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https://doi.org/10.22239/2317-269x.01481

Brazilian Health Regulatory Agency work in framing borderline products: a documentary research

Atuação da Agência Nacional de Vigilância Sanitária no enquadramento de produtos fronteira: uma pesquisa documental

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Received: Mar 11, 2020
Approved: Jun 03, 2020

ABSTRACT

Introduction: The majority of products subject to health regulation can be easily classified into medicines, medical devices, cosmetics, sanitizers or food, for purposes of regularization at the Brazilian Health Regulatory Agency (Anvisa). However, there are products, called "borderline products", that share characteristics of several of these categories simultaneously, making it difficult to comply with the current health legislation. **Objective:** To describe Anvisa's role in the regulatory framework for borderline products for marketing purposes in Brazil. **Method:** Documentary research of a descriptive nature and qualitative and quantitative approach carried out based on documents produced by Anvisa, such as normative acts, reports and technical opinions and minutes of meetings. The elaboration of the narrative was based on a selective, judicious and iterative process. The numerical values were expressed in absolute and relative frequencies, the median being used as a measure of central tendency. **Results:** Twenty-seven documents were analyzed. Anvisa instituted a technical committee in October 2015, with the task of subsidizing decisions of its Collegiate Board (Dicol) on the framing of borderline products. It is formed by representatives from the marketing authorization areas, post-market monitoring, inspection and improvement of regulatory quality. The committee adopted five borderline demarcation criteria, based on the experience of other international regulatory agencies. Between 2017 and 2019, the committee issued ten opinions that had Dicol's deliberations. In five cases, the border demarcation involved two types of product categories, namely: drug products and medical devices. Sixty-two citations were identified in the eight borderline product framing opinions, most of which were classified as gray literature (n = 53; 85.5%). **Conclusions:** Anvisa has recently taken a more systematic and integrated approach to the issue of framing borderline products, with the creation of a technical committee formed by representatives of the areas responsible for product marketing authorization, inspection, monitoring and regulation. The current conformation of the committee produced, in 2019, a greater number of opinions in relation to the previous years studied.

KEYWORDS: Brazilian Health Regulatory Agency; Previous Analysis of Products; Brazil; Borderline Product; Products Registration

RESUMO

Introdução: Os produtos sujeitos à vigilância sanitária, em sua maioria, podem ser facilmente enquadrados em medicamentos, produtos para a saúde, cosméticos, saneantes ou alimentos, para fins de regularização na Agência Nacional de Vigilância Sanitária (Anvisa). Entretanto, existem produtos, designados de "produtos fronteira", que compartilham características de várias destas categorias simultaneamente, dificultando seu enquadramento à luz da legislação sanitária vigente. **Objetivo:** Descrever a atuação da Anvisa no enquadramento de produtos fronteira para fins de comercialização no Brasil. **Método:** Pesquisa documental de natureza descritiva e abordagem quali-quantitativa realizada com documentos produzidos pela Anvisa. A elaboração da narrativa foi baseada

em um processo seletivo, criterioso e iterativo. Os valores numéricos foram expressos em frequências absolutas e relativas, sendo a mediana utilizada como medida de tendência central. **Resultados:** Foram analisados 27 documentos. A Anvisa instituiu um comitê técnico, em outubro de 2015, com atribuição de subsidiar decisões da sua Diretoria Colegiada (Dicol) sobre enquadramento de produtos fronteira. É formado por representantes das áreas de registro, monitoramento pós-mercado, fiscalização sanitária e melhoria da qualidade regulatória. O comitê adotou cinco critérios de demarcação de fronteira, com fundamento na experiência de outras agências reguladoras internacionais. Entre 2017 e 2019, o comitê emitiu dez pareceres que tiveram deliberações da Dicol. Em cinco casos, a demarcação de fronteira envolveu dois tipos de categoria de produtos, a saber: medicamento e produto para a saúde. Foram identificadas 62 citações nos oito pareceres de enquadramento de produtos fronteira, sendo a maioria classificadas como literatura cinzenta (n = 53; 85,5%). **Conclusões:** É recente a atuação da Anvisa, de forma mais sistematizada e integrada, no tema de enquadramento dos produtos fronteira, com a criação de um comitê técnico formado por representantes das áreas responsáveis pelo registro de produtos, fiscalização, monitoramento e regulamentação. A conformação atual do comitê produziu, em 2019, maior número de pareceres em relação aos anos anteriores estudados.

