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Pharmacopeial specifications and analytical data from post-marketing quality sampling and testing programs: a perspective beyond out-of-specification results

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Highlights

- Different pharmacopeial specifications have impacts on medicine quality assessment.
- Analytical results that meet specifications can help develop sampling and testing programs.

- Analytical results that meet the specifications can also support new GMP inspections.
- Harmonization should focus on acceptance criteria of individual monographs.
- Multiple analytical options are essential for nations with limited resources.

Abstract

Ensuring that marketed medicines meet acceptable standards (safety, quality, and efficacy) involves aspects of product development, compliance with good manufacturing practices, and monitoring and testing of these products already on the market. Pharmacopeias are one of the main tools used by regulatory authorities in the analytical testing for quality assessment; there are almost 60 pharmacopeias in the world. Thus, this research evaluated the potential impacts of the differences between the pharmacopeial specifications in the quality assessment of these products. It also assessed the use of analytical data to strengthen these surveillance systems. The pharmacopeial specifications for assay determination and dissolution test from United States Pharmacopeia (USP), British (BP), Brazilian (FB), Portuguese (FP), Argentine (FA), and International (Ph. Int.) Pharmacopeias were compared. The quality control reports and results of the Brazilian conformity assessment program were used to support the research. The possibility of selection of medicines or manufacturers for monitoring, sampling, and testing, as well as good manufacturing practice inspections based on analytical data were observed, even considering compliant cases or those within the tolerance limits. An important impact of acceptance criteria given in the individual monographs of different pharmacopeias regarding quality testing was also observed. Strengthening of the pharmacopeial

harmonization projects and universalization of the requirements provided by the individual monographs can help in supporting the internationalization of the pharmaceutical market and improving access to medicines.

Abbreviations

AC, acceptance criteria; ANVISA, Brazilian Health Regulatory Agency; API, Active Pharmaceutical Ingredient; BDDCS, Biopharmaceutics Drug Disposition Classification System; BP, British Pharmacopeia; $C_{(01-49)}$, Company; CI, Confidence Interval; FA, Argentine Pharmacopeia; EAC, East African Community; FB, Brazilian Pharmacopeia; FP, Portuguese Pharmacopeia; GMP, Good Manufacturing Practices; HPLC, High-Performance Liquid Chromatography; ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; ICMRA, International Coalition of Drug Regulatory Authorities; NSAID, Non-steroidal Anti-inflammatory Drug; PAHO, Pan American Health Organization; $P_{(01-45)}$, Product; PDG, Pharmacopeial Discussion Group; Ph. Int., International Pharmacopeia; PROVEME, National Program for Quality Control of Medicines; QC-R, Official Quality Control Report; SADC, Southern African Development Community; USP, United States Pharmacopeia; UV-Vis, ultraviolet or visible; WHO, World Health Organization.

Keywords: medicines, quality control, post-marketing, pharmaceutical products, harmonization, pharmacopeia.

1. Introduction

The regulatory system related to quality assurance of drug products involves a wide and varied network of interconnected elements with different levels of complexity. It begins with the technical and scientific evaluation of the

development of these products, which is the technical basis for the authorization of product introduction on market 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 monitoring of these products already on the market through pharmacovigilance activities and procedures that involve the collection of samples and their subsequent laboratory evaluation [1-4].

Historically, substandard medicines have represented a barrier to therapeutic efficacy, which resulted in the depletion of financial reserves of public health systems [1]. In the United States, 2.38% of the analyzed products failed at meeting the standards of quality in 2016 [5], whereas in the European Union, this value was 4.25% according to data from 2014 [6]. Between 2016 and 2017, these numbers reached 12.6% and 14.1% in Colombia and Brazil, respectively [7, 8].

Therefore, laboratory evaluation of drug products introduced in the market is an essential part of the post-marketing surveillance. It integrates the inspection services and serves as a basis for the execution of administrative or legal actions by the regulatory authority, whenever necessary [2]. The selection of products to be evaluated, and the definition of the tests to be performed should add value to the regulatory process by focusing on medicines that are most likely to pose a risk to patients. Therefore, the adoption of a risk-based approach is appropriate [3]. Thus, it is important to prioritize pharmaceutical products produced by manufacturers for which the evidence of compliance with GMP is sparse or with a history of non-compliance, products whose consumers reported complaints regarding suspected quality defects or suspected adverse reactions related to quality defects, and narrow therapeutic index drugs, among others [2, 3, 9].

