 2015). Thus, the sampling and testing programs involves the selection of products to be evaluated, defining the tests to be performed, the collection of the samples for analysis, and the adoption of legal actions, whenever necessary (WHO, 2016).

Post-market sampling and testing programs for licensed medicinal products

Most of the RAs cited in this review conduct sampling and testing of licensed medicinal products through periodic programs, such as "Sampling and Testing Programme" conducted by EMA (EMA, 2016c), the "market supervision program" executed by INFARMED (Infarmed, 2018), the "DeMuestra La Calidad" program of INVIMA (Invima, 2017), and the "Drug Quality and Sampling Testing Compliance Program" of FDA (FDA, 2015). In contrast, the Brazilian program is non-periodic, but performs routine market supervision (Brazil, 1973; Brazil, 2013).

Nonetheless, the regulations enforced by the FDA and EMA differ. While the FDA has a strictly centralized process, the EMA is decentralized through a network of nationally centralized agencies with synchronized regulations preserving national "autonomy"; post-market testing of medicinal products is not an exception (Van Norman, 2016). In the American market, medicinal products are tested in FDA laboratories or its designated laboratory (FDA, 2018). EMA uses the expertise and laboratories under the responsibility of EU member countries, the Official Medicines Control Laboratories (OMCL) network. All member states mutually recognize the laboratory results without further confirmatory testing (EDQM, 2016a).

A regulatory system similar to FDA is observed in INVIMA and INFARMED, when Portuguese RA is observed off the topic of the EU. Both are national RAs accountable to evaluate, authorize, control, and test the medicinal products introduced in the market, also acting as Reference Laboratory on the Quality Control of Medicines (Portugal, 2012; Colombia, 2015).

However, according to the Colombian procedures, when a non-compliance event is reported, the manufacturer's laboratory is responsible for conducting a retention sample testing under the supervision of INVIMA. Colombian RA maintains that such procedure is necessary to ensure if the identified non-compliance is due to the manufacturing process or due to transportation, storage, method of analysis or other correlated factors (Invima, 2017).

In these analytical aspects, the Brazilian RA and EMA have characteristics in common; since ANVISA does not have a laboratory it relies on the expertise of laboratories from other levels of the Federation or seeks assistance from a specialized laboratory (Brazil, 2015; Brazil, 2017).

Owning a laboratory is not a requirement for carrying out post-marketing sampling and testing programs. It is possible to hire external laboratories. However, it can be a limiting factor. Some common barriers to implement these programs in countries with limited resources are poor laboratory infrastructure, lack of equipment, untrained personnel, difficulties in acquiring the reagents and supplies required to perform quality control analysis (WHO, 2010; Pribluda *et al.*, 2014).

Thus, sharing of analytical data can minimize this difficulty. Though this kind of sharing is on the agenda of the harmonization projects, it is still far from being realized, except for EU. Perhaps, it may be due to the fear of loss of autonomy by many countries, limitations in the integration of national and regional databases, or even difficulties in recognizing the identity of medicinal products since RAs cannot always be sure they are referring to the same product (EMA, 2016a).

Table I shows test results from the sampling and testing programs mentioned in this review. It is important to note that despite the current discussion on transparency and access to information, there is limited access to data related to quality of medicinal products. Although many technologies could be used to improve transparency, it has been found that they are not used efficiently. Data are not up to date and do not provide sufficient information for generating reports or surveys. This includes laboratory data, guidelines, and procedures. Thus, there is inefficient communication of RAs with the society.

TABLE I - Data from periodic sampling and testing of licensed medicinal products programs

Countries and regulatory authorities	Date/ Period	Products tested (N)	OOS products (%)	OOS requirements/ test	Reference
Brazil/ ANVISA	2016-2017	284	14.1%	U	(Anvisa, 2018b)
Colombia/ INVIMA*	2016	204	S1- 12.6% S2- 10.1%	Assay and uniformity of content: S1 and S2 pH: Only S2	(Invima, 2017)
EU/ EMA	2014	47	4.25%	U	(EMA, 2016c)
Portugal/ INFARMED	2017	1000	1.5%	Dissolution test, characteristics of dosage form	(Infarmed, 2017)
USA/ FDA	2016	84	2.38%	Assay and impurities	(FDA, 2018)

U, unidentified; N, number; OOS, out-of-specification; S, stage. See the text for further details.
*- S1: Data from samples collected from distributors, retailers, hospitals, health services, etc. S2: Results from samples taken at manufacturers after OOS in S1.

Selection of medicinal products or groups of products and manufacturers

Products included in the post-marketing quality control testing programs for medicinal products are selected through a risk-based approach. Testing focuses on medicinal products, holders of the marketing authorization or medicinal product manufacturing companies, dosage forms, and active pharmaceutical ingredients (API), for example, using targeting products that are most likely to pose a risk to patients. Examples include products indicated by the offices based on their regulatory intelligence: narrow therapeutic index drugs, products whose consumers reported complaints, companies with a past history of non-compliance, produced by manufacturers for whom there is sparse evidence of compliance with the principles of GMP (EDQM, 2014; FDA, 2015; Anvisa, 2016; Sindusfarma, 2016; Invima, 2017; Infarmed, 2018; WHO, 2018a).