PALAVRAS-CHAVE: Agência Nacional de Vigilância Sanitária; Análise Prévia de Produtos; Brasil; Produto Fronteira; Registro de Produtos

INTRODUCTION

There is a variety of products marketed globally to promote the population's well-being, health, and quality of life. These products are organized into categories like medicines, medical devices, cosmetics, sanitizers, and food. Many of them are subject to health control done by regulatory agencies that—among other strategies—follow the rules established by regulations for each category.[1,2] These rules are particularly aimed at ensuring the safety, efficacy/performance and quality of the products, according to the purpose of their intended use.[1]

Most products can easily be placed into one of the categories mentioned above. However, some products, often called borderline products, share characteristics of some of these categories simultaneously, which makes their regulatory classification more difficult according to the health legislation in force in the country.[3,4] These products are called borderline products until their regulatory classification is determined.[5]

Delimiting the regulatory boundaries of these products is not always a simple process, and they must be assessed by a multifactorial approach. These products are subject to lengthy debates within the regulatory authority and between the regulatory authority and manufacturers/importers, which makes the decision to place a product in a certain category even more difficult.[6,7] In some cases, the classification of borderline products has to be determined through legal proceedings.[6,8]

Demarcation criteria have been advocated by some authors[3,9] and used by health regulatory authorities, like those from the United Kingdom[10] and South Africa,[11] to facilitate and standardize the classification process of borderline products. Therapeutic claims, the purpose for which the product is intended as proposed by the manufacturer and duly supported by clinical and scientific data, and the mode of action by which the main intended effect in human beings is achieved are some of these criteria.[3,9,10,11] The classification of these products can also be supported by information like composition, labeling, instructions for use, and promotional materials.[3,11,12] The existence of health risks has traditionally been one of the criteria used by courts of law in Europe to classify a product into a certain category.[13]

The UK regulatory agency, Medicines and Healthcare Products Regulatory Agency (MHRA), for example, classifies chlorhexidine into different categories according to the purpose for which it is intended. Medicine, if the product containing chlorhexidine is used as topical disinfectant for clinical use (for example, preoperatively); medical device, if the purpose is to disinfect medical equipment; or biocide, a category not provided for in Brazilian health legislation, if the intention is to market the product as a general disinfectant, for example, for hand asepsis.[14]

Another example is cough syrups available on the European market, which are classified into different categories according to their composition, mode of action, and the potential risk they present when compared to the benefits of their use. Therefore, on the European market, there are cough syrups classified into the categories of medicines, food supplements, and medical devices (risk class I or IIa).[3]

The Brazilian Health Regulatory Agency (Anvisa) is a federal regulatory agency under the Ministry of Health whose mission is to promote and protect the health of the population. This mission includes the regularization of various products like medicines, medical devices, cosmetics, sanitizers, products derived or not from tobacco, food, and pesticides[15]. For example, in 2018, 827 medicines were granted marketing authorization and 5,780 new medical devices, 51,259 cosmetics, and 7,337 sanitizing products were regularized.[15]

The Joint Board (Dicol) is the highest decision-making level of Anvisa. It is formed by five directors appointed by the Presidency of the Republic and approved by the Federal Senate. One of the directors is appointed Chief Executive Officer, pursuant to Law n. 9.782 of January 26, 1999.[1] Dicol's resolutions are made by the majority of those present at the meetings, either internal or public (broadcast in real time), or Deliberative Circuits through the manifestation/collection of votes and recorded in minutes.[16]

Anvisa has acquired expertise and skills to work on various objects and topics defined as of interest to health regulation,

including the classification of borderline products. The objective of this study was to describe Anvisa's role in the regulatory classification of borderline products for commercial purposes in Brazil.

METHOD

Study design

Documentary research of a descriptive nature and a quali-quantitative approach based on digitized institutional documents, contemporary or retrospective, considered scientifically authentic (not fraudulent)[17] and produced by Anvisa, including regulations, reports and technical opinions, and minutes of meetings. The research was conducted between January and February 2020.

The choice of the research method was driven by the following aspects:[18] a) official documents produced at the organizational level give us insight into the context and culture of the organization where the work is done; b) documentary research, compared to other methods, is relatively "non-reactive", since the information already exists and its collection process is less likely to interfere with the quality of the data; and c) documentary research has been widely used in social sciences and in historical investigation to describe and compare social facts and establish their characteristics or trends.[17]

Document collection

The tacit knowledge of the authors about the systematic work done by Anvisa on the classification of borderline products guided the identification and selection of documents whose information could meet the research objective. Tacit knowledge is intuitive, individualized knowledge about how to do something, learned from experience. It also includes the beliefs, attitudes, skills, and abilities that an individual has to perform an activity in the organization.[19]

The consulted documents were published between 2015 and 2019 and accessed in the following data sources: i) Service bulletin;[20] ii) Official Gazette of the Union;[21] iii) Electronic Information System (SEI/Anvisa);[22] and iv) Anvisa's website[23] (Chart 1).

