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Article

New drugs registered in Brazil from 2003 to 2013: analysis from the perspective of child health

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This study aims to analyze the new drugs registered in Brazil from 2003 to 2013 from the perspective of childcare needs, drug safety and considering the disease burden of the country. This is a retrospective cohort study including new drugs registered in Brazil between 2003 and 2013. Drug indications were related to the Disability-Adjusted Life Year (DALY) of the 2015 Global Burden of Disease Study. Association between the number of new drugs and DALY was determined by Spearman's coefficient. Post-marketing safety alerts specific to the pediatric population have been identified in the WHO Drug Information Bulletin and on websites of drug regulatory agencies. A total of 134 new drugs were included in the cohort and 46 (34.3%) had a pediatric indication. There was no evidence of an association between the disease burden in children in Brazil and the number of pediatric drugs. The safety alert data associated with the pediatric population published after registration of the new drugs were scarce. The number of new drugs launched in Brazil with a pediatric indication was small, reflecting the international challenges of developing effective and safe medicines for children. No association was found between the number of new drugs and the disease burden.

Keywords: New drugs. Approval of medications. Pediatric. Safety alert. Disease burden.

INTRODUCTION

Medicines are an important health technology in child health (Kimland, Odlind, 2012). Despite the widespread use of drugs in the prevention, treatment and diagnosis of pediatric diseases, availability of medicines that are appropriate to the needs of children and with information based on evidence from clinical research is insufficient to ensure effective and safe use (Kimland, Odlind, 2012; MacLeod, 2017; García-López *et al*., 2017). The ethical and methodological challenges related to the development of pediatric drugs, together with the pharmaceutical industry's considerations of market size and profitability determine this setting that is common to several countries (García-López *et al*., 2017; Bourgeois, 2012).

Health professionals committed to providing safe and quality childcare recognize the need for scientifically validated medications. In this context, there is a growing concern to encourage the development of research in the different fields of pediatric clinical pharmacology and the training of human resources for research and teaching in this area (MacLeod, 2017; MacLeod, 2015). Clinical research should be promoted and encouraged by looking at the burden of children diseases in countries; this strategy will contribute to expand the therapeutic alternatives for treatment of children-prevalent diseases, including neglected tropical diseases in the case of low- and middle-income countries (Bourgeois *et al*., 2014; Catalá-López *et al*., 2010).

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Expanding the provision of adequate and safe medicines that meet children's therapeutic needs is an ongoing initiative in Europe and the United States over the past decade. In the United States, highlight legislations such as the *Pediatric Research and Equity Act* and *The Best Pharmaceutical for Children Act*, and in Europe, the *EU Pediatric Regulation* (Finney, 2011; Wimmer *et al*., 2014; Samiee-Zafarghandy, Mazer-Amirshahi, Van Den Anker, 2014). Few legislations and regulatory initiatives aimed at facilitating the development of pediatric medicines and reducing the prevalence of off-label use have been implemented in other countries (Turner *et al*., 2014). The World Health Organization launched in 2007 the "*Make Medicines Child Size*" campaign aimed at improving research, regulation and access to pediatric medicines (Finney,2011).

Brazil currently lacks a policy to foster clinical research geared to the pediatric population and the National Health Surveillance Agency (Anvisa) does not have specific regulations for the registration of child-specific medicines. Investigations on new drugs in Brazil did not address particularities of the different age groups (Gava *et al*., 2010; Vidotti, Castro, Calil, 2008). The off-label use of medications by children at different levels of care has been described in the country (Marinho, Cabral, 2014). Therefore, this study aims to analyze the new drugs registered in Brazil from 2003 to 2013 from the perspective of child health's needs, drug safety and considering the disease burden of the country.

METHODS

This retrospective cohort study included new drugs registered from January 2003 to December 2013 by Anvisa, the authority responsible for drug approval in Brazil. The definition of the cohort investigated was detailed in a previous study (Botelho *et al*., 2017). The cohort was defined after the identification of new drugs launched in other countries during the period of the research and which were concurrently approved by Anvisa.

New drugs registered in the United States during the study period were identified in the Drugs@FDA (Food and Drug Administration) database. Drugs registered in other countries were identified using the annual "To Market, To Market" review articles published by Annual Reports in Medicinal Chemistry. The register of new drugs in Anvisa were surveyed in site of Brazilian government responsible for official publications. The drugs were surveyed using the drug names adopted in Brazilian Portuguese from international non-proprietary names (Botelho *et al*., 2017). Drugs that were still marketed in Brazil were identified in the January 2016 list of medicines prices published by Anvisa (ANVISA, 2016a). In this investigation, we analyzed drugs registered from 2003 to 2013 and whose sales were upheld in January 2016.

Drugs were classified according to the third pharmacological therapeutic level of the Anatomical Therapeutic Chemical (ATC) Classification of the World Health Organization (WHO, 2018). The following drug characteristics were also identified: first-in -class, orphan drug, small molecule or biological drug, referring to the Food and Drug Administration (FDA) database and the "To Market, To Market" review articles (Botelho *et al*., 2017).

The algorithm published by Motola *et al.* in 2005, which classifies medicines as important, moderate, modest, pharmacological or technological innovations was used to evaluate therapeutic innovation. Clinical studies that supported the registration of new drugs with the FDA and the information published in the "To Market, To Market" review papers were used to determine the level of therapeutic innovation.

It was verified whether medicines were registered for pediatric use at Anvisa and the therapeutic indication referring to Anvisa's electronic drugs' package inserts (ANVISA, 2016b). When the package insert was not available on Anvisa's website, we requested the manufacturer's laboratory by email.