It is important to note that the manufacturers and the selection of their products based on respective analytical history can be an important tool for the risk-based approach. It has been identified that some manufacturers tend to produce drugs with API values towards lower tolerance limits. Although still within tolerance limits, this indicates deficiencies in compliance with GMP (Neves, de Sales, Silveira, 2019).

This risk-based approach is reinforced by WHO guidelines, which emphasize that laboratory testing should focus on medicinal products or companies most likely to pose risk to patients, and it should be performed if it adds value to the evaluation since these analyses demand considerable resources (WHO, 2018a). Moreover, this risk-based approach allows the laboratories to concentrate their limited resources on those medicinal products considered to have a high risk of quality defects (EDQM, 2016b). The use of this approach is a common point among the cited RAs.

The samples are collected throughout the production and distribution chain, that is, from manufacturers, distributors, wholesalers, retailers, hospitals, health services, and pharmacy support (EDQM, 2014; FDA, 2015; Anvisa, 2016; Sindusfarma, 2016; Invima, 2017; Infarmed, 2018; WHO, 2018a).

Quality specifications in post-market quality control

As mentioned earlier, laboratory analyses should add value to the evaluations performed. Therefore, the specifications to be applied must be in line with the answers sought (WHO, 2018a). Specification, by definition, contains a list of tests, analytical procedures, tolerances limits or acceptance criteria to which product should conform (ICH, 1999).

Thus, evaluating impurities or dissolution without performing the assay is not reasonable. Likewise, if the purpose is to verify the compliance of a product with registered specifications, the information approved by RAs or regulatory specifications should be used. However, if products containing the same API and dosage from different manufacturers are to be evaluated, pharmacopeial or official specifications are recommended (WHO, 2018a).

Considering this, although the pharmacopeial specifications are a public statement of the appropriate quality adopted in a country or region, i.e., their regulatory expectations, they are not always considered a conclusive quality requirement. The analysis performed using the pharmacopeial specifications should be seen as quality screening (Calam, 1995; Conceição *et al.*, 2014; EDQM, 2014; WHO, 2016; Heyward *et al.*, 2018). However, by applying a strong official quality standard, nonconformity in a public monograph can be a fast and efficient way to remove a substandard product from the marketplace, as opposed to lengthy administrative or legal action (Heyward *et al.*, 2018).

The specifications developed by the manufacturers involve several factors, such as dosage form, clinical aspects of the API of medicinal products, critical attributes, parameters of the product related to manufacturing process, statistical sampling plans, among others (Dong, Tsong, Shen, 2015; Burdick *et al.*, 2017). In contrast, pharmacopeial specifications are supported in literature reviews and marketing authorization data. In light of this, official quality standards are likely to have broader specifications than those adopted by manufacturers (FDA, 1987; EU, 2001; Portugal, 2006; Anvisa, 2013; WHO, 2015; Burdick *et al.*, 2017; Anvisa, 2018a).

For marketing authorization or licensing, the FDA requires the manufacturer or marketing authorization holder to present the relevant quality requirements throughout a product's shelf life. Broader limits than those in the official specifications are not ordinarily approved as regulatory specifications (FDA, 1987; Wechsler, 2002). Additionally, some guidelines promote convergence between regulatory specifications and monographs in the United States Pharmacopeia (USP), to minimize discrepancies between them (FDA, 2014; USP, 2016; USP, 2017; USP, 2018). Thus, FDA considers USP specifications in its medicinal products sampling and testing program. If a particular monograph is not specified in the pharmacopeia or in the occurrence of out-of-specification (OOS) results, regulatory specifications are performed (FDA, 2015; FDA, 2018).