The Service Bulletin publishes several types of documents that guide Anvisa's internal administrative management, like different kinds of regulations, service contracts and acts relating to employees working at the Agency, e.g. the ordinances referred to in Table 1.[24,25,26,27] It is published weekly on the Agency's internal electronic portal (Intravisa). It derives from the requirement of Law n. 4.965, of May 5, 1966, which provides for the publication of acts relating to civil servants of the Executive Branch.[28] According to the law, administrative acts will only be legally valid upon publication in the Official Gazette of the Union or in the Service Bulletin.[28]

The Official Gazette of the Union is a publication of the Executive Branch that aims to disclose any and all matters concerning the federal administration, like Ordinance n. 180, of February 18, 2020, cited in Table 1.[29] It is published daily on the Imprensa Nacional do Brasil website. Like the Service Bulletin, the Official Gazette of the Union derives from the aforementioned legal requirement.[28]

SEI/Anvisa is an electronic document management system adopted in 2017 by the Agency that enables more agile internal administrative processes and facilitates finding and accessing documents. Administrative processes prior to that date and stored and organized in physical files can be digitized and entered into SEI/Anvisa.

The electronic Portal is Anvisa's communication channel to share and provide institutional information of interest to society and extend some services to any citizen on matters within the Agency's competence.

Information analysis

The narrative of this study was based on a selective, judicious and iterative process[30] in which one of the authors alternated between reading the documents, extracting and analyzing information, and synthesizing and interpreting it in several cycles that were repeated a few times, so as to produce a manuscript about following subtopics: (a) evolution of Anvisa's approach to classifying borderline products; (b) the work process of the Committee for Classification of Products subject to Health Regulation (COMEP) in the classification of borderline products; and (c) COMEP/Anvisa opinion numbers: 2017 to 2019.

This study also sought to quantify citations from scientific or gray literature mentioned in footnotes or in a specific section of product regulatory classification opinions as a way to track the use of science to warrant regulatory decisions. Gray literature was considered as:

> documents of several types, such as reports, manuals, handouts, abstracts, various websites, among others, available in the most varied forms (both electronic and printed) that were not published in regular channels of scientific knowledge and, therefore, were not submitted to prior analysis by a reviewer or an editorial committee.[31]

For example, the same reference that was mentioned in three opinions was counted three times for the purpose of total quantification of citations. Numerical values were expressed as absolute and relative frequencies, and the median was used as a measure of central tendency. Some products were identified by capital letters of our alphabet, aiming to minimize possible induction of the demand for one or another product. This conduct, in the authors' opinion, did not compromise the results of this study.

Ethical considerations

Given the nature of the study and also the fact that the data analyzed were obtained in the context of health regulation, submitting it to a Research Ethics Committee was not necessary.

Chart 1. Characterization of documents included in the study (n = 27).

Document	Description/Subject	Data source
Anvisa Ordinance n. 1.287, of October 22, 2015	Provides for the creation and composition of CEPVS	Service Bulletin
Anvisa Ordinance n. 1.288, of October 22, 2015	Provides for the designation of CEPVS members	
Anvisa Ordinance n. 1.354, of July 4, 2016	Provides for the creation and composition of COMEP and other related measures	
Anvisa Ordinance n. 1.744, of September 12, 2016	Provides for the COMEP bylaws and other related measures	
Ordinance n. 180, of February 18, 2020	Appoints COMEP representatives	Official Gazette of the Union
CEPVS Activity Report (March 2016)	Report prepared by CEPVS coordination	Electronic Information System (SEI)
Report n. 010/2016	CEPVS activities report prepared then by DIARE	
Dicol deliberation extract - ROI n. 002/2016	Presentation of the CEPVS Activities Report and proposal of a new Ordinance for the composition of the Committee	
Opinion n. 1/2017/SEI/COMEP/Anvisa	Nicobloc® Product Classification	
Opinion n. 2/2017/SEI/COMEP/Anvisa	Product Classification - pacifiers, baby bottles, teats and nipple protectors	
Opinion n. 1/2018/SEI/COMEP/Anvisa	It is a process that aims at classifying and regulating flower therapies (Bach and others)	
Opinion n. 2/2019/SEI/COMEP/Anvisa	Classification of Nasal Wash Products for health regularization purposes at Anvisa	
Opinion n. 3/2019/SEI/COMEP/Anvisa	Classification of products based on animal bile extract, bile sodium acid and porcine mucosa extract	
Opinion n. 4/2019/SEI/COMEP/Anvisa	Classification of Pliazon® for health regularization purposes at Anvisa	
Opinion n. 5/2019/SEI/COMEP/Anvisa	Classification of Electric Ink Stencil Fix® and Electric Ink Stencil Transfer IT® products for health regularization purposes at Anvisa	
Opinion n. 6/2019/SEI/COMEP/Anvisa	Classification of Under Skin Medical Doctor - Generation Expert Peel - Salicylic Acid® and other similar products for health regularization purposes at Anvisa	
Opinion n. 7/2019/SEI/COMEP/Anvisa	Classification of Brisajet® containing 0.04% sodium hyaluronate and 1.0% dexpanthenol	
Dicol deliberation extract - ROP n. 22/2017	Proposal for the classification of the Episkin® product (reconstructed skin)	Anvisa's website
Dicol deliberation extract - ROP n. 14/2018	Classification of the Nicobloc® product	
Dicol deliberation extract - ROP n. 28/2017	Proposal for product classification - pacifiers, baby bottles, teats and nipple protectors	
Dicol deliberation extract - ROP n. 26/2018	Classification of flower therapies	
Dicol deliberation extract - ROP n. 14/2019	Classification of saline solutions for washing the nasal cavity	
Dicol deliberation extract - ROP n. 12/2019	Classification of products based on animal bile extract, bile sodium acid and porcine mucosa extract	
Dicol deliberation extract - ROP n. 18/2019	Analysis of the classification of Pliazon® for health regularization purposes at Anvisa	
Dicol deliberation extract - ROP n. 23/2019	Classification of Electric Ink Stencil Fix® and Electric Ink Stencil Transfer IT® products for health regularization purposes at Anvisa	
Dicol deliberation extract - ROP n. 23/2019	Classification of Under Skin Medical Doctor - Generation Expert Peel - Salicylic Acid® and other similar products for health regularization purposes at Anvisa	
Dicol deliberation extract - ROP n. 26/2019	Classification of Brisajet® for health regularization purposes at Anvisa	