In this context, pharmacopeial specifications (including list of tests, analytical procedures and tolerance limits, or acceptance criteria to which products should be in conformity) are one of the main screening tools used by regulatory authorities in analytical testing for quality assessment, since they represent the regulatory expectation with respect to the country or region, and express the quality standards for the concerned products [4, 9]. However, there are 59 pharmacopeias around the world (55 national, 3 regional or sub-regional, and 1 international). Despite efforts to harmonize pharmacopeias, there are still many differences between them [3, 10]. This fact represents a limiting factor for international trade of medicines, and consequently, difficulty in implementing drug product access policies [11].

Given this scenario, this research evaluated the potential impacts of the differences between the pharmacopeial specifications when pharmacopeias are used as a starting point, or as a method of screening, in the quality assessment of products introduced in the market. We also evaluated how analytical data, even in compliance, can aggregate information to a risk-based approach, supporting further regulatory actions. Finally, considering the regulatory needs of the different countries, the use of official compendiums was presented accordingly.

2. Materials and methods

This study was based on 240 Official Quality Control Reports (QC-Rs) from a database of the National Program for Quality Control of Medicines (PROVEME), which is the quality control testing program of Brazilian Health Regulatory Agency (ANVISA). This research considered the QC-Rs issued between October 15, 2016 and June 12, 2017.

Results of the assay and dissolution tests included in PROVEME's QC-Rs were compared with quality specifications from Brazilian (FB) [12], Portuguese (FP) [13], Argentine (FA) [14], British (BP) [15], International (Ph. Int.) [16] and United States (USP) pharmacopeias [17].

Data were evaluated using a mixed-effects model with a random effect in the intercept [18]. Microsoft Excel® 2010 and the free statistical software "R" (3.5.0) were used in this search for the shape of the distribution, tendency, and the scatter in the data under study.

The electronic supplementary material provides detailed information about all QC-Rs (Supplementary Material I) and other considerations.

2.1. Drug products classification

The 240 QC-Rs included in the study were classified according to the active pharmaceutical ingredient (API), dosage forms, and strength dose of the tested samples. Uncoated tablets, film-coated tablets, and sugar-coated tablets were grouped. The same procedure was carried out for powder for suspension and suspension, and powder for solution and solution, resulting in 45 products (hereinafter referred to as P01 to P45) in different dosage forms: 28 tablets, 3 capsules, 4 oral solutions, 4 oral suspensions, 4 solutions for injection, and 2 suspensions for injection. These products were manufactured by 49 different manufacturers (from now on referred to as C01 to C49).

Biopharmaceutics drug disposition classification system (BDDCS) list [19] was used to discuss drug solubility. Table 1 shows details of these products, their BDDCS classification, and number of QC-Rs.

Insert Table 1.

3. Results and discussion

3.1. Selection of medicines or groups of products and manufacturers

The outcomes in this study endorsed a risk-based approach and provided additional indicators to this approach. In this context, according to the QC-Rs, some drug therapeutic categories presented API values under the labeled amount in all or almost all the samples of batches submitted for analysis. Although within limits, quantified values are typically in the lower or upper extremes of this tolerance. Considering antihypertensive agents available as oral tablets, 100% of P08 and P25 samples, 86% of P30 samples, and 67% of P33 and P38 samples presented assay values under the labeled amount, as shown in Figure 1. In addition, 100% of P20 samples (tricyclic antidepressants), P16 (antifungal), and P23 (antiemetic); 86% of P35 samples (an antiretroviral drug used in the treatment of HIV); 67%-70% of P01 samples (antiviral), P07 (beta-lactam antibiotic), and P34 (non-steroidal anti-inflammatory drug - NSAID) presented assay values under the labeled amount.