Figure 1 shows the general process of medicinal products sampling and testing as well as highlights the need for convergence between regulatory and official specifications.
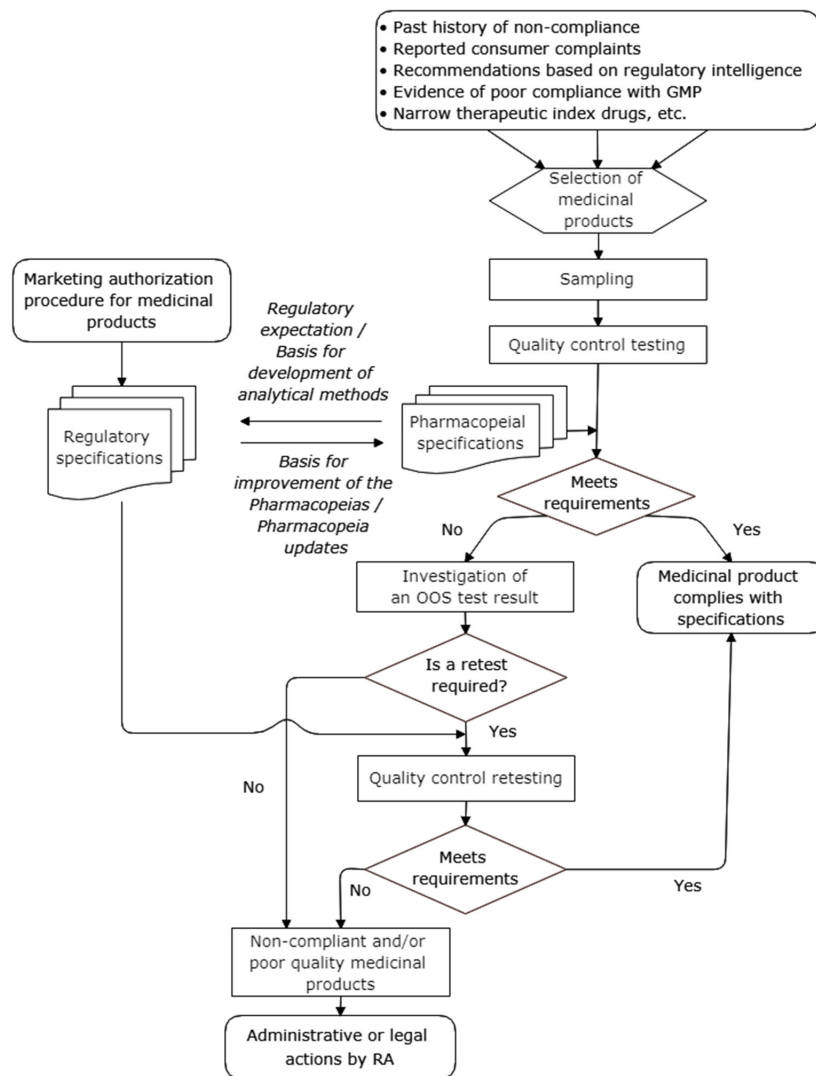
FIGURE 1 - General procedure for sampling and testing of medicinal products employing pharmacopeial specifications and approved regulatory specifications by government authorities for marketing authorization.

GMP, Good manufacturing practices; RAs, regulatory authorities; OOS, out-of-specification.

European RAs expect more restrictive in-house product release specifications than regulatory and official specifications. Many manufacturers implement in-house fairly tight limits that provide more assurance that their product will remain within established acceptance criteria throughout its shelf life (Wechsler, 2002). Therefore, in both scenario European or American, pharmacopeias describe the minimum and mandatory requirements applicable to all medicinal products placed in the market. However, a more restrictive analytical profile is discernible in the European market.

Nevertheless, European RAs post-marketing sampling and testing programs do not always adopt pharmacopeial specifications as the screening tool. INFARMED, for example, performs direct regulatory specifications as a starting point in the market surveillance national program (Infarmed, 2018). As a form of screening, EMA sampling and testing program evaluates EMA centrally authorized products, which is carried out based on its own analytical protocol, the "Common Test Procedure." This protocol is established based on a defined list of parameters to be tested including the variety of regulatory specifications, API, variations in the dosage form, specifications from European Pharmacopeia, and OMCL in-house methods. With OOS results, new analyses are performed using the regulatory specifications for the sample in question (EDQM, 2014).

It is important to mention that the European Pharmacopeia has a limited number of specific monographs for finished products. Among the almost 2400 existing monographs, only 1% is related to finished products. It is a compendium that only describes the general requirements for the different dosage forms and specific monographs of API (EDQM, 2017; Conceição *et al.*, 2019). This justifies disuse of compendium as a primary reference for the analysis of finished products.

The Brazilian and Colombian RAs, on the other hand, require manufacturers to meet specifications of the recognized pharmacopeias in the Country (Colombia, 1995; Anvisa, 2009; Invima, 2017). It is important to mention that besides Brazilian Pharmacopeia, several other Pharmacopeias are recognized in Brazil: German, US, Argentine, British, European, French, International, Japanese, Mexican, and Portuguese (Anvisa, 2009).

Colombia recognizes US, British, French, German, European, and International Pharmacopeia (Colombia, 1995). However, this country does not have its official compendium (Colombia, 1995; WHO, 2018b).

The Brazilian guidelines related to monitoring the quality of medicinal products is scattered and sometimes with divergent outlooks. In this manner, these guidelines are not clear about the definition of quality specifications and their applications in this conformity assessment process (Brazil, 1976; Anvisa, 2009; Anvisa, 2010). Also, there are no procedures that converge the approved specifications with that described in the national pharmacopeia (Lima, 2017; Neves, de Sales, Silveira, 2019). Thus, although this convergence seems to be well established in the American regulatory system, it is not institutionally planned in the Latin American context (FDA, 2014; USP, 2016; USP, 2017; USP, 2018). Non-harmonized quality testing standards can lead to substandard products remaining in the market with questionable clinical efficacy and, not infrequently, judicialization of regulatory actions (Heyward *et al.*, 2018).

For the Brazilian sampling and testing program 2016, the analysis was performed according to Brazilian Pharmacopeial specifications (Anvisa, 2016; Sindusfarma, 2016). In the Colombian sampling and testing program (2016), the analyses were performed using USP specifications (Invima, 2017). Both programs performed regulatory specification in the eventuality of OOS results (Anvisa, 2016; Sindusfarma, 2016; Invima, 2017).