The pediatric indication at the time of registration, inclusion of pediatric indication and expanded child's age range after registration were searched in the following FDA documents: *Medical Review, Pharmacology Review and Approval Letter, available in the sections Approval History, Letters, Reviews and Related Documents or in the European Public Assessment Reports and Summary of Product Characteristics of the European Medicine Agency* (FDA, 2016; EMA, 2016). This strategy was adopted because Anvisa does not provide new drug registration supporting documents. It established the time lapse (in months) to include this information regarding pediatric use.

The main indication for medicines was classified according to the International Classification of Diseases (ICD-10), using the first three ICD-10 characters. Drugs' indications were related to the categories of diseases of the classification system defined in the 2015 Global

Burden of Disease Study (WHO, 2015a). The study is developed by the World Health Organization (WHO) to establish the disease burden in the population and to obtain information on prevalence, incidence, severity, disability and mortality of more than 100 causes of diseases. The Disability-Adjusted Life Year (DALY) of the different categories of diseases for the Brazilian population aged 0-14 years was collected in the Estimated DALYs ('000) table by cause, gender and WHO Member State (1), 2015 (WHO, 2015b).

Medications were also classified in relation to the indication for Pediatric Complex Chronic Conditions using the Pediatric Complex Chronic Conditions Classification System version 2: updated for ICD-10 (Feudtner *et al*., 2014).

Among the drugs registered as exclusive adult use, we identified those with potential interest for pediatric indication considering, besides the occurrence of the disease in this age group, the possibility of applying the action mechanism of the drug's therapeutic class in clinical conditions of pediatric interest, such as, for example, drugs classified in groups B01A, C10A, GO4B, N03A, N06A, R03A; to validate this classification, the availability of clinical trials involving children with drugs of these groups in Anvisa's and Clinical Trials' databases was investigated (ANVISA, 2016c, NIH, 2016). The antineoplastic agents of groups L01B, L01C, L01X, L03A and L04A were considered of potential pediatric interest.

Specific post-marketing safety alerts for the pediatric age group published up to October 30, 2016 were investigated by searching: the Drug Safety and Availability database, available on FDA's website, information available on Anvisa's website – Pharmacovigilance (ANVISA, 2016d) and WHO Drug Information accessed on WHO's website (WHO, 2016). The time elapsed (in months) between approval of the drug and the publication of the first safety alert related to the pediatric age group in Brazil and abroad was recorded. The justification for published the post-marketing safety alert was also recorded.

Statistical Analysis

For categorical variables, frequency and proportions were calculated. The quantitative variables were described showing measures of central tendency and variability. Normality was assessed through the Kolmogorov-Smirnov and Shapiro-Wilk tests, considering a statistically significant p-value <0.05. The association between the number of new medicines with pediatric indication and the DALY indicator was verified by correlation using Spearman's coefficient, considering p value <0.05. The Statistical Package for the Social Sciences (SPSS for Windows, version 21.0 (SPSS Inc, Chicago, Illinois) software was used to perform the statistical analyses.

RESULTS

From January 2003 to December 2013, 159 new drugs were registered in Brazil. However, the sale of 25 drugs was suspended in the country following registration. The cohort investigated consisted of 134 new drugs that were being sold in January 2016. At the time of registration abroad, 110 (82.1%) of these drugs received indications exclusively for adults and 24 (17.9%) for pediatric and adult use. None of the medicines had a specific indication for children. Regarding registered pediatric drugs, nine received additional pediatric information related to expanded age and one received new pediatric indication. After registration, of the 110 new drugs without a pediatric indication, 22 received a pediatric indication, of which 6 had expanded age range. The number of pediatric drugs included in the cohort was 46 (34.3%) (Figure 1).

Regarding indication, of the 110 drugs with registrations exclusively for adults, 6 were indicated for adult-specific clinical condition and 30 drugs had a potential pediatric indication considering the drug's action mechanism.

Of the 46 drugs, only 37 had a pediatric indication in Brazilian package inserts registered with Anvisa. The nine drugs that had pediatric registration abroad and had no registration in Brazil are anidulafungin, aprepitant, duloxetine, denosumab, eltrombopag, asenapine maleate, etravirine, palonosetron, dexlansoprazole.

Of the 46 pediatric medicines, 31 (67.4%) were small molecules, 15 (32.6%) were biological drugs, 11 (23.9%) were first -in- class and 5 (10.9%) were orphan medicines. Regarding the level of therapeutic innovation, 21 (45.7%) were classified as pharmacological, 10 (21.7%) moderate and 9 (19.6%) were important. The most frequent drugs were of the following ATC groups: A-Alimentary tract and metabolism (26.1%), J-Antiinfectives for systemic use (21.7%), L-Antineoplastic and immunomodulatory agents (13%) and R-Respiratory system (10.9%). The ATC classification of the 46 drugs is shown in Table I.