Additionally, P11, P13 (cephalosporin antibacterial), P19, P27 (benzodiazepine), P31 (loop diuretic, antihypertensive agent), P32 (antipsychotic drug), and P40 (NSAID) are considered as liquid pharmaceutical forms, while P06 (beta-lactam antibiotic) and P44 (NSAID) are considered as capsules.

Insert Fig 1.

However, by taking into consideration a 95% confidence interval (CI), only the products P12, P13 (cephalosporin antibacterial), and P24 (antihistamine) presented assay values above the labeled amount, whereas P11, P14 (cephalosporin antibacterial), P25 (antihypertensive agent), P40, and P44

(NSAID) presented assay values under the labeled amount. These data are shown in Figure 2. For more details about the CI evaluation, see Supplementary Material II.

Insert Fig 2.

The difference between the product categories identified in both types of assessment (Figure 1 and Figure 2) can be justified by the small number of samples for certain products as well as by the type of graphic representation adopted. Nevertheless, these data indicate that the drug therapeutic categories are an important factor to be considered in a post-marketing quality control testing program. Moreover, it suggests that product selection based on the respective analytical history can be an important tool to help identify drugs whose measured assay results are extremely close to the lower or upper specification limits. Even if all the assay values were plotted inside the control limits and behave in a systematic or nonrandom manner, this could be an indicator that the process was out of control [20]. Boxplot representation was especially useful in comparing assay values.

Another way to evaluate these analytical results is to focus on the marketing authorization holders or medicine manufacturing companies. While grouping by companies, wide assay variations in medicines batches were observed with a trend towards to the lower tolerance limits.

Within this context, taking into consideration companies with 4 or more batch samples analyzed, 75% to 100% of the samples presented assay values below the labeled amount for C04, C07, C14, C18, C28, C37, and C48. One the

other hand, 75% to 100% of samples presented assay values above the labeled amount for C11 e C20 (Figure 3).

Insert Fig 3.

Although these results might be regarded as statistically non-significant (95% CI), they are essential data for identifying potential medicines and manufacturers for prioritization in this risk-based approach. This affirmation is possible because of the tendency of active ingredient quantification directed towards values under the labeled amount or trend towards the lower tolerance limits. By analogy, these data are incompatible with the production process in the in-control state, in which a stable random variation around the process target (100%) can be observed [20]. The absence of this requirement indicates deficiencies in the compliance with GMP. Consequently, it suggests that medicines selection should focus on a portfolio of these manufacturing companies, and stresses again the importance of historical analytic assessment, even considering compliant cases or those within the tolerance limits.

Grouping by dosage form or BDDCS class does not lead to any additional evidence factors.

Thus, this type of evaluation helped to identify medicines or manufacturers that are most likely to pose a risk to patients, allowing laboratories to concentrate their resources on those products which are most likely to exhibit quality deviations [3].

The reported findings are not sufficient to make inferences about the clinical impact of these variations - and it is not the goal. However, some authors showed that a wide activity variation in medicine batches with a tendency for sub-potent performance has resulted in a decrease in the therapeutic effect or a

high rate of antibiotic resistance [21], bioinequivalence [22], as well as differences in the coagulation profile in enoxaparin-based biological products [23].

Mistakenly, some authors have correlated substandard medicines with generic products, especially in cases of under-dose and high variability between batches. However, it should be noted that GMP compliance, safety, and efficacy are not requirements unique to generic drugs. Batch-to-batch variability or cases of substandard pharmaceutical products also exist for brand name drugs, as well for generic drugs. Therefore, the most important action is the regulatory effectiveness and monitoring of all the pharmaceutical chain, regardless of whether it is generic or not [24].

3.2. Different regulatory expectations and their implications

There are several efforts focused on health harmonization regulatory systems, both regionally and internationally. For example, the work of the Pan American Health Organization (PAHO) and World Health Organization (WHO), the East African Community (EAC), the Southern African Development Community (SADC), and the International Coalition of Drug Regulatory Authorities (ICMRA). Specifically, while addressing the harmonization of analytical quality standards, it is important to highlight the overall effect of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and consequently, the Pharmacopeial Discussion Group (PDG) harmonization initiatives. As the ICH is a council of regulatory authorities and representatives of the pharmaceutical industry that discusses scientific and technical aspects related to worldwide quality and harmonization, a draft

harmonized by the PDG is transmitted to the ICH interest group for evaluation from the point of regulatory compliance [11].