In this context of diversity of pharmacopeias, it is observed that there is a certain similarity between the Latin American and European scenario. Although there are instruments for the mutual recognition of analytical data and product licensing in the EU, to our knowledge, there is no available tools to promote convergence between analytical specifications in the individual monographs of the 16 national pharmacopeias in the European block (EDQM, 2016a; EMA, 2016b; WHO, 2018b). Considering this, if the marketing authorization holder chose to market the product in different countries of the EU, it will have to observe different quality metrics established in these different compendiums (Bouin, Wierer, 2014).

From the perspective of the RAs, it is not reasonable to authorize a product or supervise the market using different rules for the same product. Therefore, it

seems logical to establish guidelines for the use of those compendia when the same product is described in more than one pharmacopeia, which are recognized in the country or region and serve as the basis for the registration of a product whose circulation will be beyond national borders.

Table II compares the profile of post-authorization sampling and testing programs considering the information already described. Although significant similarities are seen in the selection criteria of the samples, there are some major differences in the screening process at the analytical stage. It is important to note that in the context of the diversity of pharmacopeias, clear criteria have not been found (and it is unlikely that they exist) when more than one official compendium exist. Despite this, all RAs perform regulatory specification for final decision-making in the case of OOS results.

TABLE II - Comparing the profile of post-authorization sampling and testing programs of various regulatory authorities

Description	Countries and regulatory authorities (RAs)				
	Brazil/ ANVISA[1]	EU/ EMA[2]	Portugal/ INFARMED[3]	Colombia/ INVIMA[4]	USA/ FDA[5]
About RAs:					
Is there laboratory with legal competence to test the medicinal products introduced on the market?	Yes	Yes	Yes	Yes	Yes
Does RA have its own laboratory structure?	No	No	Yes	Yes	Yes
Post-marketing quality control testing programs for medicinal products.					
Is there institutional post-market sampling and testing programs for medicinal products?	No	Yes	Yes	Yes	Yes
Is it a periodic sampling and testing program?	No	Yes	Yes	Yes	Yes
Are there analytics data that demonstrate the continuity of the program?	No	Yes	Yes	Yes	Yes
Does the program have defined criteria for product selection?	Yes	Yes	Yes	Yes	Yes
Are there public guidelines that describe the procedure for sampling and testing of medicinal products?	Yes	Yes	Yes	Yes	Yes
Are the pharmacopeial specifications adopted as first quality standard on the samples tested?	Yes	No	No	Yes	Yes
Are the regulatory specifications (approved specifications and methods) adopted as first quality standard on the samples tested?	No	No	Yes	No	No
Are the official medicines control laboratories in-house methods adopted as first quality standard on the samples tested?	No	Yes	No	No	No
When a doubtful, aberrant, or suspected result (OOS result) is identified, are the samples retested using the approved method for marketing authorization?	Yes	Yes	Yes	Yes	Yes

(continues on the next page...)

TABLE II - Comparing the profile of post-authorization sampling and testing programs of various regulatory authorities

Description	Countries and regulatory authorities (RAs)				
	Brazil/ ANVISA[1]	EU/ EMA[2]	Portugal/ INFARMED[3]	Colombia/ INVIMA[4]	USA/ FDA[5]
About pharmacopeias:					
Is there own national pharmacopeia?	Yes	N/A	Yes	No	Yes
Nationally, in addition to the national pharmacopeia, if any, are other foreign pharmacopeias recognized by RA?	Yes	N/A	No	Yes	No
If RA recognizes foreign pharmacopeias, is it allowed to adopt as an alternative to the national pharmacopeia, if any, is the monograph specified in the national pharmacopeia?	No	N/A	N/A	N/A	N/A
Is it allowed to adopt foreign pharmacopeias as complementary tools to the national/ regional pharmacopeia?	Yes	N/A	U	N/A	Yes
If the monograph is not specified in the national pharmacopeia, if any, are there criteria, system, or organization in which non-national pharmacopeias are relevance-ranked?	No	N/A	N/A	No	N/A
Is there own regional pharmacopeia?	No	Yes	Yes	No	No
If RA recognizes regional pharmacopeias, is it adopted instead of the national pharmacopeia (if any) even if the monograph is specified in the national pharmacopeia?	N/A	Yes	Yes	N/A	N/A
Is it allowed to adopt national pharmacopeias as complementary tools to regional pharmacopeia?	N/A	N/A	Yes	N/A	N/A
Are there institutionalized procedures by RA that promote convergence between regulatory and official specification, which minimizes divergence between them?	No	Yes	Yes	N/A	Yes
Quality specifications					
Do the guidelines express the purpose and distinction between method and specification approved in the marketing authorization application, in-house release specifications and pharmacopeia specification?	No	Yes	Yes	No	Yes
Do the marketing authorization procedures prevent or hamper the adoption of wider ranges for acceptance criteria or tolerance limits, the inferior performance of the analytical procedure and less selective analytical techniques than those of that pharmacopeia adopted in the country?	No	Yes	Yes	Yes	Yes

(continues on the next page...)