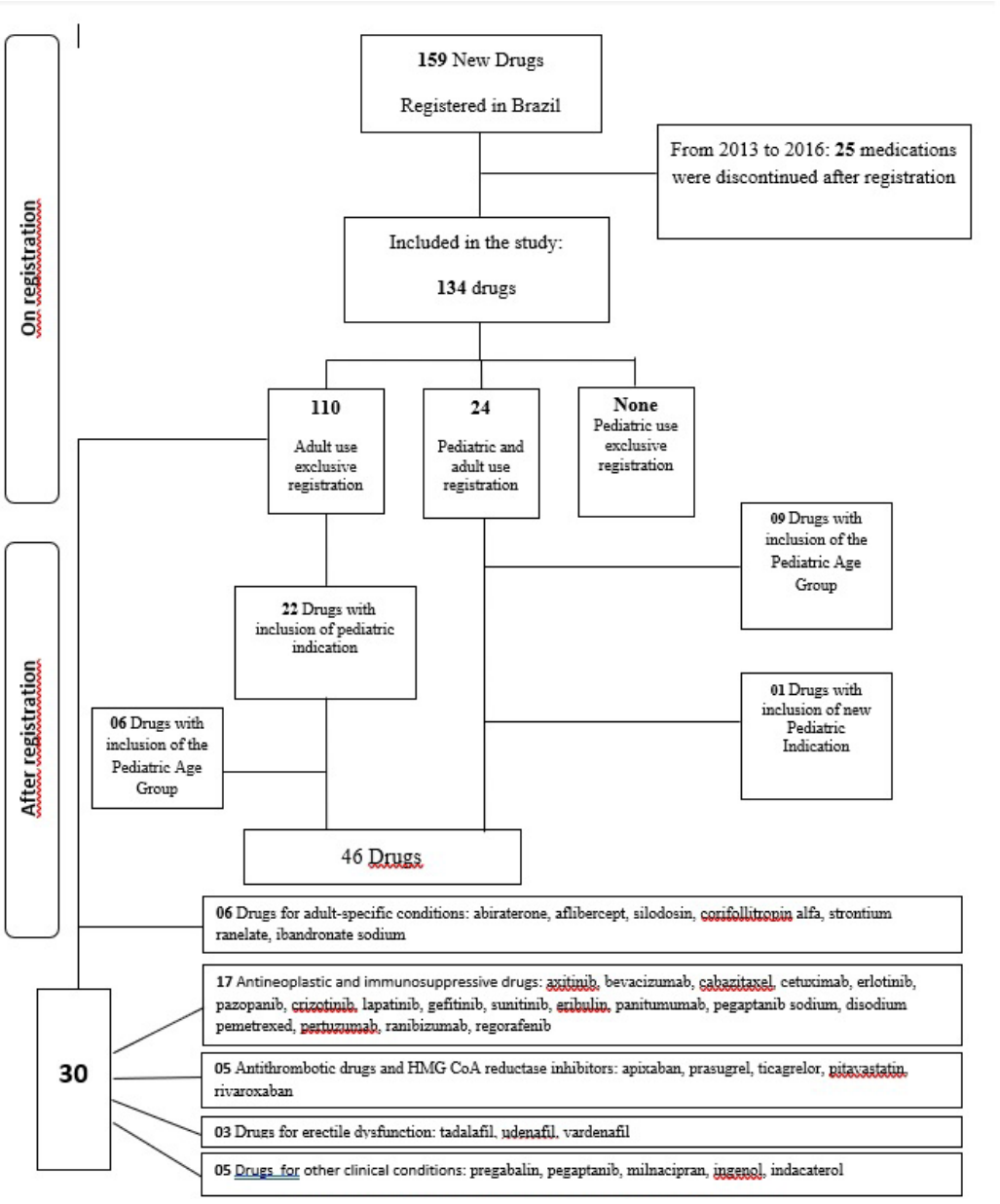

FIGURE 1 – Flow chart of pediatric medicines from 2003 to 2013.

TABLE I – Anatomical Therapeutic Chemical Classification of the 46 pediatric drugs identified in the cohort of new drugs registered from 2003 to 2013

ATC Classification		n	%
ALIMENTARY TRACT AND METABOLISM		**12**	**26.2**
A02B	**Drugs For Peptic Ulcer and Gastro-Oesophageal Reflux Disease (GORD)**: dexlansoprazole	1	2.2
A04A	**Antiemetics and Antinauseants**: aprepitant. palonosetron	2	4.4

(continuing)

TABLE I – Anatomical Therapeutic Chemical Classification of the 46 pediatric drugs identified in the cohort of new drugs registered from 2003 to 2013

ATC Classification		n	%
A10A	**Insulins and Analogues**: insulin detemir. insulin glulisine	2	4.4
A16A	**Other Alimentary Tract and Metabolism Products**: alglucosidase alfa, velaglicerase alfa, sapropterin, galsulfase, idursulfase, laronidase, miglusta	7	15.2
CARDIOVASCULAR SYSTEM		**1**	**2,2**
C10A	**Lipid Modifying Agents, Plain**: rosuvastatin	1	2.2
ANTIINFECTIVES FOR SYSTEMIC USE		**10**	**21.3**
J02A	**Antimycotics for Systemic Use**: anidulafungin, micafungin, posaconazole	3	6.5
J05A	**Direct Acting Antivirals**: enfuvirtid, entecavir, darunavir, etravirine, fosamprenavir, raltegravir potassium, atazanavir	7	15.2
ANTINEOPLASTIC AGENTS AND IMMUNOMODULATORY AGENTS		**6**	**13.0**
L01X	**Other Antineoplastic Agents**: nimotuzumab	1	2.2
L04A	**Immunosuppressants**: abatacept, adalimumab, canaquinumab, everolimus, tocilizumab	5	10.9
RESPIRATORY SYSTEM		**5**	**11.0**
R01A	**Decongestants and Other Nasal Preparations For Topical Use**: ciclesonide, fluticasone	2	4.4
R03D	**Other Systemic Drugs for Obstructive Airway Diseases**: omalizumab	1	2.2
R06A	**Antihistamines for Systemic Use**: bilastine, rupatadine	2	4.4
NERVOUS SYSTEM		**4**	**8.8**
N05A	**Antipsychotics**: asenapine, paliperidone	2	4.4
N06A	**Antidepressants**: duloxetine	1	2.2
N06B	**Psychostimulants, Agents Used For Adhd And Nootropics**: lisdexanfetamine	1	2.2
GENITOURINARY SYSTEM AND HORMONES		**2**	**4.4**
G03A	**Hormonal Contraceptives for Systemic Use**: dienogest+estradiol, drospirenone+ethinylestradiol	2	4.4

(continuing)