However, even within the ICH, movements related to pharmacopoeial harmonization have focused primarily on the harmonization of pharmaceutical ingredient monographs and general quality requirements such as weight determination, uniformity content and mass, capsule and tablet disintegration and dissolution tests, and their evaluation criteria [3, 10]. Harmonization related to individual monographs of finished products is limited. Moreover, aspects related to the legal framework of each country, the need for flexibility regarding regional specificities, or even regional political factors limit the processes of harmonization of quality standards [11].

Given this context and considering the products evaluated, the outcomes of this study translated a more restrictive profile of European (BP, FP and Ph. Int.) compendium when comparing with the American (USP) and Latin American (FB, FA) ones. In the BP, approximately 53% of the monographs establish tolerance limits for assays, ranging from 95 to 105% of the label claim; in FP, 27% of the monographs also adopt these limits, and another 45% mention tolerance ranging from 92.5% to 107.5%. The USP, on the other hand, presents wider tolerance intervals or regulatory expectations, since approximately 70% of the monographs determine limits of 90% to 110% for quantification of the active ingredient, while 73% of FA and 49% FB monographs preconize this tolerance limit (Figure 4).

Insert Fig 4.

MA, monograph absent; FB, Brazilian Pharmacopeia; USP, United States Pharmacopeia; BP, British Pharmacopeia; FA, Argentine Pharmacopeia; FP, Portuguese Pharmacopeia; Ph. Int., International Pharmacopeia.

Thus, this study indicated that tolerance limits established in the individual monographs of the different pharmacopeias should be taken into account when harmonization is considered, as these limits can influence decisions on products conformity, and consequently, upon the effectiveness of early screening stage in quality testing.

In this context, comparing the analytical results of the QC-Rs with the tolerance limits for the assay from the pharmacopeial individual monograph, 3 samples were found to be out-of-specification when considering the FB limits; 1 sample when considering the FA, Ph. Int., and USP; and 13 samples when considering the BF (Table 2 and Figure 5). Therefore, depending on the pharmacopeia adopted for the comparison, the decision on the conformity of the sample was strongly influenced by the acceptance criteria or the tolerance limit applied, which affected 1 to 13 samples and 1 to 10 manufacturers.

The key findings are presented in Figure 5 and Table 2. For the totality of samples, see Supplementary Material III.

Insert Fig 5.

API, active pharmaceutical ingredient; TI, Tolerance interval; FB, Brazilian Pharmacopeia; USP, United States Pharmacopeia; BP, British Pharmacopeia; FA, Argentine Pharmacopeia; FP, Portuguese Pharmacopeia; Ph. Int., International Pharmacopeia.

Insert Table 2.

A similar situation was observed in the dissolution test. Five samples were found to be out-of-specification when compared with the FB acceptance criteria, 3 with the FP, 6 with the FA and USP, 2 with the Ph. Int., and 3 with the BP, affecting 2 to 6 samples and 2 to 5 manufacturers. Table 3 and Figure 6

show these key findings. For the totality of samples, see Supplementary Material III.

Insert Fig 6.

API, active pharmaceutical ingredient; AC, acceptance criteria; P, products; FB, Brazilian Pharmacopeia; USP, United States Pharmacopeia; BP, British Pharmacopeia; FA, Argentine Pharmacopeia; FP, Portuguese Pharmacopeia; Ph. Int., International Pharmacopeia.

Insert Table 3.

In an overall assessment of the dissolution test, besides the official acceptance criteria, there is a critical dissonance between analytical methods when comparing the particular monographs of each product between the different pharmacopeias.