TABLE II - Comparing the profile of post-authorization sampling and testing programs of various regulatory authorities

Description	Countries and regulatory authorities (RAs)				
	Brazil/ ANVISA[1]	EU/ EMA[2]	Portugal/ INFARMED[3]	Colombia/ INVIMA[4]	USA/ FDA[5]
Do the guidelines express clearly that requirements of the pharmacopeia monograph are mandatory for all medicinal products / Meet the pharmacopeial specifications are required in the sampling testing programs?	No	Yes	Yes	N/A	Yes
Do the guidelines express clearly that in case of dispute, regarding the OOS results, the pharmacopeial text, shall prevail?	No	Yes	Yes	N/A	Yes

U, unidentified; N/A: Not applicable. OOS, out-of-specification; RAs, regulatory authorities; 1 - (Brazil, 1973; Brazil, 1976; Anvisa, 2009; Anvisa, 2010; Brazil, 2013; Brazil, 2015; Anvisa, 2016; Sindusfarma, 2016; Lima, 2017; WHO, 2018b; Anvisa, 2019; Neves, de Sales, Silveira, 2019) and General guideline of the National Program for Quality Control of Medicines – PROVEME unpublished work; 2 - (EU, 2001; Wechsler, 2002; EDQM, 2014; EDQM, 2016a; EMA, 2016c; EMA, 2016b; WHO, 2018b); 3 - (EU, 2001; Portugal, 2012; Infarmed, 2017; Infarmed, 2018; WHO, 2018b); 4 - (Colombia, 1995; Colombia, 2015; Invima, 2017; WHO, 2018b); 5 - (FDA, 1987; Wechsler, 2002; FDA, 2014; FDA, 2015; USP, 2016; USP, 2017; FDA, 2018; USP, 2018; WHO, 2018b).

Other regulatory tools

In addition to the sampling and testing programs described here, other tools can be used as auxiliaries for market surveillance. One of these tools is the "Three-Level Approach", proposed by the PQM program. This approach uses three interlinked approaches with increasing level of complexity, to strengthen the quality assurance systems of medicinal products. The first level includes a visual and physical inspection to assess the packaging conditions and the physical characteristics of the actual medicinal products. The second level consists of rapid analytical tests that evaluate a limited number of quality attributes and can be easily performed by trained personnel. The third level involves quality control testing by the regulatory specifications and is performed at an appropriate laboratory. This approach is applicable mainly to countries with limited resources, laboratories with poor infrastructure, and those with difficulty in structuring a robust medicinal products monitoring program in their market (Pribluda *et al.*, 2014).

Example of other tools are portable devices to track substandard medicinal products. There are a multitude of devices for this purpose. However, these tools lack cost-effectiveness, and accuracy and specificity of scientific data. Moreover, some devices require processing of complex and specific calibration models. These factors limit the use of this tool (Vickers *et al.*, 2018).

Limitations

This study was supported by public information from RAs. In doing so, it was difficult to obtain clear information on these procedures. Thus, some of the regulatory guidelines may not have been identified during this review. Furthermore, there are regulatory procedures that are not publicized or interpretations not explicit in the guidelines, which could not be validated since they cannot be referenced. Therefore, although regulatory transparency should be an essential feature of RAs, this requirement remains fragile and fragmented. This hampers access of information to all stakeholders, including regulators, the regulated sector, health care professionals, academics, or the community (Sousa, Ramalho, Silveira, 2016).

CONCLUSION

It has been observed that the procedures for sampling and testing of authorized medicinal products are very

similar among RAs, although limitations in transparency regarding the implementation of these procedures in some countries are evident.

For countries or regions where more than one official compendium is recognized, there is a need for greater clarity in the procedures used for market surveillance and guidelines for the use of these pharmacopeias. It is also worth emphasizing the need to frequently update the national compendium, when it exists, to avoid discrepancies between the specifications approved by the RAs and those that are officially required.

Therefore, it is important to strengthen the actions developed by EDQM in the EU and PANDRH in Latin America. Moreover, the actions related to the Mercosur Pharmacopeia, that was created as a tool for regulatory strengthening and pharmaceutical production in South America, but which has been stalling for a long time are also factor that can contribute to the improvement in regulatory standards in Latin America.

In conclusion, sharing analytical data in Latin American region to strengthen the monitoring of the quality of medicinal products circulating in the region or as a tool to reduce the excessively high costs, is inherent to these analyses.

ACKNOWLEDGEMENTS

FOOTNOTES

Conflicts of Interest: The authors have no conflicts of interest to declare.

Disclaimer: Authors hold sole responsibility for the views expressed in this manuscript, which may not necessarily reflect the opinion or policy of the Brazilian Health Regulatory Agency (ANVISA).

REFERENCES

Anvisa. Brazilian Health Regulatory Agency (Brazil). Resolution of the Collegiate Board of Officers - RDC nº 37 of July 06, 2009, which deals with the admissibility of foreign pharmacopoeias. Brazilian Federal Register, Jul 08, 2009, p. 40, Section 1.

Anvisa. Brazilian Health Regulatory Agency (Brazil). Resolution of the Collegiate Board of Officers - RDC nº 49 of November 23, 2010. It approves Brazilian Pharmacopoeia, 5th edition and provides further remedies. Brazilian Federal Register, Nov 24 2010, p. 80, Section 1.