Source: Prepared by the authors, 2020.
Anvisa: National Health Regulation Agency.; CEPVS: Committee for the Classification of Products subject to Health Regulation; COMEP: Committee for the Classification of Products subject to Health Regulation; DIARE: Health Authorization and Approval Board; ROI: Ordinary Internal Meeting; ROP: Ordinary Public Meeting; Dicol: Joint Board.

RESULTS

A total of 27 documents were analyzed: five ordinances, two technical reports, 11 extracts from meeting minutes, and nine opinions. Chart 1 presents the characteristics of the documents analyzed with their respective data sources. SEI/Anvisa (n = 12) and the Anvisa website (n = 10) were the main sources of data for the study.

History of Anvisa's work in the classification of borderline products

Until mid-October 2015, Anvisa did not have a formalized body that was representative of its potentially involved technical areas to discuss and prepare consensual proposals for the classification of borderline products to be presented for deliberation by Dicol.

With the publication of Ordinance n. 1.287/Anvisa,[24] of October 22, 2015, Anvisa created the Committee for Classification of Products subject to Health Regulation (CEPVS). It is a collegiate consultative body whose objective is to support the classification of borderline products.

The CEPVS had representatives from areas involved in the process of approval, inspection, regulation, and monitoring of products subject to health regulation within the scope of the administrative composition of Anvisa's superintendences, in an attempt to come to more comprehensive and sound technical understandings on the classification of borderline products. As part of this setup, the coordination of the committee was in charge of a representative of one of the superintendences, responsible for the areas of approval of medical devices, cosmetics, sanitizing products, and food. At the time, this was up to the superintendence of food and related products.

The bylaws, also enacted by the aforementioned Ordinance, established that, after analysis of the demands by CEPVS, the coordination should submit the administrative process of each case, with the definition of the proposal for classification of the product, to the approval board for subsequent referral to Dicol's deliberation. Since the creation of CEPVS, only three cases of borderline product classification had been analyzed, of which only the Nicobloc® product was effectively submitted to and deliberated by Dicol.

Because of changes in the organizational structure of the Agency in early February 2016, with the suppression of the superintendence model, reassessing the representation and redefining CEPVS' functioning and administrative rites was necessary. The definition of a cross-sectional area with potential impartiality to coordinate the committee's activities also contributed to these changes, given that the classification of these products requires the joint work of several areas responsible for product approval. The proposal for changes in CEPVS was approved by Dicol in April 2016. It was then the responsibility of the Health Regulation Board.

Such changes resulted in the publication of Anvisa Ordinance n. 1.354,[26] of July 4, 2016, which instituted a new committee with the same name and duty, but including the competence to propose whether a product is subject or not to regularization by Anvisa. However, there was a change in the acronym, which was renamed COMEP.

Other changes occurred both in its composition and in its coordination, which came to be exercised by the General Management of Regulation and Good Regulatory Practices (GGREG/Anvisa) (Chart 2). This General Management is a cross-sectional organizational unit responsible for improving regulatory quality at the Agency without any duty of approving products subject to health control.

