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Article

Topical ophthalmic antimicrobials: unfulfilled demands and possibility of new investments in Brazil and in the United States

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In general, topical ophthalmic drug products, especially those used for treating infections, present low effectiveness because of various reasons, from unfavorable drug physicochemical properties to physiological protective mechanisms of the eye. The fact is such group of products holds room for improvement, which could mean the development of better drugs or dosage forms. To achieve this, the knowledge of market composition is essential. The present work studied and compared the antimicrobial ophthalmic markets of Brazil and of the United States (US). Official databank of Brazilian Health Regulatory Agency and of US Food and Drug Administration were assessed for registered antimicrobial topical ophthalmic drug products. Brazilian market has registered greater number of drug products (119) than the US (94), but the latter involves more variety of substances and dosage forms. In both countries, non-innovative products registered as solutions of antibacterials, especially fluoroquinolones and aminoglycosides lead the market. Despite the clinical demand, the US has only one group of antimycotics (polyenes) registered, while in Brazil, there is not any ophthalmic antimycotic product marketed. This study evidences there is not only space for development of newer drugs and formulations but also a demand for already existing technologies and products in both countries.

Keywords: Ophthalmologic drug products. Registration/Brazil. Registration/United States.

INTRODUCTION

Ophthalmic infections (i.e., orbital cellulitis, endophthalmitis, blepharitis, conjunctivitis and keratitis) can affect many ocular anatomical structures and are caused by different etiological agents (virus, bacteria, fungi and parasites). These infections are a common cause of morbidity around the world. An epidemiological study of primary ophthalmic inpatient admissions in the United States (US) from 2001 to 2014 showed the majority of the diagnoses was infectious (Iftikhar *et al.*, 2017). Accordingly, infections were the second most prevalent cause of eye diseases in Brazilian emergencies centers, affecting mainly the economically active population (Vicente *et al.*, 2016). According to the World Health Organization, corneal opacities, mostly triggered by infectious diseases, are the 4th cause of blindness and visual impairment globally (WHO, 2002a; WHO, 2002b). Still, effective topical ophthalmic drug products are difficult to be developed because of unfavorable drug physicochemical properties of commonly used drugs, but mainly because of the particularities of the eye anatomy and physiology.

Eyes have constant lachrymal secretion and rapid nasolachrymal drainage, which added to the eyelid movements can wash out administrated medicines within 4 to 23 minutes. Furthermore, the maximum volume the open eye can accommodate is limited between 20 and 30 µL. Ophthalmic bioavailability is usually low due to natural anatomical barriers and short residence time of ophthalmic solutions (Gratieri *et al.*, 2010a; Gratieri *et al.*, 2011). As a result, to achieve therapeutic results, frequent administration of concentrated formulations is needed (Labcharoenwongs *et al.*, 2012). Moreover, ophthalmic products must be sterile and non-irritating (Mandal *et al.*, 2012). As conservatives can be toxic to ocular surface

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(Liang *et al.*, 2011), stability is also an issue. In vitro experiments may also be problematic, as viable tissue properties must be maintained (Gratieri *et al.*, 2010b). Growing resistance of ocular infections, especially against antibacterial drugs (Miller *et al.*, 2017), is another factor demanding investments and research.

Despite the pharmaceutical technology field improvements in the last years, there is still a long way to reach the optimum treatment of infectious ophthalmic diseases (Coates, Hall, Hu, 2011). The knowledge of pharmaceutical market composition regarding topical ophthalmic drug products in different countries can be useful in designing development strategies and focusing investments. Such information is spread and often difficult to be obtained. To our knowledge, this is the first detailed analysis of current available products in Brazil. A comparison was performed with the US market through quantitative and qualitative analyzes of registered products aiming to determine gaps with potential for investment and pharmaceutical development.