TABLE I – Anatomical Therapeutic Chemical Classification of the 46 pediatric drugs identified in the cohort of new drugs registered from 2003 to 2013

ATC Classification		n	%
Sense Organs		**2**	**4.4**
S01A	**Antiinfectives**: besifloxacin	1	2.2
S01G	**Decongestants And Antiallergics**: alcaftadine	1	2.2
Dermatological		**1**	**2.2**
D06A	**Antibiotics For Topical Use**: retapamulin	1	2.2
MUSCULOSKELETAL SYSTEM		**1**	**2.2**
M05B	**Drugs Affecting Bone Structure and Mineralization**: denosumab	1	2.2
BLOOD AND HEMATOPOIETIC ORGANS		**1**	**2.2**
B02B	**Vitamin K and Other Hemostatics**: eltrombopag olamine	1	2.2
VARIOUS		**1**	**2.2**
V03A	**All Other Therapeutic Products**: sugammadex	1	2.2
	Total	46	100.0

The main pediatric indications of the 46 new drugs were infectious and parasitic diseases (10, 21.7%), endocrine, nutritional and metabolic diseases (10, 21.7%), respiratory diseases (5, 10.9%), mental and behavioral disorders (4, 8.7%) and rheumatoid arthritis (4, 8.7%) (Table II). For 16 medicines (34.8%), indication was a pediatric complex chronic condition.

TABLE II – Indication of the 46 medicines with pediatric indication identified in the cohort of new drugs registered from 2003 to 2013

Indications	**On Registration**			**Post-Registration**		
	Drugs	**n**	**%**	**Drugs**	**n**	**%**
Infectious and Parasitic Diseases						
Viral hepatitis		-	-	entecavir	1	4.5

(continuing)

TABLE II – Indication of the 46 medicines with pediatric indication identified in the cohort of new drugs registered from 2003 to 2013

Indications	On Registration			Post-Registration		
	Drugs	n	%	Drugs	n	%
Treatment of children living with Human Immunodeficiency Virus (HIV)	enfuvirtide	1	4.2	atazanavir, darunavir, etravirine, fosamprenavir, raltegravir	5	22.8
Fungal Infections	anidulafungin, posaconazole	2	8.3	micafungin	1	4.5
Neoplasms						
Glioma	nimotuzumab	1	4.2	-	-	-
Subependymal giant cell astrocytoma	-	-	-	everolimus	1	4.5
Nutritional and Metabolic Endocrine Diseases						
Diabetes Mellitus	insulin detemir	1	4.2	insulin glulisine	1	4.5
Aromatic Amino Acids Metabolism Disorders: Hyperphenylalaninemia	sapropterine	1	4.2	-	-	-
Other Carbohydrate Metabolism Disorders: Pompe's Disease	alglucosidase alfa	1	4.2	-	-	-
Sphingolipids Metabolism Disorders and Other Lipid Deposits Disorders: Gaucher's Disease Type I	velaglicerase alfa, miglustat	2	8.3	-	-	-
Glycosaminoglycan Metabolism Disorders: Mucopolysaccharidosis I and II Maroteaux-Lamy Syndrome	galsulfase, idursulfase, laronidase	3	12.4	-	-	-
Lipoproteins Metabolism Disorders and Other Lipidemias	-	-	-	rosuvastatin	1	4.5
Mental and Behavioral Disorders						
Schizophrenia	-	-	-	asenapine, paliperidone	2	9.3
Generalized Anxiety Disorder	-	-	-	duloxetine	1	4.5

(continuing)

TABLE II – Indication of the 46 medicines with pediatric indication identified in the cohort of new drugs registered from 2003 to 2013

Indications	On Registration			Post-Registration		
	Drugs	n	%	Drugs	n	%
Attention Deficit/Hyperactivity Disorder	lisdexanphetamine	1	4.2	-	-	-
Respiratory Diseases						
Allergic and Vasomotor Rhinitis	bilastine, rupatadine, fluticasone	3	12.4	-	-	-
Asthma	ciclesonide, omalizumab	2	8.3	-	-	-
Other Diseases						
Rheumatoid arthritis	canaquinumab	1	4.2	Abatacept, adalimumab, tocilizumab	3	13.6
Conjunctivitis	alcaftadine, besifloxacin	2	8.3	-	-	-
Gastroesophageal Reflux Disease	-	-	-	dexlansoprazole	1	4,5
Impetigo	retapamulin	1	4.2	-	-	-
Treatment of skeletally mature adolescents with giant cell bone tumor	-	-	-	denosumab	1	4.5
Chemotherapy-induced Nausea and Vomiting	-	-	-	aprepitant,palonosetron	2	9.3
Contraception	dienogest+ estradiol valerate	1	4.2	drospirenone+ ethinylestradiol	1	4.5
Poisoning with neuromuscular blocker	sugammadex	1	4.2	-	-	-
Idiopathic thrombocytopenic purpura	-	-	-	eltrombopag olamine	1	4.5
Total		24	100.0		22	100.0

* Of the 24 medicines with pediatric indication at the time of registration, 09 obtained inclusion of expanded pediatric age group and 01 obtained a new pediatric indication
** Of the 22 medicines with pediatric indication after registration, 06 obtained inclusion of expanded age group

There was no evidence of association between the disease burden of children under 15 years of age in Brazil and the number of pediatric drugs (rho = 0.272, p-value = 0.448). Table III shows the number of new drugs registered in Brazil with a pediatric indication and the burden of diseases for children aged 0-14 years according to 2015 Global Burden of Disease Study, showing lack of medicines for respiratory infections, maternal conditions, neonatal conditions, nutritional deficiencies and congenital anomalies.