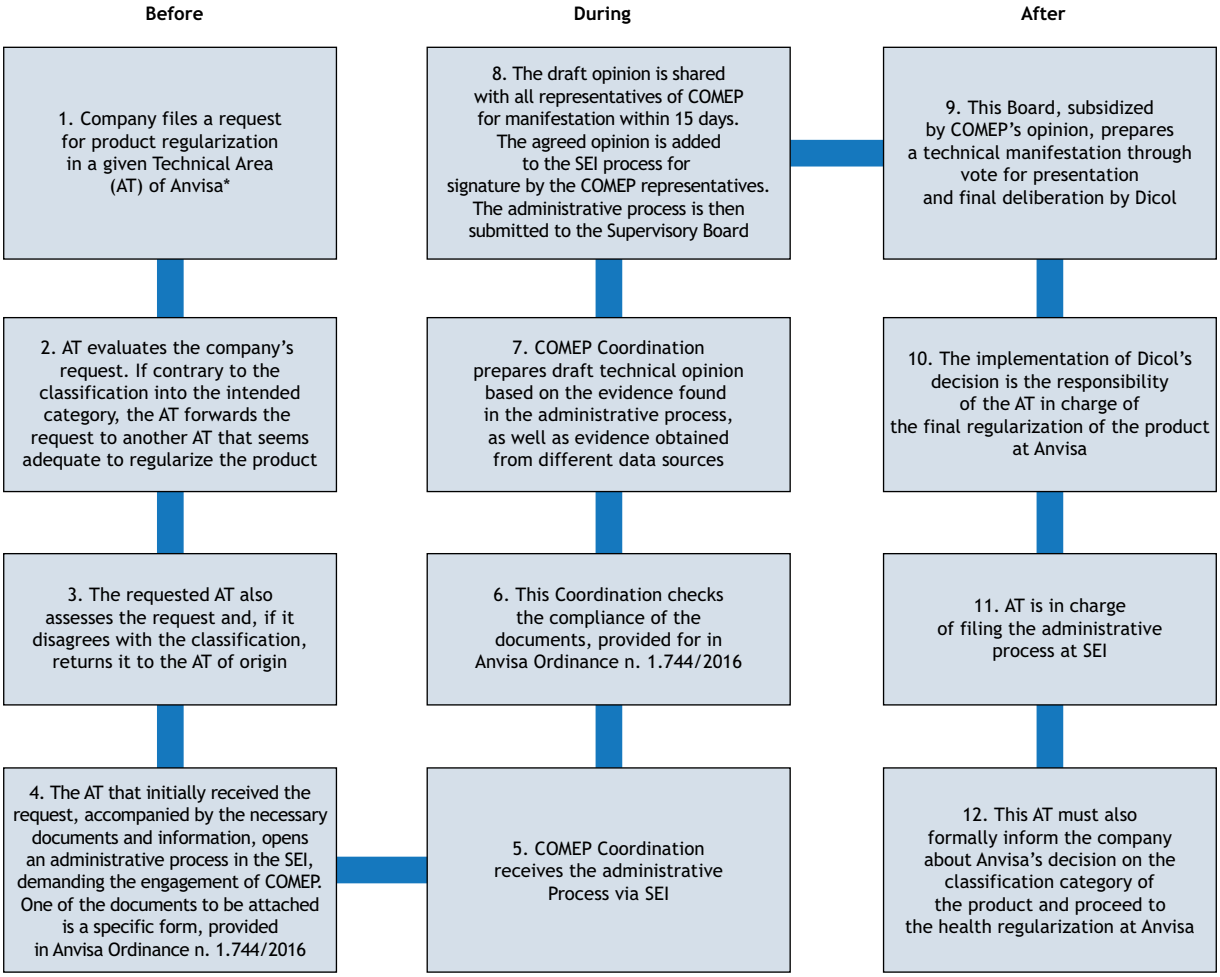
The COMEP work process to classify borderline products

The procedures for receiving, processing, and analyzing the demands made to COMEP and the flow of referrals to higher levels were established in internal bylaws, defined in Anvisa Ordinance n. 1.744,[27] of September 12, 2016. Figure 1 illustrates the workflow before, during and after a demand is made to COMEP.

Chart 2. Evolution in the composition of the Product Classification Committees subject to Anvisa's health regulation.

Committee setup	Areas represented in the committees
CEPVS - Ordinance n. 1.287/2015[24]	Superintendence of Food and Related Products*
	Superintendence of Inspection, Control and Monitoring
	Superintendence of Medicines and Biological Products
	Superintendence of Health Inspection
	Superintendence of Health Regulation and Market Monitoring
	Superintendence of Toxicology
COMEP - Ordinance n. 1.354/2016[26]	General Management of Regulation and Good Regulatory Practices*
	General Management of Medicines and Biological Products
	General Management of Toxicology
	Cosmetics Management**
	Sanitizer Management**
	General Management of Health Products Technology; DIREG:
	General Management of Inspection of Products Subject to Health Regulation
	General Management of Monitoring of Products Subject to Health Regulation

Source: Prepared by the authors, 2020.
* Exercised/exercises the coordination of the committee; ** Currently, these two departments are merged, which resulted in the creation of the Hygiene, Perfume, Cosmetic and Sanitizing Products Management.



* The demand may also be made by a letter addressed to the AT the company understands is responsible for regularizing the product.
COMEP: Committee for the Classification of Products subject to Health Regulation; SEI: Electronic Information System; Dicol: Joint Board.
Source: Prepared by the authors, 2020.