MATERIAL AND METHODS

Drug products registered by the Brazilian Health Regulatory Agency (ANVISA)

All products registered until May 31, 2016 in Brazil for commercialization under the ophthalmic, ophthalmologic and ocular routes of administration were listed using the official ANVISA databank (DATAVISA) according to ANVISA authorizations for academic research No. 604279/17-1, 604286/17-4 and 604274/17-1 – process No. 25351.200950/2017-94, respecting confidential data of legal entities. DATAVISA is an internal software in which there is administrative and technical information about the medicines under ANVISA regulation, including due date of the registry, company responsible for the registered product (applicant holder), marketed and therapeutic category, formulation, dosage forms and routes of administration of the products. From a preliminary data set, products with the archive wrong filled, invalid or expired due date for registry renewal were excluded. After data review, only valid products classified as "antimicrobials" were analyzed according to regulatory characteristics, drug substance, dosage form and applicant holder. The results were analyzed in units of registered drug products, in which drug products from the same applicant holder containing the same drug and the same dosage form, but different strengths, volumes, weights and/or pharmaceutical units, were counted individually/separately.

Drug products registered by the US Food and Drug Administration (FDA)

Similarly, products registered until May 31, 2016 in the US under ophthalmic route of administration were listed using the official databank of FDA for Approved Drugs Products with Therapeutic Equivalence Evaluations (Orange Book). The Orange Book is available as an open access website (https://www.accessdata.fda.gov/scripts/cder/ob/) and contains information as the applicant holder, marketed status, active ingredient, dosage form, route of administration and application number of the products. From this preliminary data set, products discontinued from marketing were excluded. Only products classified as "antimicrobials" were categorized according to regulatory characteristics, drug substance, dosage form and applicant holder. The results were analyzed in units of registered drug products, in which drug products from the same applicant holder containing the same drug and the same dosage form, but different strengths, volumes, weights and/or pharmaceutical units, were counted individually/separately.

RESULTS

The survey showed there were 711 commercialized topical ophthalmic drug products in Brazil and 316 in the US. From these, 119 corresponded to antimicrobial drugs in Brazil and 94 in the US. In this paper, they were classified in accordance to pharmacological groups, including antiseptics, antibacterials, antimycotics and antivirals, combined or not to corticosteroids as anti-inflammatories (Figure 1). The major group was composed of antibacterials, followed by antivirals and antimycotics.

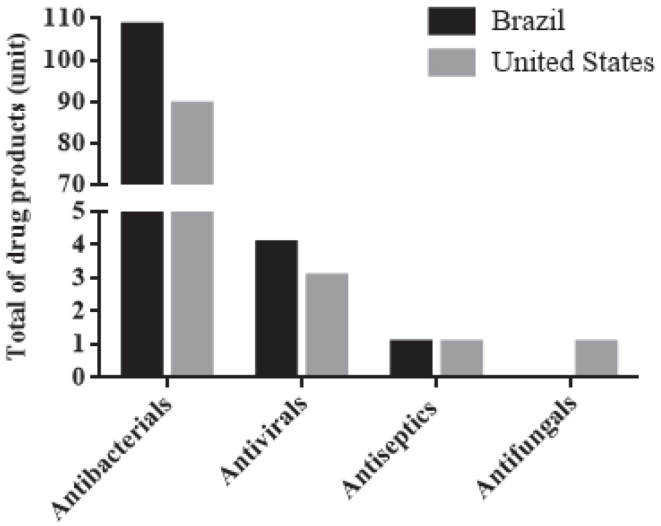

FIGURE 1 - Pharmacological groups registered for ophthalmic products in Brazil and in the United States.

Considering products with only one drug substance, fluoroquinolones represented the main group in both countries, followed by aminoglycosides. Groups of amphenicols, rifamycins and tetracyclines had little representativeness in Brazil and were not available in the US. The group of "others" included antiseptics that did not have a clear classification (Table I).

In the category of products with two or more drug substances, the main combination registered in Brazil was fluoroquinolones with corticosteroids. In the US, aminoglycosides with corticosteroids, aminoglycosides with polymixins and corticosteroids, and aminoglycosides with polymixins and peptides comprised usual combinations (Table II).

Solution was the most relevant dosage form of antimicrobial topical ophthalmic drug products in both countries, followed by ointment and suspension. The dosage form gel has only been registered in the US (Figure 2).