However, unlike assay determination, the dissolution assessment is a performance test. Whether an official specification exists or not, the dissolution method developed by the company and approved by the regulatory authority is essential to evaluate and assure the consistency of the manufacturing process, batch-to-batch quality, and the performance of a product. The performance of a particular product is not covered by the official specifications [25]. Therefore, performing the approved dissolution specification is essential to effectively infer about the quality of a drug product [25], and thus, the universalization of the individual monographs does not appear to be applicable to dissolution assessment.

3.3. Particularities in the context of building monographs and recognition of foreign pharmacopeias

Another way to approach pharmacopeial specifications is through analytical techniques listed in the assay of the active substance. There is a

tendency to replace the non-selective methods (e.g., titrimetric and spectrophotometric methods) by more selective ones (e.g., high-performance liquid chromatography - HPLC) [26]. It is possible to observe this in USP and FA (the tendency to perform analyses by HPLC), and FB and BP ([ultraviolet or visible (UV-Vis) spectrophotometry and HPLC] (Figure 7). UV-Vis spectrophotometry is preconized for dissolution tests in almost all the pharmacopeial specifications.

Except for FB and Ph. Int., monographs preconize only one analytical technique for active substance assay (Figure 7).

Insert Fig 7.

HPLC, High-performance liquid chromatography; UV-Vis, Ultraviolet-visible spectroscopy; FB, Brazilian Pharmacopeia; USP, United States Pharmacopeia; BP, British Pharmacopeia; FA, Argentine Pharmacopeia; FP, Portuguese Pharmacopeia; Ph. Int., International Pharmacopeia.

It is suggested that this is a reflection of the regulatory requirements regarding the use of more modern and selective techniques, given that regulatory specifications have served as support for the construction of the pharmacopeial monographs [27]. For example, USP 27/2004 described the determination of API content by HPLC assay in 44% of the monographs for active ingredients, titration in 40.5%, spectrophotometry in 8.5%, microbiological assay in 2.5%, gas chromatography in 2.5%, and other methods in 2% [26].

In the current version of USP and based on the 38 products of this study for which monographs are considered in this compendium, 33 monographs (86.8%) preconize HPLC, 3 monographs (7.9%) microbiological assay, and 2 monographs (5.3%) spectrophotometry. When considering the monographs of

the 31 API related to these products, HPLC assay is the technique described for 26 (83.9%), and titration for 5 (16.1%) [17].

However, the effectiveness of these changes is not consensual. Authors claim that the assay of the drug content obtained by mass balance concept is a much better quality control attribute than that obtained by HPLC due to the limited precision of the last [26, 28].

Thus, given the plethora of analytical techniques available, the modern analytical techniques have become highly popular compared to the traditional ones because they have advantages of ease of automation and consequent reduction of time for sample preparations and processing, among others [29].

Some regulatory authorities have difficulties in implementing complex quality standards or acquiring the supplies required to perform quality control analysis [30]. Thus, the possibility of recognition of pharmacopeias that provides more than one alternative method of analysis or that describes traditional analytical techniques - such as the FB, BP, and Ph. Int. - is a viable alternative to bypass technical limitations in performing analysis of products introduced into the market.

Notably, the aim of the Ph. Int. is precisely to serve as a source of reference for countries wishing to establish pharmaceutical requirements [16].

4. Limitations and suggestions for future research

It is important to mention that these outcomes should be considered in light of some limitations. First, the sampling that supported this paper reflects a list of products selected through a risk-based approach in the context of PROVEME program. In this way, it should not be considered as an assessment of the pharmaceutical market. Moreover, the absence of individual monographs in

the mentioned pharmacopeias should not be considered as a possible parameter of quality of these compendiums. In each pharmacopeia, priority is given to drug products available in the region/country market, or in the case of the Ph. Int., drugs included in the WHO Model List of Essential Drugs or those relevant according to WHO health program [16].

In addition, the results of the assay and dissolution tests from PROVEME were compared to pharmacopeial specifications, and the samples were not retested using the cited pharmacopeial specifications. Nevertheless, considering that analyses must be performed in compliance with Good Laboratory Practices guidelines and verification of compendial methods, it is reasonable to assume that the study performed under these ideal conditions would not have divergent results from that observed. Thus, for further research, it may be an important approach to reproduce this study by performing such analyses.