TABLE III – Number of pediatric new drugs registered in Brazil from 2003 to 2013 and number of DALYs of children from 0 to 14 years according to ICD-10 categorization of the indication

Indications	Number of medicines	%	DALY*10^3	%
COMMUNICABLE DISEASES				
Infectious and parasitic diseases	08	21.6	517.9	6.5
Respiratory infections	-	-	545.9	6.8
Maternal conditions	-	-	0.1	0.001
Neonatal conditions	-	-	2320.2	29.1
Nutritional deficiencies	-	-	727.6	9.1
NONCOMMUNICABLE DISEASES				
Malignant neoplasms	02	5.4	198.8	2.5
Endocrine, Immune and Blood Disorders	08	21.6	154.8	1.9
Mental Disorders and Substance Use	02	5.4	418.6	5.2
Cardiovascular diseases	-	-	204.5	2.6
Diabetes mellitus	02	5.4	13	0.2
Musculoskeletal diseases	04	10.8	54.7	0.7
Skin diseases	01	2.7	216.3	2.7
Respiratory diseases	05	13.5	398.1	5.0
Congenital anomalies	-	-	1170.3	14.7
Diseases of the sensory organ	02	5.4	23.3	0.3
Digestive diseases	-	-	45.9	0.6
Other Diseases	03	8.1	350.4	4.3
Injuries				

(continuing)

TABLE III – Number of pediatric new drugs registered in Brazil from 2003 to 2013 and number of DALYs of children from 0 to 14 years according to ICD-10 categorization of the indication

Indications	Number of medicines	%	DALY*10^3	%
Intentional and unintentional injuries	-	-	622.7	7.8
Total	37	100.0	7983.1	100.0

Inclusions of pediatric indications were mainly for drugs used in the treatment of HIV (n = 5), neoplasms (n = 3), juvenile arthritis (n = 4) and mental and behavioral disorders (n = 4). Time lapse for inclusion of pediatric indication after registration was at least 10 months and maximum of 149 months, with a mean of 66.8 months and standard deviation 36.1 months.

The safety alert data associated with the pediatric population published after registration of new drugs were identified for four drugs. Adalimumab evidenced an alert for risks of malignancy, infection and fungal tuberculosis, and lisdexamfetamine, of serious cardiovascular reactions. These alerts were published both in Brazil and abroad. Adolescent suicide risk alert was identified for duloxetine, and a risk of hypomagnesaemia was noted for dexlansoprazole. Alerts for these drugs were only published abroad. Time elapsed between approval and the first international alert ranged from 26 to 79 months, with a mean of 48.8 months and a standard deviation of 24.1 months. In Brazil, the time lapse between ANVISA's approval and the first alert ranged from 23 months to 34 months, with mean of 28.5 months and a standard deviation of 7.8 months.

DISCUSSION

The analysis of new drugs registered from 2003 to 2013 in Brazil showed that the incorporation of drugs in the pharmaceutical market does not consider children's needs and specificities, since the number of medicines with a pediatric indication at the time of registration was small, as was the number of incorporated additional information or pediatric indication at post-registration. In addition, no medicine had an exclusive pediatric indication. This setting is worrying because children with diverse clinical conditions and different age groups are deprived of access to therapeutic innovations (Ceci *et al*., 2006), which can contribute to effective treatment, prevent disease development to advanced stages, and promote the improvement of the quality of life.

In order to interrupt the designation of children as therapeutic orphans and promote access to effective, safe and adequate medicines, legislation and public policies to encourage research and development of pediatric medicines are being developed in several countries, especially in the United States and the European Union. However, these actions have little effect, as an evaluation of the drugs registered from 2003 to 2012 with the Food and Drug Administration did not show a significant increase in the registration of new medicines with pediatric information (Samiee-Zafarghandy, Mazer-Amirshahi, Van Den Anker, 2014). In Europe, after 9 years of EU Pediatric Regulation, advances in the development of pediatric medicines are also incipient, but expectations are that, in the future, it will reach a market with better and safer pediatric medicines (Chin, Joos, 2016).

In Brazil, government actions to encourage research and development of pediatric medicines have not been implemented so far, which may explain the low availability of new drugs for children in the cohort investigated. More effective initiatives to raise awareness and improve this situation have been developed by university researchers.

The Ministry of Health published in 2017 on report with recommendations and strategies for increased access and rational use of medicines in children in Brazil. This report is a measure that can significantly change the setting, since it shows a set of multi-sectoral actions to be developed in integrated fashion with universities, the pharmaceutical industry and the Brazilian Unified Health System (Brasil, 2017).

The effective implementation of these actions will lead to the development of research of interest to

pediatrics, increased availability of drugs necessary and appropriate to Brazilian children and optimizing of pediatric pharmacotherapy results.

The late approval of pediatric drugs and package inserts review remains pre-eminent compared to adults. Delay in providing clinical pharmacology data in children for new drugs contributes to pediatric pharmacotherapy's increased gap (Samiee-Zafarghandy, Mazer-Amirshahi, Van Den Anker, 2014). In Brazil, this issue is more worrisome, since about a fifth of medicines with pediatric indication abroad still did not have this information incorporated in its package inserts, which can contribute to off label prescription and bring risks to the child.

It is important to note that the development of a new drug depends on the level of research on a particular disease. In addition, some diseases may require investments of more significant resources to develop innovative medicines. Market demand is also a factor that interferes with the availability of new drugs (Catalá-López *et al.*, 2010).

To meet the needs of the health system in the development of new medicines for children, it is essential to consider the burden of diseases of different pediatric age groups (Catalá-López *et al.*, 2010; Balakrishnan *et al.*, 2006). The number of pediatric drugs launched in Brazil from 2003 to 2013 was not associated with the number of DALYs in children younger than 15 years. Therefore, the analysis of new drugs suggests that, considering children's health needs, some pediatric diseases such as respiratory infections, maternal conditions, perinatal conditions, nutritional deficiencies, respiratory diseases, congenital anomalies are more neglected than others. On the other hand, infectious diseases, musculoskeletal disorders, endocrine, immunological and blood disorders evidenced a greater number of drugs compared to the number of DALYs.