The survey also revealed the Brazilian market is constituted mostly by generic and similar drug products

TABLE I - Comparison of drug substances groups registered as simple ophthalmic products in Brazil and in the United States

Drug groups	Drug names	Registered drug products (units)						
		Brazil				United States		
		Generic	Similar	New product	Total	ANDA[a]	NDA[a]	Total
5-substituted 2'-deoxyuridine analogues	trifluridine					1	1	2
Acyclic guanosine analogues	acyclovir	2	2		4			
	ganciclovir						1	1
Aminoglycosides	gentamicin sulfate			2	2	8		8
	tobramycin	4	14		18	4	2	6
Amphenicols	chloramphenicol			1	1			
	chloramphenicol palmitate		1		1			
Fluoroquinolones	besifloxacin hydrochloride						1	1
	ciprofloxacin hydrochloride	8	6		14	6	2	8
	gatifloxacin			4	4	2	2	4
	levofloxacin					3		3
	moxifloxacin hydrochloride					3	2	5
	ofloxacin	22	2		24	7	1	8
Macrolides	azithromycin						1	1
	erythromycin					3		3
Peptides	bacitracin					1		1
Polyenes	natamycin						1	1
Rifamycins	rifamycin SV sodium		1		1			
Sulphonamides	sulfacetamide sodium					5		5
Tetracyclines	tetracycline chloridrate		1		1			
Others[b]	povidone-iodine						1	1
	silver vitellinate			1	1			

[a]Abbreviated New Drug Application (ANDA); New Drug Application (NDA); [b] The category of "Others" included antiseptics that did not have a clear classification.

TABLE II - Comparison of drug substances groups registered as combined ophthalmic products in Brazil and in the United States

Drug groups	Drug names	Registered drug products (units)						
		Brazil				United States		
		Generic	Similar	New product	Total	ANDA[a]	NDA[a]	Total
Aminoglycosides + Corticosteroids	gentamicin sulfate + prednisolone acetate						2	2
	neomycin sulfate + dexamethasone sodium phosphate		1		1			
	neomycin sulfate + fluorometholone			1	1			
	tobramycin + dexamethasone	1			1	1	3	4
	tobramycin + loteprednol etabonate			3	3		1	1
Aminoglycosides + Polymyxins	neomycin sulfate + polymyxin B sulfate			1	1			
Aminoglycosides + Polymyxins + Corticosteroids	neomycin sulfate + polymyxin B sulfate + dexamethasone					4	2	6
	neomycin sulfate + polymyxin B sulfate + hydrocortisone					1		1
	neomycin sulfate + polymyxin B sulfate + prednisolone acetate			2	2			
Aminoglycosides + Polymyxins + Peptides	neomycin sulfate + polymyxin B sulfate + bacitracin zinc					3	1	4
	neomycin sulfate + polymyxin B sulfate + gramicidin					3		3
Aminoglycosides + Polymyxins + Peptides + Corticosteroids	neomycin sulfate + polymyxin B sulfate + bacitracin zinc + hydrocortisone					2		2
	neomycin sulfate + polymyxin B sulfate + bacitracin + hydrocortisone acetate					1		1
Fluoroquinolones + Corticosteroids	ciprofloxacin hydrochloride + dexamethasone	11	20		31			
	gatifloxacin + prednisolone acetate			2	2			
	moxifloxacin hydrochloride + dexamethasone sodium phosphate			1	1			

TABLE II - Comparison of drug substances groups registered as combined ophthalmic products in Brazil and in the United States (cont.)

Drug groups	Drug names	Registered drug products (units)						
		Brazil				United States		
		Generic	Similar	New product	Total	ANDA[a]	NDA[a]	Total
Folate antagonists + Polymyxins	trimethoprim sulfate + polymyxin B sulfate					3	1	4
Peptides + Polymycins	bacitracin zinc + polymyxin B sulfate					3		3
Sulphonamides + Corticosteroids	sulfacetamide sodium + prednisolone acetate					1	1	2
	sulfacetamide sodium + prednisolone sodium phosphate					2		2
Tetracyclines + Polymycins	oxytetracycline hydrochloride + polymyxin B sulfate			5	5	1		1

[a]Abbreviated New Drug Application (ANDA); New Drug Application (NDA).