Figure 1. Workflow before, during and after the handling of a demand made by the Committee for the Classification of Products subject to Health Regulation (COMEP).

The opinions prepared by COMEP are supported by information attached to the administrative process, as determined by Anvisa Ordinance n. 1.744/2016,[27] as well as from scientific literature, including references classified as gray literature.

The information required by Anvisa Ordinance n. 1.744/2016[27] includes data from COMEP's Demand Classification Form (*Formulário de Enquadramento de Demandas*), like indication and purpose of use, ingredients and mechanism of action of borderline products. Other information that should be attached to the process preferably by the technical area that first received the product regularization request includes: i) copies of packaging, inserts, advertising material for the product; ii) information about the marketing authorization and classification of the product in other countries; and iii) opinions of the technical areas of Anvisa involved in classifying the product based on technical criteria and due legal basis.

The use of at least five criteria for borderline demarcation can be more explicitly observed in the opinion prepared in 2019 for the Pliazon® product: i) medicinal claims made by the product; ii) intended use of the product, taking into account how it is presented; iii) legal compliance; iv) means by which the main intended effect is achieved; and v) existence of similar products licensed in the domestic and/or foreign markets.

Based on the opinion about Pliazon®, we found there is some standardization of the sections in the opinions for classification of borderline products, like: i) presentation of the demand; ii) manifestations from the affected technical areas; iii) description of the product subject to the regulatory classification; iv) legal distinction between the categories of products involved; v) description of borderline products; vi) national and international regulatory situation; vii) considerations about the risk associated with the product and patient safety; ix) analysis, with the discussion of the aforementioned classification criteria; and x) conclusion, with the recommendation to fit the product into a certain category.

Numbers of COMEP/Anvisa opinions: 2017 to 2019

Between 2017 and 2019, COMEP issued ten opinions that were deliberated by Dicol, eight of which dealt with the classification of products into a certain category. Two opinions recommended that products not be subject to regularization by Anvisa (Chart 3). The technical opinion recommending not subjecting the Episkin® product (reconstructed skin) was not identified in the researched data sources.

All recommendations for classifying borderline products made by COMEP were accepted by both the Supervisory Board and Dicol. The largest number of opinions issued by COMEP was recorded in 2019, in a total of six recommendations for the classification of borderline products.

In five cases, the boundary demarcation involved two types of product category, namely medicine and medical device. Medical devices were the most frequently products in the process of defining the regulatory classification, with a total of seven cases. Of these, three were classified as medical devices (Chart 3).

Sixty-two citations were identified in the eight borderline product classification opinions, most of which were classified as gray literature (n = 53; 85.5%) (Table).

Six references were cited in more than one opinion, as follows: one reference from gray literature was cited in two opinions, while five were found in four opinions. In the latter case, one of them was from scientific literature.

The number of scientific citations in the opinions ranged from a minimum of zero to a maximum of nine, with a median of 1.5. The year of publication of the scientific articles mentioned in the opinions ranged from less than one year (2019) to 20 years (1999), with a prevalence of scientific references with more than five years of publication (n = 12; 63.1%).

We could observe that the opinions on the first four products mentioned in the Table had information obtained from other health authorities about the classification of such products in their countries. These consultations with other countries were not mentioned as references in footnotes or a specific section in the opinions of the Anvisa committee.

Chart 3. Categories for classifying borderline products established by the Joint Board (Dicol) of Anvisa, 2017 to 2019 (n = 10).

Year* (Quantity**)	Product(s) (Active ingredients)	Purpose of use	Categories affected	Final classification category
2017 (n = 2)	Episkin® (Reconstructed human skin)	Exclusive research product used to support the ban on animal testing	Not applicable	Not subject to health regularization by Anvisa
	(1) Pacifiers and nipple protectors and (2) Baby bottles and teats Not applicable	Products for use in childcare	Food and Medical Device	(1) Medical device; and (2) Food equipment (nozzles with specific claims: equipment for food and medical products)
2018 (n = 2)	Nicobloc® (Corn syrup)	Liquid applied to the cigarette filter and that retains part of the tar and nicotine	Food, Medicine, Smoking Product and Medical Device	Medical device
	Flower therapies (Usually made from flowers, plants or shrubs to which brandy or natural alcohol is added)	Products with claims related to emotional conditions	Food and Medicine	Traditional health products
2019 (n = 6)	Animal bile extract, bile sodium acid and porcine mucosa extract Not applicable	Intermediate products of animal origin, used for the production of raw materials by other industries	Not applicable	Not subject to health regularization by Anvisa
	Saline solutions for washing the nasal cavity (sodium chloride + sodium bicarbonate)	Nasal wash	Medicine and Medical Device	Medicine
	(1) Electric Ink Stencil Fix® and (2) Electric Ink Stencil Transfer IT® (Several ingredients, like (1) urea and (2) disodium EDTA)	(1) Remove excess carbon and prolongs the fixation of the design on skin; and (2) Transfer the decal design to skin	Cosmetic and Medical Device	Cosmetics
	Pliazon® (Vitamin K1)	Emulsion used on skin to relieve redness and increase epidermal moisture	Cosmetic, Medicine and Medical Device	Medical device
	Under Skin Medical Doctor - Generation Expert Peel® (Salicylic acid)	Skin exfoliant	Cosmetic, Medicine and Medical Device	Medicine
	Brisajet® (Sodium Hyaluronate and Dexpanthenol)	Nasal moisturizer	Medicine and Medical Device	Medical device