Anvisa. Brazilian Health Regulatory Agency (Brazil). Ordinance nº 452 of February 25, 2013. Approves the Internal Regulations of the Brazilian Pharmacopoeia Commission, revokes Ordinance nº 1015 of July 20, 2011 and gives other provisions. Brazilian Federal Register, Feb 26 2013, p. 102-103, Section 1.

Anvisa. Brazilian Health Regulatory Agency. Anvisa launches drug and device monitoring program: 1,800 samples will be tested [Internet]. 2016 [cited 2018 Dec 12]. Available from: https://bit.ly/2HwFYKw.

Anvisa. Brazilian Health Regulatory Agency. Brazilian Pharmacopoeia [Internet]. 2018a [cited 2018 Sep 17]. Available from: http://portal.anvisa.gov.br/farmacopeia.

Anvisa. Brazilian Health Regulatory Agency. Generic drugs: 18 years in the Brazil [Internet]. 2018b [cited 2019 May 09]. Available from: https://bit.ly/2Ju2THW.

Anvisa. Brazilian Health Regulatory Agency. Home Page for the Brazilian Health Regulatory Agency (ANVISA) 2019 [cited 2019 Apr 09]. Available from: http://portal.anvisa.gov.br/.

Bouin A-S, Wierer M. Quality standards of the European Pharmacopoeia. J Ethnopharmacol. 2014; 158:454-457.

Brazil. Law nº 5991 of December 17, 1973. Provides for the sanitary control for sale of medicines, drugs, pharmaceutical inputs and correlates, and give other provisions. Brazilian Federal Register, Dec 19, 1973, p. 13049-, Section 1.

Brazil. Law nº 6360 of September 23, 1976. Provides for the Health Surveillance that the medicines, drugs, and the pharmaceutical inputs, cosmetics & sanitizing and other products are subjected, and gives other provisions. Brazilian Federal Register, Sep 24, 1976, p. 12647-, Section 1.

Brazil. Decree nº 8077 of August 14, 2013. Regulates the registro, control, and monitoring of the products addressed by Law nº 6360 of September 23, 1976, and the conditions for the operation of companies subject to sanitary licensing, within the scope of health. Brazilian Federal Register, Aug 15, 2013, p. 18-19, Section 1.

Brazil. Law nº 13097 of January 19, 2015. Amends the Law nº 6360 of September 23, 1976, and give other provisions Brazilian Federal Register, Jan 20, 2015, p. 01-12, Section 1.

Brazil. Consolidation Ordinance nº 4 of September 28, 2017. Consolidation of the rules on health actions and services of Unified Health System (SUS). Brazilian Federal Register, Out 03, 2017, p. 288-360, Section 1 supplement.

Burdick RK, LeBlond DJ, Pfahler LB, Quiroz J, Sidor L, Vukovinsky K, et al. Specifications. Statistical applications for Chemistry, Manufacturing and Controls (CMC) in the pharmaceutical industry. Cham, Switzerland: Springer International Publishing; 2017. p. 227-267.

Calam DH. Design and international harmonization of pharmacopoeial standards. J Pharm Biomed Anal. 1995;14(1):1-5.

Colombia. Decree nº 677 of April 26, 1995. Regulates the conditions of registration and licensing, quality control and the health surveillance system for pharmaceuticals, cosmetics, pharmaceutical preparations of natural resources, grooming products, household care and other products of "domestic use". Colombian Federal Register, Apr 28, 1995, p. 20.

Colombia. Resolution nº 1619 of May 15, 2015. Implementing rules for the national laboratories network. Colombian Federal Register, May 20, 2015, p. 1-2.

Conceição J, Pita JR, Cabral-Marques HM, Sousa Lobo JM. The European Pharmacopoeia: an official book with fifty years. Acta Farm Port. 2019;8(1):17-38.

Conceição J, Pita JR, Estanqueiro M, Lobo JS. Portuguese pharmacopoeias and public health. Acta Farm Port. 2014;3(1):47-65.

Dong X, Tsong Y, Shen M. Statistical considerations in setting product specifications. J Biopharm Stat. 2015;25(2):280-294.

EDQM. European Directorate for the Quality of Medicines and HealthCare. General procedure for sampling and testing of generic Centrally-Authorised products - PA/PH/CAP (12) 32 11R [Internet]. 2014 [cited 2018 Aug 09]. Available from: https://www.edqm.eu/medias/fichiers/general_procedure_for_sampling_and_testing_of_generic_centrally_authorised_products_paphcap_12_32.pdf.

EDQM. European Directorate for the Quality of Medicines and HealthCare. Annex 7 to the GEON Terms of reference: Mutual recognition of test results - PA/PH/OMCL (16) 49 R [Internet]. 2016a [cited 2018 Aug 08]. Available from: https://www.edqm.eu/sites/default/files/geon-tor-annex7-mutual-recognition-test-results.pdf.

EDQM. European Directorate for the Quality of Medicines and HealthCare. Incorporation of a risk based approach in Market Surveillance testing at OMCLs - PA/PH/OMCL (06) 3 9R [Internet]. 2016b [cited 2018 Sep 11]. Available from: https://www.edqm.eu/sites/default/files/omcl_incorporation_of_a_rb_approach_in_ms_testing_at_omcls.pdf.