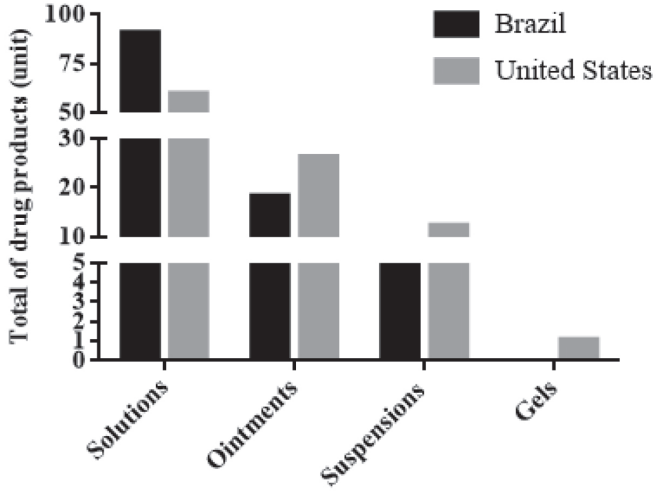

FIGURE 2 - Dosage forms registered for ophthalmic products in Brazil and in the United States.

(80.7%). This scenario is similar to the US, in which there were more Abbreviated New Drug Application (ANDA) (72.3%) than New Drug Application (NDA) (27.7%). Even though Brazilian industries are the main applicant holders in the Brazilian market (72.3%), they only commercialize similar and generic products, while multinational industries have similar, generic and new products registered (Figure 3).

DISCUSSION

ANVISA has registered a greater number of topical antimicrobial ophthalmic drug products than the FDA; however, in the US, more variety of products was encountered. While in the US there were 30 simple and combined drug substances divided into 17 groups, in Brazil there were 21 substances divided into 12 groups.

Combined ophthalmic products containing corticosteroids and antimicrobials were relevant in the markets analyzed, reaching 35.3% in Brazil and 22.3% in the US. The American Academy of Ophthalmology, at the Cornea/external disease summary benchmarks for Preferred Practice Pattern® Guidelines, highlights a series of precautions in the use of corticosteroids as adjuvant therapy for ocular infections. In general, corticosteroids, if indicated, should be prescribed at the lowest frequency and potency available. Long-term corticosteroid therapy should be avoided or reduced and, in some cases, even eliminated before the use of antimicrobials. Re-evaluations of the patient should be conducted closely to monitor adverse effects, such as corneal melting, cataract formation and increased intraocular pressure (American Academy of Ophthalmology, 2016), especially with the use of dexamethasone (Sheppard, Comstock, Cavet, 2016). Nevertheless, many of combined products have a corticosteroid in the formulation, probably pursuing a better patient compliance on a simpler and more economic therapeutic scheme.

Interestingly, the biggest combined group in Brazil, fluoroquinolones with corticosteroids, did not have a single drug product registered in the US. Indeed, when

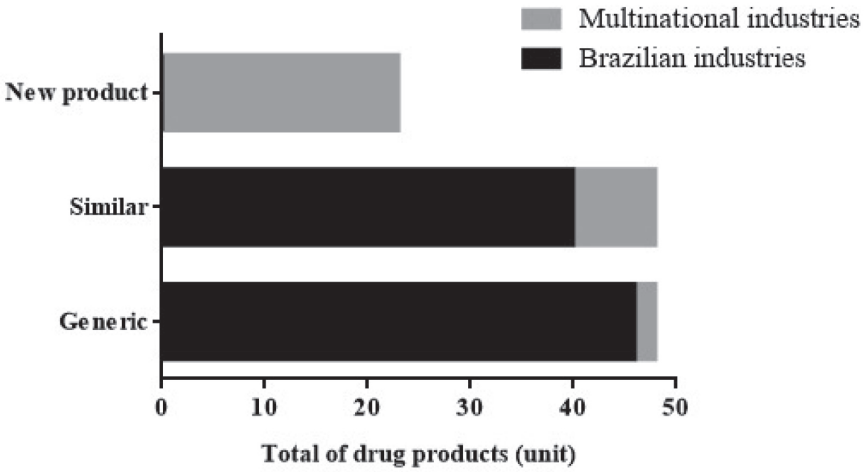

FIGURE 3 - Composition of Brazilian market for ophthalmic products.