This imbalance between the number of new drugs and DALY is in line with a study that assessed the proportionality between pediatric clinical trials and the global disease burden in different country categories, identifying under- and over-studied diseases (Bourgeois *et al*., 2014). In countries classified by the World Bank in the middle-income category, such as Brazil, among the under-studied diseases are practically the same ones that are neglected in relation to the number of new medicines in Brazil. However, for neonatal conditions and respiratory diseases, authors identified an association between disease burden and number of clinical trials. Non-respiratory infectious diseases had a greater number of clinical trials, and musculoskeletal diseases, neoplasms, respiratory diseases and diabetes were considered over-studied as well (Bourgeois *et al*., 2014).

Antiinfectives registered for children in 2003-2013 were mostly antiretrovirals, reflecting the progress made in the development of these drugs in recent years. However, the current availability of antiretrovirals is still inadequate to ensure efficient coverage of HIV-infected children (Dubrocq, Rakhmanina, Phelps, 2017). Due to the importance of invasive fungal infections, especially in immunosuppressed children, registration of new antifungal drugs reflects medications that meet pediatric demands, as morbidity and mortality from these infections are significant (Lehrnbecher, 2015). On the other hand, the lack of new antibacterials is of concern, since drugs of this class are safe and effective and are important in view of the high antimicrobial resistance in children (Garazzino *et al*., 2013). The disease burden from pediatric respiratory infections is also an important determinant of the research for new antibiotics. The potential delayed registration of new antibiotics for children leads to an increase in off label prescriptions and hampers the adequate treatment of pediatric infections (Garazzino *et al*., 2013).

With the increasing diagnosis of pediatric neoplasms, morbidity and mortality of children due to cancer becomes a social concern (Vassal *et al*., 2015). Despite advances already made in pediatric oncology, it is still necessary to expand the research of new therapeutic agents to treat these diseases in children, as well as the effectiveness of integrated actions of the industry, academia, regulatory agencies and patient relatives' associations to achieve the discovery of more effective treatments favoring healing and eliminating the burden of long periods of treatment in oncological clinics (Milne, 2017; Adamson, 2015).

Most of the immunosuppressants launched in Brazil during the period investigated were biological drugs, cytokine modulators and were registered for treatment of juvenile rheumatoid arthritis. The inclusion of biological drugs in therapy has shown significant advances in pediatric rheumatology, but due to the high cost and safety profile, requires well-defined criteria to ensure a rational prescription (Horneff, 2015; Blazina *et al*., 2016).

The frequency of drugs that were important therapeutic inovation and first-in- class in the cohort investigated was reduced. There was a predominance of pharmacological innovations, an aspect also identified in the evaluations of new adult-specific drugs (Botelho *et al*., 2017) that is an international trend (Ward *et al*., 2014; Vitry, Shin, Vitre, 2013). The small molecule ratio

also showed the same pattern detected in studies on adults. There is a growing perspective of using biological drugs in the treatment of pediatric diseases (Horneff, 2013), justifying that these drugs account for a third of medications.

Significant advances in the understanding of the biochemical and molecular bases of inborn errors of intermediate metabolism have provided an increasing therapeutic arsenal for the management of many of these rare genetic diseases in children (Schwartz, Souza, Giugliani, 2008; Das AM, 2016). The registration of seven new substances for enzymatic replacement in pediatric metabolic diseases contributed to the fact that ATC's group A was the class of medications included in the cohort with the highest frequency.

Research, development and registration of drugs in the category of orphan drugs have contributed significantly to the development of enzyme replacement therapies in rare metabolic diseases (Das AM, 2016). However, in pediatrics, for rare genetic and oncologic diseases, the results of this strategy are still incipient (Rose, 2017). Thus, in order to achieve deep improvements in the availability of effective treatment for the countless rare diseases in children, the social need has to be one of the guiding elements of the new drugs research. Academia plays a prominent role because the industry is often guided by market profitability (Rose, 2017). Given the morbidity and mortality profile of these diseases in the country, regulatory agency must implement actions that contribute to the development of new drugs.

Among the various challenges of pediatrics is the provision of adequate treatment for children with complex chronic conditions (Cohen, Patel, 2014), the drug therapy research that significantly influences the course of the disease and the improvement of symptoms and contributes to better quality of life becomes a priority. Considering the diverse complex chronic conditions and the lack of previous publications on new drugs for these conditions, the significance of the finding of about 40% of these drugs does not provide conclusions on the impact for the medical therapy of these diseases.

The therapeutic potential of a new pediatric drug should be investigated by considering the mechanism of drug action, since many drugs that were originally indicated exclusively for adults, with another indication, may be used in children. In our study, it was shown that among adult condition-specific drugs were phosphodiesterase inhibitors that are used in the treatment of pulmonary hypertension in children and drugs that act on coagulation and platelet aggregation, which can be used in pediatric conditions that compromise homeostasis. The largest share was found in antineoplastic drugs. It has been described that, while indicated for tumors that are often rare in children, the adult-specific drug's action mechanism may have potential value in other pediatric malignancies (Samiee-Zafarghandy, Mazer-Amirshahi, Van Den Anker, 2014; Vassal, Geoerger, Morland, 2013), and many drugs evaluated for cancer in adults act on different growth factors and signaling pathways that may contribute to the development of new pediatric oncology drugs.