EDQM. European Directorate for the Quality of Medicines and HealthCare. Annual Report 2017 - European Directorate for the Quality of Medicines & HealthCare (EDQM) 2017 [cited 2018 Set 11]. Available from: https://www.edqm.eu/sites/default/files/annual-report-edqm-2017.pdf.

EMA. European Medicines Agency. Connecting the dots - Towards global knowledge of the international medicine regulatory landscape: mapping of international initiatives [Internet]. 2016a [cited 2018 Nov 10]. Available from: https://www.ema.europa.eu/documents/leaflet/connecting-dots-towards-global-knowledge-international-medicine-regulatory-landscape-mapping_en.pdf.

EMA. European Medicines Agency. The European regulatory system for medicines: A consistent approach to medicines regulation across the European Union [Internet]. 2016b [cited 2018 Sep 24]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2014/08/WC500171674.pdf.

EMA. European Medicines Agency. Results of the sampling and testing programme for the year 2014 - Human and veterinary products [Internet]. 2016c [cited 2018 Aug 13]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/07/WC500211428.pdf.

EU. European Union. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Official Journal European Union, L311, 2001, p. 67-128.

FDA. Food and Drug Administration. Guideline for submitting supporting documentation in drug applications for the manufacture of drug products [Internet]. 1987 [cited 2018 Nov 10]. Available from: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm149499.htm.

FDA. Food and Drug Administration. Guidance for industry ANDA submissions — Content and format of Abbreviated New Drug Applications [Internet]. 2014 [cited 2018 Sep 20]. Available from: https://www.fda.gov/downloads/drugs/guidances/ucm400630.pdf.

FDA. Food and Drug Administration. Drug quality sampling and testing (DQST) - Human drugs - Program 7356.008 [Internet]. 2015 [cited 2018 Sep 10]. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM273078.pdf.

FDA. Food and Drug Administration. Drug quality sampling and testing programs [Internet]. 2018 [cited 2018 Aug 28]. Available from: https://www.fda.gov/Drugs/ScienceResearch/ucm407277.htm.

Hajjou M, Krech L, Lane-Barlow C, Roth L, Pribluda VS, Phanouvong S, et al. Monitoring the quality of medicines: Results from Africa, Asia, and South America. Am J Trop Med Hyg. 2015;92(Suppl 6):68-74.

Heyward J, Padula W, Tierce JC, Alexander GC. The value of U.S. Pharmacopeial Standards: A review of the literature. J Pharm Sci. 2018;107(10):2611-2617.

ICH. Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances Q6A. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use; 1999 Oct 6; Geneva, Switzerland: ICH; 1999.

Infarmed. National Authority of Medicines and Health Products. Supervisão do mercado [Internet]. 2017 [cited 2018 Sep 08]. Available from: http://www.infarmed.pt/web/infarmed/entidades/medicamentos-uso-humano/controlo-laboratorial-de-medicamentos/supervisao-do-mercado.

Infarmed. National Authority of Medicines and Health Products. Laboratory Drug Control [Internet]. 2018 [cited 2018 Aug 09]. Available from: http://www.infarmed.pt/web/infarmed/entidades/medicamentos-uso-humano/controlo-laboratorial-de-medicamentos.

Invima. National Food and Drug Surveillance Institute. Demonstrate Quality Program - Drug Products (DeMuestra La Calidad) [Internet]. 2017 [cited 2018 Dec 20]. Available from: https://www.invima.gov.co/images/pdf/farmacovigilancia_alertas/INFORME-PROGRAMA-DEMUESTRA-LA-CALIDAD-2016.pdf.

IQVIA Institute. The global use of medicine in 2019 and outlook to 2023: Forecasts and areas to watch [Internet]. 2019 [cited 2019 Mar 15]. Available from: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-global-use-of-medicine-in-2019-and-outlook-to-2023.pdf.

Lima LMTR. Pharmacopeia and ANVISA: A Necessary Symbiosis. Rev Bras Farm Hosp Serv Saúde. 2017; 8(4):4-7.

Lybecker KM. Social, ethical, and legal issues in drug development, marketing, and pricing policies setting priorities: pharmaceuticals as private organizations and the duty to make money/maximize profits. The Power of Pills. Social, Ethical and Legal Issues in Drug Development, Marketing and Pricing. London: Pluto Press; 2006. p. 25-31.

Neves EO, de Sales PM, Silveira D. Pharmacopeial specifications and analytical data from post-marketing quality sampling and testing programs: a perspective beyond out-of-specification results. J Pharm Biomed Anal. 2019:112935.

Newton PN, Green MD, Fernández FM. Impact of poor-quality medicines in the 'developing' world. Trends Pharmacol Sci. 2010;31(3):99-101.

Ozawa S, Evans DR, Bessias S, Haynie DG, Yemeke TT, Laing SK, et al. Prevalence and estimated economic burden of substandard and falsified medicines in low- and middle-income countries: A systematic review and meta-analysis. JAMA Netw Open. 2018;1(4):e181662-e181662.