Source: Prepared by the authors, 2020.
*Year in which the deliberation meeting by Dicol took place; **Number of technical opinions prepared by COMEP, with final deliberation by Dicol.

Table. Number of citations from the scientific and gray literature in the opinions prepared by the Committee for Classification of Products subject to Health Regulation (COMEP), 2017 to 2019 (n = 8).

Year	Opinion/product	Literature		Total
		Scientific	Gray	
2017	Pacifiers and nipple protectors and Baby bottles and teats	1	1	2
2018	Nicobloc®	0	0	0
2018	Flower therapies	1	4	5
2019	Saline solutions for washing the nasal cavity	0	1	1
2019	*Electric Ink Stencil Fix® and Electric Ink Stencil Transfer IT®*	3	12	15
2019	Pliazon®	2	9	11
2019	*Under Skin Medical Doctor - Generation Expert Peel®*	9	18	17
2019	Brisajet®	3	8	11
	Total	19	53	62

Source: Prepared by the authors, 2020.

DISCUSSION

Borderline products have challenged traditional product concepts and classifications provided for in health legislation. Although there is no specific regulation so far, Anvisa, faced with this challenge, set up a technical committee to support the decisions of its Dicol related to the classification of borderline products for the purposes of health regularization.

By setting up this committee, Anvisa signals to the market its commitment to minimizing uncertainties in the classification of borderline products. These uncertainties can have a significant impact for manufacturers or importers that cannot identify the right "entrance door" for their products into the market, with increased expenses and delays, especially for small and medium enterprises.[3] Another point that is worth emphasizing is that with this strategy, Anvisa contributes to the harmonization of the classification of products subject to health regulation between Brazil and other countries, expanding global trade and the free circulation of goods.

Unlike Anvisa's technical committee in terms of objectives and conformation, the Medical Devices Expert Group (MDEG) on Borderline and Classification is a group chaired by the European Commission that, in addition to discussing border demarcations between medical devices and medicines, cosmetics, biocides, and other products, defines the risk class of a given medical device.[12] It is formed by experts from the competent authorities of all member countries of the European Union, the European Free Trade Association and Turkey, the services of the European Commission and representatives of other stakeholders, like trade associations and those linked to the medical device industry.[12]

Considering the studied period, the Anvisa committee has already produced some results for society, given the increase in the number of product regulatory classifications from 2019. The new composition of the committee and its consequences may be one of the explanations for the increase in the opinions instructed and submitted to Dicol's deliberation. The greater acquisition of knowledge and skills by professionals and managers at Anvisa who are dedicated to classifying borderline products may be another factor that explains this increase. There are factors that influence the learning process for performing repeated tasks, with emphasis on: i) training policy adopted by the organization; ii) staff motivation to perform the required tasks; and iii) existence of prior knowledge (experience) in the execution of the task.[32]

The definition of more explicit criteria that enable determining the correct and adequate classification of borderline products was another change observed in 2019. The World Health Organization (WHO) recommends that in order to be predictable and transparent, the regulator should establish criteria and mechanisms to determine the appropriate regulatory regime for borderline products and may consider determinations made by regulatory authorities from other countries.[4] One of the criteria used by the Anvisa committee for the classification of borderline products meets the WHO recommendation to consider the international regulatory regime for the product.

For the European Court of Justice, the classification of a borderline product must be done on a case-by-case basis. Criteria like qualitative and quantitative composition, purpose indicated by the manufacturer, instructions for use, distribution channel and packaging, and pharmacological properties must be considered according to the current state of scientific knowledge, consumer perception or existing business practice and potential risks.[13] However, not all criteria apply to all cases. For example, for medicines, cosmetics and medical devices, the substance itself and its concentration can be determining factors in the product's regulatory classification.