Post-marketing surveillance is an important part of the life cycle of a drug, especially for pediatric use, because after registration, safety knowledge is restricted due to the limited number of children in clinical trials (Turner *et al*., 2014). In order to put pressure on governments, industry and health professionals to improve the monitoring of safe use of medicines in the pediatric population, WHO published in 2007 the document "*Promoting safety of medicines for children*" (Who, 2007; Clavenna, Bonati, 2009).

However, the specific alerts for children identified with the new drugs investigated were few, a finding similar to a study that evaluated pediatric drugs registered with the FDA (Gava *et al*., 2010). Expanding knowledge about pediatric drug safety is an important step towards improving the rational use of medicines by children.

One limitation of this investigation is the systematic identification of the drug registration in the site of Brazilian government responsible for official publications, which may have led to failures in the identification of new drug registrations in Brazil. There would be greater accuracy if Anvisa's website made registration information available, as well as regarding the inclusion of new indications such as occurs on the FDA's and EMA's websites. Another limitation is showing the disease burden considering only the DALYs of 0-14 years because the organization structure of data provided in the 2015 Global Burden of Disease Study does not allow showing that of 0-18 years, but nevertheless the profile of disease burden in children is representative. A strength of the study is the search

for safety alerts in the WHO Drug Information Bulletin and on Anvisa's and FDA's websites, increasing accuracy in the identification of alerts. In addition, it is the first research on new pediatric drug registered in Brazil.

CONCLUSION

The number of new medicines launched in Brazil from 2003 to 2013 with a pediatric indication at the time of registration was small, reflecting the international challenges of developing effective and safe medicines for children. The incorporation of additional information or pediatric indication in post-registration was scarce.

New drugs with important therapeutic innovations for pediatric pharmacotherapy have not been reported in expressive numbers. There is no association between the number of new drugs and the burden of disease. The publication of post-marketing safety alerts related to drug use in children has to be increased in order to expand knowledge about medicines safety and curb the risk of adverse reactions.

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REFERENCES

Adamson PC. Improving the outcome for children with cancer: development of targeted new agents. CA Cancer J C. 2015;65: 212-220.

Agência Nacional de Vigilância Sanitária. Lista de preços de medicamentos. 2016a. Available from: http://portal.anvisa.gov.br/consulta-lista-de-preco-de-medicamento/; Accessed 31.01.16.

Agência Nacional de Vigilância Sanitária. Bulário Eletrônico. 2016b Apr 10]. Available from: http://portal.anvisa.gov.br/bulario-eletronico1/; Accessed 30.01.016.

Agência Nacional de Vigilância Sanitária. Consulta de Ensaios Clínicos Autorizados pela Anvisa. 2016c Apr 10]. Available from:http://www7.anvisa.gov.br/Datavisa/Consulta_Comunicados/Consulta_CE_Autorizados.asp/; Accessed 30.08.16.

Agência Nacional de Vigilância Sanitária. Farmacovigilância. 2016d Apr 10]. Available from: http://portal.anvisa.gov.br/alertas/; Accessed 30.11.16.

Balakrishnan K, Grieve J, Tordoff J, Norris P, Reith D. Pediatric licensing status and the availability of suitable formulations for new medical entities approved in the United States between 1998 and 2002. J Clin Pharmacol. 2006;46(9):1038-1043

Blazina S, Markelj G, Avramovič MZ, Toplak N, Avčin T. Management of juvenile idiopathic arthritis: a clinical guide. Pediatr Drugs. 2016;18(6):397-412.

Botelho SF, Martins MA, Vieira LB, Reis AM. Postmarketing safety events relating to new drugs approved in Brazil between 2003 and 2013: a retrospective cohort study. J Clin Pharmacol. 2017;57(4):493-499.

Bourgeois FT, Avillach P, Kong SW, Heinz MM, Tran TA, Chakrabarty R, Bickel J, et al. Pediatric versus adult drug trials for conditions with high pediatric disease burden. Pediatrics. 2012;130(2):285-292.

Bourgeois FT, Avillach P, Kong SW, Heinz MM, Tran TA, Chakrabarty R, Bickel J et al. Association between pediatric clinical trials and global burden of disease. Pediatrics. 2014;133(1):78-87.

Brasil. Ministério da Saúde. Assistência Farmacêutica em Pediatria no Brasil: recomendações e estratégias para a ampliação da oferta, do acesso e do Uso Racional de Medicamentos em crianças.2017. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/assistencia_farmaceutica_pediatria_brasil_recomendacoes.pdf/; 2017. Accessed March 30.03.2017

Catalá-López F. García-Altés A, Alvarez-Martín E, Gènova-Maleras R, Morant-Ginestar C.. Does the development of new medicinal products in the European Union address global and regional health concerns? Popul Health Metr. 2010;8(34).

Ceci A, Felisi M, Baiardi P, Bonifazi F, Catapano M, Giaquinto C, et al. Medicines for children licensed by the European Medicines Agency (EMEA): the balance after 10 years. Eur J Clin Pharmacol. 2006;62(11):947-952.

Chin WWL, Joos A. Moving toward a paradigm shift in the regulatory requirements for pediatric medicines. Eur J Pediatr. 2016;175(12):1881-1891.

Clavenna A, Bonati M. Adverse drug reactions in childhood: a review of prospective studies and safety alerts. Arch Dis Child. 2009;94(9):724-728.

Cohen E, Patel H. Responding to the rising number of children living with complex chronic conditions. Can Med Assoc J. 2014;186(16):1199-1200.

Das AM. Pharmacotherapy of inborn errors of metabolism illustrating challenges in orphan diseases. J Pharmacol Toxicol Methods. 2016;81:9-14.

Dubrocq G, Rakhmanina N, Phelps BR. Challenges and opportunities in the development of HIV medications in pediatric patients. Pediatr Drugs. 2017;19(2):91-98.