5. Conclusion

The analytical results assessment, even in compliance, was able to identify different products and manufacturers with a trend toward to the lower tolerance limits. Therefore, it can constitute important data for selection of medicines, product groups, or companies through the risk-based approach for the post-marketing sampling and testing programs.

In addition, an important impact of acceptance criteria given in the individual monographs from different pharmacopeias was observed regarding quality testing of drug products. This impact is more associated with the assay determination than with the dissolution test. Thus, considering pharmacopeial harmonization, the convergence of tolerance limits remains an unsolved problem, which should be addressed in the harmonization process. Such convergence

would avoid the need for duplication of analyses by manufacturers, reduce production costs, and promote internationalization of medicines.

6. Acknowledgements

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7. 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).

8. Appendix A. Supplementary data

Insert Supplementary Material I
Insert Supplementary Material II
Insert Supplementary Material III

9. References

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Figure 1. Boxplot representation of the comparison between measured active pharmaceutical ingredient assay and labeled amount (red line) by products ($P_{(01-45)}$). *, outliers.

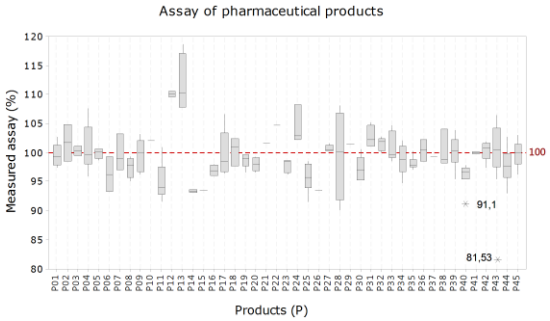

Figure 2. Comparison between measured active pharmaceutical ingredient assay and labeled amount by products ($P_{(01-45)}$).

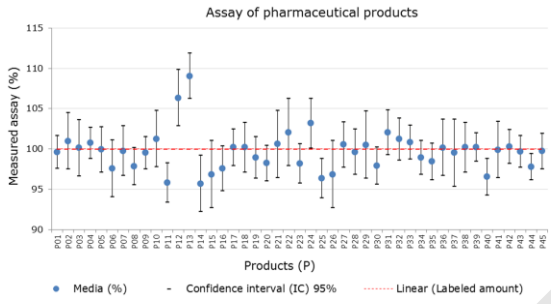

Figure 3. Graphical representation of samples tested, samples with assay values under the labeled amount, or with a trend toward to the lower tolerance limits per manufacturer ($C_{(01-49)}$).

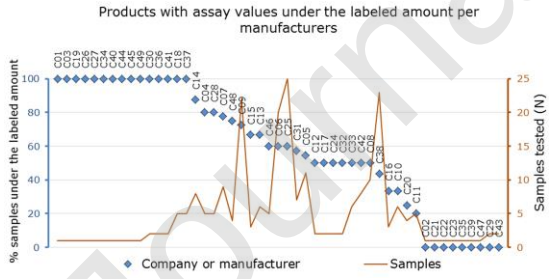

Figure 4. Frequency of citation of tolerance limits for assay determination by pharmacopeial monographs.

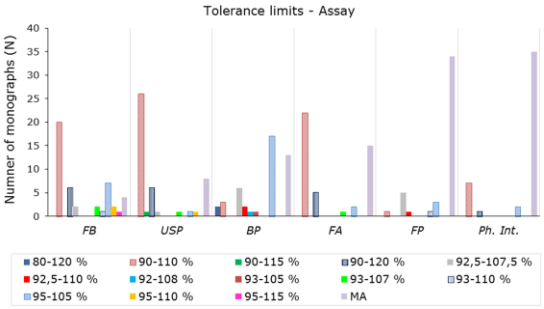

Figure 5. Samples affected by "non-harmonized" tolerance limit in assay of individual monographs.