Portugal. Decree-Law nº 176 of August 30, 2006. Establishes the legal system of the medicinal products for human use and is usually referred as Medicinal Products Statute. Official Journal, Aug 30, 2006, p. 6297-6383, Section I.

Portugal. Decree-Law nº 46 of February 24, 2012. Approves the organic statute of INFARMED - National Authority of Medicines and Health Products, I.P. Official Journal, Feb 24, 2012, p. 884-890, Section I

Pribluda VS, Barojas A, Coignez V, Bradby S, Dijiba Y, El-Hadri L, et al. The three-level approach: a framework for ensuring medicines quality in limited-resource countries. Pharm Regul Aff. 2014;3(1):117.

Priyanka P, Jayshree D. In vitro Comparison of Generic and Branded Preparations of Amoxicillin with Potassium Clavulanate. J Clin Diagn Res. 2016;10(9):FC07-FC09.

Rägo L, Santoso B. Drug regulation: history, present and future. In: Van Boxtel CJ, Santoso B, Edwards IR, editors. Drug benefits and risks: International textbook of clinical pharmacology. Amsterdam and Washington, DC: IOS Press; 2008. p. 65-77.

Ratanawijitrasin S, Wondemagegnehu E. Effective drug regulation: A multicountry study. Geneva, Switzerland: World Health Organization; 2002.

Sindusfarma. Association of the Pharmaceutical Industry in the State of São Paulo. Lecture of ANVISA at Sindusfarma: Brazilian Health Regulatory Agency starts its programmed tests on 1.800 drug samples – São Paulo on December 19, 2016 [Internet]. 2016 [cited 2018 Aug 08]. Available from: http://sindusfarma.org.br/arquivos/Apresentacao2_19dez2016.pptx.

Sousa VD, Ramalho PI, Silveira D. Sharing regulatory data as tools for strengthening health systems in the Region of the Americas. Rev Panam Salud Publica. 2016;39(5):245-254.

Teixeira T, Kweder SL, Saint-Raymond A. Are EMA, FDA and other international regulators talking to each other? Clin Pharmacol Ther. 2019;107(3):7p.

USP. United States Pharmacopeia. USP Guideline for submitting requests for revision to the USP–NF: General information for all submissions [Internet]. 2016 [cited 2018 Dec 10]. Available from: http://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/general-information-for-all-submissions.pdf.

USP. United States Pharmacopeia. Pending Monograph Guideline [Internet]. 2017 [cited 2019 Jan 20]. Available from: https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/pending-monograph-guideline.pdf.

USP. United States Pharmacopeia. United States Pharmacopeia (USP 41-NF 36) [Internet]. 2018 [cited 2018 Aug 23]. Available from: https://www.uspnf.com/Subscription required.

Van Norman GA. Drugs and devices: Comparison of European and U.S. approval processes. JACC Basic Transl Sci. 2016;1(5):399-412.

Vickers S, Bernier M, Zambrzycki S, Fernandez FM, Newton PN, Caillet C. Field detection devices for screening the quality of medicines: a systematic review. BMJ Glob Health. 2018;3(4):e000725.

Wechsler J. Harmonizing Standards and Specifications. Pharm Tech. 2002;26(5):14-22.

Weyer K. Concept paper for discussion: A stepwise approach for pharmaceutical companies in developing countries to attain WHO GMP standards. WHO Drug Information. 2016;30(2):186-198.

WHO. World Health Organization. Effective medicines regulation: ensuring safety, efficacy and quality. WHO Policy Perspectives on Medicines. Geneva, Switzerland: WHO Press; 2003.

WHO. World Health Organization. WHO good practices for pharmaceutical quality control laboratories. Forty-fourth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Geneva, Switzerland: WHO Press; 2010.

WHO. World Health Organization. WHO Procedure for the development of monographs and other texts for The International Pharmacopoeia. Forty-ninth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Geneva, Switzerland: WHO Press; 2015.

WHO. World Health Organization. Guidelines on the conduct of surveys of the quality of medicines. Fiftieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Geneva, Switzerland: WHO Press; 2016.

WHO. World Health Organization. A study on the public health and socioeconomic impact of substandard and falsified medical products [Internet]. 2017a [cited 2019 Mar 02]. Available from: https://www.who.int/medicines/regulation/ssffc/publications/SE-Study_EN_web.pdf?ua=1.

WHO. World Health Organization. WHO Global Surveillance and Monitoring System for substandard and falsified medical products [Internet]. 2017b [cited 2019 Mar 02]. Available from: https://www.who.int/medicines/regulation/ssffc/publications/GSMS_Report_layout.pdf?ua=1.

WHO. World Health Organization. Considerations for requesting analysis of medicines samples. Fifty-second report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Geneva, Switzerland: WHO Press; 2018a.

WHO. World Health Organization. Index of world pharmacopoeias and pharmacopoeial authorities - Working document QAS/11.453/Rev.10 [Internet]. 2018b [cited 2018 Aug 02]. Available from: http://www.who.int/medicines/publications/pharmacopoeia/index-of-pharmacopoeias_17012018.pdf?ua=1&ua=1