

## Characterization of the import applications for unavailable vital medicines in 2016 and 2017 in Colombia

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**Abstract** *This study analyzed the import applications for unavailable vital medicines (MVND) submitted to INVIMA and the records of MVND reimbursement requests submitted to the ADRES in the 2016-2017 period. Approximately 76% of the 2,321 MVND import applications were authorized. Eighty-eight applicants, 73 therapeutic subgroups, 195 active ingredients, and 368 diagnoses were identified. Most of the patients registered in the import applications (66%) are linked to the contributory regime, to a lesser extent to the subsidized regime and the Special or exceptional regimes. The total value of the reimbursement requests related to MVND granted by lawsuits, was USD 8,577,583, equivalent to 38,483 UPCs. The results showed that the implementation of Decree N° 481/2004 has ensured access to medicines for rare diseases. However, it is not alien to the structural inequality of access to health services and medicines of the Colombian Health System, which impacts public health and the allocated budget, either because of the high cost of importing MVND or because of the lack of MVND regulation within the national market.*

**Key words** *Access to essential medicines and health technologies, Rare diseases, Orphan drugs, Drug costs, Colombia*

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## Introduction

In Colombia, the General Social Security in Health System (SGSSS)<sup>1</sup> is based on the insurance model, and affiliation is mandatory<sup>2</sup>. The SGSSS has two regimes, depending on the people's economic capacity: contributory and subsidized<sup>1</sup>. Employees, people with monthly income equal to or greater than one minimum wage, and pensioners; those who make a monthly contribution to their insurer (also known as Health Promotion Company - EPS) belong to the Contributory regime<sup>3,4</sup>. Insured who cannot pay<sup>1</sup>, people with fewer resources, and those in vulnerable conditions who are unable to contribute to the health system<sup>4,5</sup> but who also have access to health services belong to the subsidized regime. Also, some special or exception regimes cover particular groups, such as the military forces<sup>5</sup>.

All people insured with the SGSSS have the right to receive the medicines included in the Health Benefits Plan (PBS), divided into two parts according to the financing mechanism. There is a list of medicines financed by the Capitation Payment Unit-UPC<sup>6</sup>, which corresponds to the monetary amount received by the EPS for each insured<sup>1</sup>. This list is known as PBS medicines charged to the UPC (PBS-UPC). However, according to the statutory health law, patients have the right to access any procedure or service not financed by the UPC resources if they so require<sup>7</sup>. This list is known as Non-PBS-UPC medicines. Two access routes are available when a patient requires a Non-PBS-UPC medicine: administrative and judicial. The first consists of an authorization by the EPS for the patient to have access to the medicine, and EPS supplies it. In the second case, faced with the refusal of the EPS to deliver the requested medicine, patients resort to the courts to file a claim, which, if ruled in their favor, forces the EPS to deliver the medicine. The EPS can request reimbursement in both cases. The entity that makes the reimbursement depends on the regime to which the patient belongs. If insured with the contributory regime, the reimbursement is requested from the Health System Resource Administrator (ADRES), while patients insured with the subsidized regime the reimbursement is responsibility of the Departmental or District Health Secretariats<sup>5</sup>.

Access to health services is an indication of how States safeguard their citizens (8). In the case of medicines, in Colombia, policies have been established around continuity and timeliness<sup>9</sup> directly linked to dispensing<sup>10</sup> through the mech-

anisms mentioned above. However, a patient can access medicines only if they are available, a variable that depends, in turn, on factors such as research and development, manufacturing, authorization, distribution, and marketing within the national territory<sup>10</sup>.

Depending on all the variables described above, the total availability of medicines is not always possible, even more so when we refer to medications to treat low-prevalence diseases<sup>11</sup>, which becomes a global issue. In Colombia, in 2004, in order to establish mechanisms that allow sufficient supply and access to medicines unavailable in the Colombian market but required for the health care of patients in the country, the then Ministry of Social Protection, together with the Ministry of Commerce, Industry and Tourism issued Decree N° 481 "*By which regulations are issued to encourage the supply of unavailable vital in the country*"<sup>12</sup>, whose implementation has not been evaluated to date in terms of which medicines are requested via this route and what economic cost they attached to the SGSSS. According to Article 2 of Decree N° 481/2004, an Unavailable Vital Medicine (MVND) is *an indispensable and irreplaceable medicine to safeguard the life or alleviate the suffering of a patient or a group of patients and that, due to low profitability conditions in its sale, is not available in the country or the available amount is insufficient*<sup>12</sup>. This Decree establishes the criteria, modalities, and requirements that allow the importation and facilitate access to this type of essential and irreplaceable medicines for a patient or group of patients, through the exemption from marketing authorization, which has meant a social advance in terms of access to medicines that are difficult to obtain or those necessary to treat orphan diseases<sup>11</sup> which are defined as severe, life-threatening, and with a prevalence of less than 1 case per 5,000 people<sup>13</sup>. This Decree also contributes to safeguarding the right to health declared in 2015 through Statutory Law No. 1751, *by which the fundamental right to health is regulated, and other provisions are issued*<sup>7</sup>.