European Medicine Agency. Search for medicines.2016 Available from: http://www.ema.europa.eu/ema/; Accessed 30.01.16.

Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. BMC Pediatrics. 2014;14:199.

Finney E. Children's Medicines: a situational analysis. Available from: http://www.who.int/childmedicines/progress/CM_analysis.pdf/; 2011. Accessed 30.01.16.

Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. 2016 Available from: http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm/; Accessed 30.01.16.

Garazzino S, Lutsar I, Bertaina C, Tovo PA, Sharland M. New antibiotics for paediatric use: A review of a decade of regulatory trials submitted to the European Medicines Agency from 2000 - Why aren't we doing better? Int J Antimicrob Agents. 2013;42(2):99-118.

García-López I, Fuentes-Ríos JE, Manrique-Rodríguez S, M Fernández-Llamazares C. Off-label and unlicensed drug use: results from a pilot study in a paediatric intensive care unit. An Pediatr. 2017;86(1):28-36.

Gava CM, Bermudez JA, Pepe VL, Reis ALA. Novos medicamentos registrados no Brasil: podem ser considerados como avanço terapêutico. Ciênc Saúde Coletiva. 2010;15(Suppl. 3):3403-3412.

Horneff G. Update on biologicals for treatment of juvenile idiopathic arthritis. Expert Opin Bio Ther. 2013;13(3):361-376.

Horneff G. Safety of biologic therapies for the treatment of juvenile idiopathic arthritis. Expert Opin Drug Saf. 2015;14(7):1111-1126.

Lehrnbecher T. Antifungal prophylaxis in pediatric patients undergoing therapy for cancer: drugs and dosing. Curr Opin Infect Dis. 2015;28(6):523-531.

Kimland E, Odlind V. Off-label drug use in pediatric patients. Clinical Clin Pharmacol Ther. 2012;91(5):796-801.

MacLeod SM. A quarter century of progress in paediatric clinical pharmacology: a personal view. Br J Clin Pharmacol. 2015;81(2):228-234.

MacLeod SM. Improving medicines use for children: a global imperative. Clin Pharmacol Ther. 2017;101(6):715-717.

Marinho, RNA, Cabral CHK. Estudo de adaptações de formulações farmacêuticas em um hospital universitário pediátrico. Rev Bras Farm Hosp Serv Saúde. 2014;5:12-17.

Milne CP. More efficient compliance with European Medicines Agency and Food and Drug Administration Regulations for pediatric oncology drug development: problems and solutions. Clin Ther. 2017;39(2):238-245.

Motola D, De Ponti F, Rossi P, Martini N, Montanaro N. Therapeutic innovation in the European Union: analysis of the drugs approved by the EMEA between 1995 and 2003. Br J Clin Pharmacol. 2005;59(4):475-478.

National Institutes of Health. Clinical Trial.gov. Available from: https://clinicaltrials.gov/ct2/search/advanced/; Last updated October, 2016. Accessed 30.10.16.

Rose, K. New drugs for rare diseases in children. Clin Ther. 2017;39(2):246-252.

Samiee-Zafarghandy S, Mazer-Amirshahi M, Van Den Anker JN. Trends in paediatric clinical pharmacology data in US pharmaceutical labelling. Arch Dis Child. 2014;99(9):862-865.

Schwartz IV, Souza CFMD, Giugliani R. Treatment of inborn errors of metabolism. J Pediatr (Rio J). 2008:84(Suppl.4):S8-S19.

Turner MA, Catapano M, Hirschfeld S, Giaquinto C, Global Research in Paediatrics. Paediatric drug development: the impact of evolving regulations. Adv Drug Deliv Rev. 2014;73:2-13.

Vassal G, Geoerger B, Morland B. Is the European pediatric medicine regulation working for children and adolescents with cancer? Clin Cancer Res. 2013;19(6):1315-1325.

Vassal G, Rousseau R Blanc P, Moreno L, Bode G, Schwoch S, et al. Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children

and adolescents with cancer. Eur J Cancer. 2015;51(2):218-224.

Vidotti, CCF., Castro, LLCD., Calil, SS. 2008. New drugs in Brazil: do they meet Brazilian public health needs? Rev Panam Salud Pública. 2008;24(1):36-45.

Vitry, AI, Shin NH, Vitre, P. Assessment of the therapeutic value of new medicines marketed in Australia. J Pharm Policy Pract. 2013;6:2.

Ward DJ, Slade A, Genus T, Martino OI, Stevens AJ. How innovative are new drugs launched in the UK? A retrospective study of new drugs listed in the British National Formulary (BNF) 2001–2012. BMJ Open. 2014;4(10):e006235.

Wimmer S, Rascher W, McCarthy S, Neubert A. The EU paediatric regulation: still a large discrepancy between therapeutic needs and approved paediatric investigation plans. Pediatr Drugs. 2014;16(5):397-406.

World Health Organization. Promoting safety of medicines for children. World Health Organization, Geneva, 2007. Available from: http://www.who.int/medicines/publications/essentialmedicines/Promotion_safe_med_childrens.pdf

World Health Organization. WHO methods and data sources for country-level causes of death 2000-2015. 2015a http:// Available from: http://www.who.int/healthinfo/global_burden_disease/GlobalCOD_method_2000_2015.pdf/; Accessed 01.03.17.

World Health Organization (2016) WHO Drug Information. Available from: http://www.who.int/medicines/publications/druginformation/en/; Accessed November 30.11.16.

World Health Organization. Health statistics and information systems. Disease Burden. DALY estimatives, 2002-2015. 2015b WHO Member States. Available from: http://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html/; 2017 Accessed 04.03.17.

World Health Organization. ATC/DDD Available from: Index. http://www.whocc.no/atc_ddd_index/; 2018 Accessed 24.01.18.

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