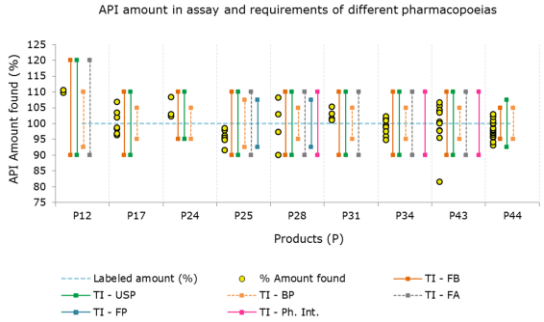

Figure 6. Samples affected by "non-harmonized" acceptance criteria in dissolution test of individual monographs.

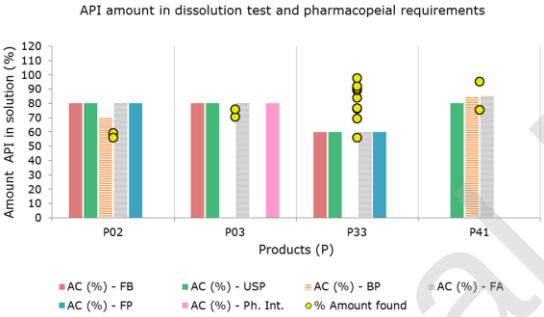

Figure 7. Representation of the planned elaboration of monographs by the different pharmacopeias considering the variability of analytical techniques for assay.

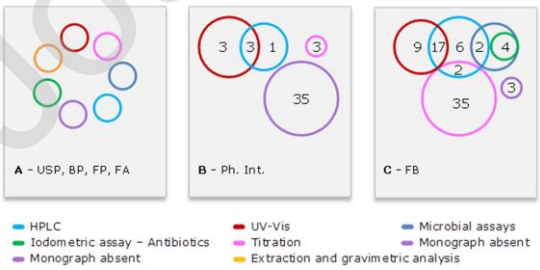

Table 1. Classification of products and medicines in the current research.

Products	Generic name	Dosage forms	Strength dose	BDDCS	N
P01	Acyclovir	TB	200 mg	4	10
P02	Aspirin/ Acetylsalicylic acid	TB	100 mg	1	2
P03	Albendazole	TB	400 mg	2	2
P04	Amoxicillin	CP	500 mg	3*	11
P05	Amoxicillin	PO OR SUS or OR SUS	50 mg/mL	3*	4
P06	Ampicillin	CP	500 mg	3	2
P07	Ampicillin	TB	500 mg	3*	3
P08	Atenolol	TB	25, 50, 100 mg	3	7
P09	Bromazepam	TB	3, 6 mg	1	10
P10	Bromopride	TB	10 mg	absent	2
P11	Bromopride	OR SOL	4 mg/mL	absent	6
P12	Cephalexin	C TB	500 mg	3*	2
P13	Cephalexin	PO OR SUS or OR SUS	50 mg/mL	3*	4
P14	Ceftriaxone	PO SUS INJ	1 g	3	2
P15	Ceftriaxone + Lidocaine	PO SUS INJ	500 mg	3	1
P16	Ketoconazole	TB	200 mg	2	4
P17	Cimetidine	TB and C TB	200, 400 mg	3	7
P18	Clonazepam	TB and C TB	2 mg	1	3
P19	Clonazepam	OR SOL	2.5 mg/mL	1*	5
P20	Amitriptyline hydrochloride	TB and C TB	10, 25, 75 mg	1	8
P21	Bupivacaine hydrochloride	SOL INJ	5 mg/mL	1	1
P22	Lidocaine hydrochloride	SOL INJ	50 mg/mL	1	1
P23	Metoclopramide hydrochloride	TB	10 mg	3	6
P24	Promethazine hydrochloride	C TB	25 mg	1	3
P25	Propranolol	TB	40 mg	1	6