fluoroquinolones are combined with corticosteroids, the maximum recommended treatment period is shorted in comparison to fluoroquinolones alone, possibly because of adverse effects risks of long-term corticosteroid therapy. Another drawback of corticosteroid combinations is the limited possibilities of the antibacterial treatments. E.g., simple product containing ciprofloxacin hydrochloride is indicated for the treatment of infections caused by *Pseudomonas aeruginosa*, but the combined product with corticosteroid does not have this indication, according to product labels. Considering that *P. aeruginosa* is an important etiological agent of ocular infections in the US, combined products are not useful in the clinical practice. Moreover, the US has a history of microbial resistance against fluroquinolones (Asbell *et al.*, 2015) greater than the resistance observed in Brazil (Vola *et al.*, 2013), which may demand longer treatment periods. Therefore, clinical practice in the US has detached the use of fluoroquinolones from corticosteroids, explaining the registered products pattern. The large presence of fluoroquinolones combined with corticosteroids in Brazil may result from differences in the profile of microbial resistance and/or the possibility of saving in marketing a more complete product by the value of the simple antimicrobial product (CMED, 2017).

One of the most serious aspects raised from this survey is the high amount of drugs absent from the Brazilian market, e.g. 5-substituted 2'-deoxyuridine analogues, macrolides, peptides, polyenes, sulphonamides and folate antagonists, either in simple or combined forms despite the demand. Moreover, Brazil had fewer options of newer quinolones generations when compared to the US. While Brazil has registered ciprofloxacin hydrochloride and ofloxacin (second generation quinolones), gatifloxacin and moxifloxacin (fourth generation quinolones), the US has registered all previous and also levofloxacin (third generation quinolone) and besifloxacin hydrochloride (fourth generation quinolone).

In the US, the Gram-positive *Staphylococcus aureus* is the most common bacteria affecting the eye globe, mainly the conjunctiva. Still, the Gram-negative *Pseudomonas aeruginosa* has been reported as the mainly causative agent for keratitis (Gratieri *et al.*, 2010b). In Brazil, microbial keratitis is predominantly related to Gram-positive bacteria, in special coagulase-negative *Staphylococcus* (Yu, Höfling-Lima, Furtado, 2016), e.g *Staphylococcus epidermidis* (Ibrahim *et al.*, 2011), or *Staphylococcus aureus* (Uesugui *et al.*, 2002). In conjunctivitis, other important agents include *Haemophilus* spp. (Silva *et al.*, 2012), besides the mentioned *Staphylococcus aureus* (Uesugui *et al.*, 2002). Even with some differences in etiological agents in both countries, bacteria were relevant infective organisms, both Gram-negative and Gram-positive. Hence, the clinical routine demands wide spectrum antibacterial drugs. To manage bacterial keratitis, Preferred Practice Pattern® Guidelines published by the American Academy of Ophthalmology recommends the use of fluoroquinolones for the majority of antibiotic therapy against Gram-negative and Gram-positive organisms and even when no organism is identified or multiple types of organisms are associated to the condition (American Academy of Ophthalmology, 2016).

The first marketed quinolone compound was the nalidixic acid, being norfloxacin, a 6-fluorinated substance, the first fluoroquinolone more similar to the modern ones (Appelbaum, Hunter, 2000). Initially, quinolones were mostly active against Gram-negative bacteria, but evolution of fluoroquinolones molecules and newer generations broadened the spectrum of action of these substances making them also potent against Gram-

positive bacteria (Blondeau *et al.*, 2000). *Staphylococcus* spp have been related to all kinds of ocular infections worldwide with recognized cases of antibiotics resistance. Such resistant strains exhibited susceptibility rates above 80% for fourth-generation fluoroquinolones (Vola *et al.*, 2013).