In general, the above criteria have been considered when gathering information to support the opinions of the Anvisa committee. However, three criteria suggested by Agostinho[3] to be used specifically in the classification of medical devices were not identified in the information requested or considered by the Anvisa committee. The criteria are: i) the

manufacturer has an implemented quality management system; ii) the quality management system includes ISO 13485, which seeks to ensure the quality of medical devices and regulatory compliance; and iii) the product has a constituent that meets the definition of medicine, without which it ceases to have the indicated purpose.[3]

Most of the demands submitted to the Anvisa committee involved the delimitation of the regulatory border between medical devices and other products, especially medicines. The comprehensive definition of medical device may be one of the explanations for the greater frequency of these products in the demands made to the committee.[3]

The therapeutic claims that characterize medicines and medical devices enable us to distinguish them from other products subject to health regulation. However, the delimitation between medical device and medicine is perhaps the most difficult because there are more and more products that combine the potential of these two technologies.[12] The main difference is that medical devices do not use pharmacological, immunological or metabolic means to perform their main function in human beings, although their functioning can be supported by such means.[33] However, there is no definition in Brazilian health legislation of what is meant by pharmacological, immunological and metabolic means.[2,33]

According to Tseliou,[6] the terms pharmacological, immunological or metabolic are still unclear. One of the reasons is that scientists continue to argue about how some substances act in human body, which often results in scientific evidence that points to opposite directions. The uncertainty around these terms and the need to clarify them through regulation were observed in court cases dealt with by the Court of Justice of the European Union.[6]

There was a greater proportion of references from gray literature in the committee's opinions when compared to the presence of articles published in indexed journals. This proportion may be even higher, since in some opinions the consultations made to regulatory authorities from other countries, which had been mentioned in the text, were not quantified as gray literature due to what was established in the methodological procedure of this study.

Despite the caution of the academic community in the use of gray literature, in many cases it is the only source of information available on a given subject.[31] This type of literature has different levels and it is possible to find highly reliable documents in it,[31] like those made available by regulatory agencies in other countries.

Several borderline products are considered innovative products[3] and their classification into one or another category often lacks a reasonable amount of scientific evidence. This may help explain the scarce use of scientific studies in the committee's opinions. Furthermore, the classification of products subject to health regulation into different legal categories is perhaps a more administrative and legal need than a scientific one.[34]

We observed that the references found in more than one committee report were intended to support the general content on the topic and were not used specifically to support the classification of the product under discussion. For example: the reference to the Medicines Control Council. Department of Health. Republic of South Africa. Borderline products 2017,[11] cited in four opinions, was used to define what is meant by pharmacological, immunological, and metabolic means.

The findings of this study need to be considered in light of its limitations. There is the possibility that the selected documents are not fully representative of all the documentation related to the subject, despite the tacit knowledge of the authors about Anvisa's work in the classification of borderline products. It is likely that this study has some subjective elements in its narrative. The lack of information on bibliographic references in the committee's opinions hindered a better characterization of the literature used to support the regulatory classification of borderline products. However, the non-identification of the opinion on the Episkin® product was not characterized as a limitation for the purposes of this study.

A recommendation that would make the Anvisa committee's task less complex is to rethink the definition of some products in Brazilian health legislation, including what is meant by pharmacological, immunological, and metabolic action. For example, the definition of medicine—pharmaceutical product, technically obtained or prepared, with prophylactic, curative, palliative or diagnostic purposes—provided for in Law n. 5.991, of December 17, 1973[2] and still in force does not facilitate the regulatory classification of borderline products.

A clearer and more restrictive definition that prevents the inclusion of several products is given by the Portuguese health legislation, which defines medicine as

> any substance or combination of substances presented as having curative or preventive properties of diseases in humans or their symptoms or that can be used or administered in humans with a view to establishing a medical diagnosis or, by exercising a pharmacological, immunological or metabolic action, to restore, correct or modify physiological functions.[35]

It would be advisable for Anvisa to share the results of its assessments with society, in particular with the productive sector. It could also use the international forums in which it participates to support the creation of a global database that includes the categories of classification of borderline products in the countries where they are being marketed. These recommendations could greatly contribute to a transparent process and greater international regulatory convergence.

CONCLUSIONS

As shown, Anvisa has recently adopted a more systematized and integrated approach to the classification of borderline products with the creation of a technical committee formed by representatives of the areas responsible for product approval, inspection, and monitoring, in addition to

the "cross-sectional" and impartial coordination of GGREG/Anvisa. This signals to the society the institution's commitment to minimizing uncertainties and expediting the approval of the product for marketing and use in the country, without therapeutic harm to the population or economic losses to the regulated sector.

In 2019, the current composition of the committee produced a greater number of opinions in comparison with the previous years. The predominance of citations classified as "gray" in the committee's opinions confirms the current gap in scientific literature, which in turn reinforces the importance of the information shared in this study.

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Authors' Contribution

Mota DM - Conception, planning (study design), analysis, interpretation of data and writing of the manuscript. Nascimento AF, Aquino NC, Marcolongo R and Troncoso GCBCC - Analysis, interpretation and writing of the manuscript. All authors approved the final draft of the manuscript.

Disclosures

The authors report that there is no potential conflict of interest with peers and institutions, nor political or financial conflicts in this study. The opinions, findings, conclusions and recommendations expressed in this scientific article are exclusively those of the authors and do not reflect the official opinion of Anvisa.