	hydrochloride				
P26	Diazepam	TB	5 mg	1	1
P27	Diazepam	SOL INJ	5 mg/mL	1*	4
P28	Phenobarbital	TB	50, 100 mg	1	4
P29	Flurazepam	C TB	30 mg	1*	1
P30	Furosemide	TB	40 mg	4	7
P31	Furosemide	SOL INJ	10 mg/mL	4*	4
P32	Haloperidol	OR SOL	2 mg/mL	2*	5
P33	Hydrochlorothiazide	TB	25 mg	3	9
P34	Ibuprofen	TB and C TB	200, 300, 400, 600 mg	2*	9
P35	Lamivudine	C TB	150 mg	3	7
P36	Enalapril maleate	TB	5, 10 mg	1	2
P37	Mebendazole	OR SUS	20 mg/mL	2*	1
P38	Methyldopa	TB	250 mg	3	3
P39	Nimesulide	TB	100 mg	2	15
P40	Nimesulide	OR SUS	50 mg/mL	2*	7
P41	Norfloxacin	C TB	400 mg	4	2
P42	Acetaminophen	TB	500, 750 mg	1	9
P43	Acetaminophen	OR SOL	200 mg/mL	1*	11
P44	Piroxicam	CP	20 mg	2	19
P45	Prednisone	TB	5, 20 mg	2	8
			Total		240

N, quantity of Official Quality Control Reports or samples; $P_{(01-45)}$, product; TB, tablets; C TB, coated tablets; CP, capsules; SOL INJ, solution for injection; PO SUS INJ, powder for suspension for injection; PO OR SUS, powder for oral suspension; OR SOL, oral solution; OR SUS, oral suspension; BDDCS, Biopharmaceutics Drug Disposition Classification System [19]; *, dosage form diverges from the BDDCS list.

Table 2. Number of samples and manufacturers affected by non-harmonized pharmacopeial tolerance limits for assay.

Product	QC-R	C*	FB	C	USP	C	FA	C	FP	C	Ph. Int.	C	BP	C
P12	-	-	-	-	-	-	-	-	-	-	-	-	1	C09
P17	-	-	-	-	-	-	-	-	-	-	-	-	1	C25
P24	-	-	-	-	-	-	-	-	-	-	-	-	1	C08
P25	-	-	-	-	-	-	-	-	1	C25	-	-	1	C25
P28	-	-	-	-	-	-	-	-	2	C08, C42	-	-	2	C08, C42
P31	-	-	-	-	-	-	-	-	-	-	-	-	1	C43
P34	-	-	-	-	-	-	-	-	-	-	-	-	1	C14
P43	1	C34	1	C34	1	C34	1	C34	-	-	1	C34	3	C09, C11, C34
P44	1	C06	2	C06, C07	-	-	-	-	-	-	-	-	2	C06, C07
Total	2	2	3	3	1	1	1	1	3	3	1	1	13	10

QC-R, Official Quality Control Reports; $P_{(01-45)}$, product; $C_{(01-49)}$, company or manufacturer; FB, Brazilian Pharmacopeia; USP, United States Pharmacopeia; BP, British Pharmacopeia; FA, Argentine Pharmacopeia; FP, Portuguese Pharmacopeia; Ph. Int., International Pharmacopeia.

* Manufacturers and number of samples that were found to be out-of-specification by PROVEME protocol.

Table 3. Samples and manufacturers affected by non-harmonized pharmacopeial acceptance criteria for dissolution test.

Product	QC-R	C*	FB	C	USP	C	FA	C	FP	C	Ph. Int.	C	BP	C
P02	2	C17	2	C17	2	C17	2	C17	2	C17	-	-	2	C17
P03	1	C15	2	C05, C15	2	C05, C15	2	C05, C15	-	-	2	C05, C15	-	-
P33	1	C25	1	C25	1	C25	1	C25	1	C25	-	-	-	-
P41	1	C07	-	-	1	C07	1	C07	-	-	-	-	1	C07
Total	5	4	5	4	6	5	6	5	3	2	2	2	3	2

QC-R, Official Quality Control Reports; $P_{(01-45)}$, product; $C_{(01-49)}$, company or manufacturer; FB, Brazilian Pharmacopeia; USP, United States Pharmacopeia; BP, British Pharmacopeia; FA, Argentine Pharmacopeia; FP, Portuguese Pharmacopeia; Ph. Int., International Pharmacopeia.

* Manufacturers and number of samples that were found to be out-of-specification by PROVEME protocol.