Aminoglycosides were the second major group registered as simple products in both countries. This group presents a similar activity spectrum to quinolones since it is mostly effective against Gram-negative bacteria, especially *P. aeruginosa* (Kirst, Marinelli, 2014), but it has a lower efficacy against Gram-positive strains (Vola *et al.*, 2013). In the US, with the high prevalence of *P. aeruginosa* at keratitis infections, it was compatible that there were more products containing aminoglycosides (simple and combined) than in Brazil. Aminoglycosides, such as tobramycin or gentamicin, are recommended to treat bacterial keratitis when no organism is identified or multiple types of organisms are associated to the condition (American Academy of Ophthalmology, 2016). In this way, they are a good option at the empirical treatment, according to the American Academy of Ophthalmology.

Although the good efficacy of these antibacterial groups, some strains are also developing resistance to fluroquinolones (Jhanji *et al.*, 2007), then there is still a need to develop new drug substances (Aggen *et al.*, 2010).

Antiviral groups 5-substituted 2'-deoxyuridine analogues and acyclic guanosine analogues had few representatives registered in both countries: in Brazil, only four drug products of acyclovir ointment were available; in the US, one drug product of ganciclovir gel and two drug products of trifluridine solution were available. All these medicines are indicated for topical treatment of keratitis caused by herpes simplex virus, according to their labels. Ganciclovir gel has also presented good clinical efficacy against cytomegalovirus corneal endotheliitis (Koizumi *et al.*, 2016). However, viral conjunctivitis and keratoconjunctivitis are mostly caused by adenoviruses (62% to 80.3%) having the herpes simplex virus low prevalence (2.3% to 4.8%). Indeed, adenoviruses seem to be more common than bacterial as etiological agent in keratoconjunctivitis overall. Thus, antiviral ophthalmic market may appear non-correlated to the clinical profile. This situation is not exclusive to markets from Brazil and the US, since the academic effort has also been prioritizing the development of treatments for herpes virus infections (Skevaki *et al.*, 2011). Nonetheless, the morbidity of these diseases may be considered. Adenoviral conjunctivitis is a self-limited disease that can be cured in three weeks, while ocular herpes simplex can cause blindness (Liesegang *et al.*, 1989) and has recurrence and a chronicity tendency (Tran *et al.*, 2016). This could explain the pharmaceutical industry focus on more severe infections caused by herpes simplex virus. Beyond that, viral infection diagnosis, both laboratorial and clinical, are complicated, leading to various misdiagnosis as bacterial conjunctivitis (Sharma, 2012). In fact, in many cases, there is indeed a secondary bacterial infection to adenoviral eye infections. Generally antibacterial drugs are presumptively prescribed or topical corticosteroids used for symptomatic relief (American Academy of Ophthalmology, 2016; Skevaki *et al.*, 2010). Anyhow, the drugs to treat adenoviral ocular infections can be a health need unfulfilled by the industries.

Fungal keratitis is far less common than bacterial keratitis, but represents one of the ocular infections with poorer prognosis. Since 2006 an alteration at etiological agents has been noted: initially caused by yeasts, filamentary fungi have become more common (Ong *et al.*, 2016). In the US, among the non-bacterial isolates, the recovery of molds is the most common, above the yeasts (Miller, 2017), e.g. *Curvularia spp* [33]. In general, the most common filamentous species are *Fusarium* and *Aspergillus*, while the most common yeast at ocular infections is *Candida spp* (Thomas, Kaliamurthy, 2013). In Brazil, *Fusarium* spp is the major etiological agent (Ibrahim *et al.,* 2011; Ibrahim *et al.*, 2009), in special the specie *Fusarium solani* (Yu, Höfling-Lima, Furtado, 2016). The recommended treatment for keratitis depends on the disease extent, but for superficial lesions the topical treatment includes topical azoles, amphotericin B, natamycin and caspofungin (amphotericin B or fluconazole are especially recommended against yeast, while topical natamycin is recommended against hyphae) (Thomas, Kaliamurthy, 2013). However, only one ophthalmic suspension of natamycin is registered in the US by the FDA. There is no antifungal ophthalmic drug product registered in the Brazilian market in the period analyzed, despite the health demand.

According to Brazilian epidemiological data collected in reference centers in the state of São Paulo between the years of 2000 and 2004, 66 cases of fungal keratitis were confirmed by microbiological analysis. Among the treatments performed, evisceration was implemented in 15.2%, conjunctival flap was conducted in 10.6% and therapeutic penetrating keratoplasty was conducted in 39.4% of the patients. Even after treatment, 57.7% of the patients who passed through therapeutic penetrating keratoplasty presented recurrence of fungal keratitis or underwent further surgeries, including evisceration. These data confirm the high morbidity of this disease, which is an important cause of visual loss

related to the cornea. Low availability of antifungal agents is one of the pointed causes to this overwhelming scenario (Ibrahim *et al.,* 2009).

Regarding the dosage form, the majority of ophthalmic drug products registered as solutions are compatible to the characteristics of the ophthalmic route. Solutions usually are presented as a simple formulation that is easy to produce and sterilize, besides has a good patient acceptance, causing less discomfort to the patient than the semisolid dosage forms (Gratieri *et al.*, 2011). However, solutions are easily drained out, while semisolid dosage forms can provide longer permanence *in situ*, extending drug release (Labcharoenwongs *et al.*, 2012). Another advantage of ointments is the administration of lipophilic substances (Hazarika, Singh, 2015). The gel dosage form was only registered in the US, being the most recent ophthalmologic antiviral medicine registered by the FDA. Gel is one of the evolutions related to ophthalmic formulations because it can incorporate hydrophilic compounds, just as solutions, but presents an extended release in comparison to eye drops (Ranch *et al.*, 2017). At the same time, being more appealing and comfort to the patients than the ointments. Nevertheless, there is still a need for improvement in terms of bioavailability and controlled or sustained drug action. To achieve these goals, research has been conducted on *in situ* gelling solutions (Gratieri *et al.*, 2011; Gratieri *et al.*, 2010a), nanostructured lipid carriers (Andrade *et al.*, 2016) or liposomes for ophthalmic delivery (de Sá *et al.*, 2015). Despite the several papers found in the literature that prove the superiority of innovative formulations, the present survey reveals none of these efforts have been translated to the market.

Three categories or application types compose the Brazilian market of synthetic drugs: new, similar and generic products. The last two are registered as copies from the innovator product and, to be approved by ANVISA, they must follow specific rules established by sanitary legislation. In the US, the equivalent applications are denominated Abbreviated Drug Application (ANDA) and New Drug Application (NDA). Even with these differences, the majority of the medications were copies from the innovators in both countries. In comparison to the US, Brazil presented a lower rate of new products registered. Considering only the Brazilian market, Brazilian industries held most of the applications overall, but only referred to similar and generic products. All the innovator products applications were held by multinational industries. In Brazil, new drugs presented the highest revenue amongst all the medicine categories, even with a lower commercialized quantity than generic and similar drugs (ANVISA, 2016). The high added value to new products provide an excellent incentive to Brazilian industries grow interest in their development.

CONCLUSIONS

Brazilian market has registered greater number of drug products (119) than the US (94), but the latter involves more variety of substances and dosage forms. Simple ophthalmic products were more common than combined ones, reaching 59.7% in Brazil and 61.7% in the US. The high amount of antibacterial, chiefly fluoroquinolones and aminoglycosides, registered as topic ophthalmic drug products were compatible with the clinical aspects and recommendations in Brazil and in the US. Meanwhile, there is need, space and financial incentive to develop new antimicrobial drugs and more effective ophthalmic formulations, especially to fungal and adenoviral ocular infections.

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DECLARATION OF INTEREST

Bianca Kollross is employee of ANVISA. The remaining authors declare no conflict of interests. This article reflects the views of the authors and should not be construed to represent ANVISA's views or policies.

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