The National Institute for Food and Medicines Surveillance (INVIMA) is the entity that determines when a medicine is a MVND from three criteria mentioned in Article 4 of Decree N° 481: a) That it is not in the clinical research phase; b) That it is not sold in the country or, if sold, the amounts are insufficient to meet the needs; c) That it does not have substitutes in the market. INVIMA also periodically publishes the MVND list and receives import applications of

MVND, which can be submitted under three modalities: authorized import for a specific patient, for exclusive use in clinical emergency, and for more than one patient<sup>12,14</sup>.

This study aims to characterize the MVND import applications received by INVIMA in 2016 and 2017 and the costs of this type of medicines required by lawsuits and reimbursed by ADRES in the same period.

## Materials and methods

This is a retrospective, descriptive, and cross-sectional observational study. The databases of MVND import applications and the reimbursements of MVND requested through lawsuits were requested from INVIMA and ADRES based on the provisions of article 7 of Law No. 1,712/2014<sup>15</sup>. For the characterization of the MVND import applications during 2016 and 2017, we obtained data on the type of application; decisions made regarding the request; applicant type, whether it was a natural or legal person, and in the second case, the type of company and the economic activity it engaged in.

Also, the prescribing doctors, the patient's diagnoses, and the medicine (identified by the non-proprietary name) requested were characterized, the latter based on the ATC codes registered in the database. Data on the SGSSS regime to which the beneficiary patient belonged (contributory, subsidized, or exception) were also collected by searching the Unique Insured Database (BDUA)<sup>13</sup>. The study period was defined by the availability of a database of MVND applications at INVIMA. For the characterization of the costs to the SGSSS associated with the reimbursement of MVND requested by lawsuits in the contributory regime, the number and date of lawsuit ruling received for each year were considered vs. the value reimbursed, the diagnoses reported vs. reimbursed value and the value in health spending. The values were converted to U.S. Dollars at an exchange rate of 2,951 pesos (mean value of the US\$ in 2017)<sup>16</sup>.

Concerning ethical considerations, according to what is established in article 11 of Resolution 8430/1993 (17), this study is considered a risk-free investigation. The database was under the custody of a researcher on a single computer under the provisions of Law 1581/2012<sup>18</sup> to safeguard the identity of the patients benefiting from the applications. Once the health system regime to which the patients belonged was searched,

the database was anonymized, and the analysis were carried out with this version of the INVIMA database. The ADRES database was provided anonymized by the entity. The variables were analyzed by descriptive statistics with Microsoft Excel<sup>®</sup> 365 software.

## Results

### Distribution by type of application and result of the technical study of the application

A total of 2321 applications were identified in the INVIMA database of import applications for MVND during 2016 and 2017, 1,342 in 2016, and 979 in 2017. Of the total, 11% (n=250) corresponded to applications for more than one patient, 68% (n=1,572) for a specific patient, and 21% (n=499) for clinical emergency. Around 76% (n=1,754) were authorized, 18% (n=427) denied for not meeting the criteria established in the Decree, and 6% (n=132) was resolved by tacit withdrawal, which is granted when the user does not present a response once the terms of an application have expired, and 0.3% (n=8) by express withdrawal, granted at the request of the petitioner. Also, at least 2% (n=35) of the 1,754 authorizations granted in the two years of study were in response to a court ruling, that is, lawsuits where the judge ordered INVIMA to authorize the application, regardless whether or not the application met the requirements stipulated in Decree N° 481/2004.

### Characteristics of applicants

A total of 88 applicants were identified, of which five (5.7%) corresponded to patients, and the remaining 83 (94.3%) were companies whose main economic activity in most cases (n=57; 69.5%) was "wholesale trade of pharmaceutical, medicinal, cosmetic, and personal care products". In general (n=80; 97.6%), the applicant companies developed activities related to the provision of health services or the medicines manufacture and marketing; economic activities barely related to the pharmaceutical and medical fields were evidenced only in a couple of cases (2.4%). The five companies that with the most import applications in the two years of the study accounted for more than half (n=1,275; 54.9%) of all the applications filed with INVIMA.

### Therapeutic subgroups and active ingredients most in demand

In the 2,321 applications, 195 medicines belonged to 73 therapeutic subgroups (level 3 of the ATC code). One hundred thirty-five (68.05%) of the total medicines were not included in the MVND list defined by INVIMA. The ten most requested therapeutic subgroups correspond to 64% (n=1,493) of the total applications (Table 1). The most requested groups of medicines correspond to other antineoplastic agents, that is, medications used for the treatment of cancer (n=535; 23.0%). Next are direct-acting antivirals (n=208; 8.9%), which are indicated to treat chronic hepatitis C virus infection. Table 2 lists the ten most requested medicines by type of application.

### SGSSS regime to which the beneficiary patients belonged

This analysis could be carried out in the 2,071 applications corresponding to a single patient or clinical emergency. Around 66.6% (n=1,547) of the patients were insured in the contributory regime, and to a lesser extent to the subsidized (15%; n=347) and the special or exception regimes (8%; n=177). The remaining 250 applications corresponded to applications for more than one patient, that is, applications in which clinical information is not received from patients under the requirements established in Article 10 of Decree N° 481/2004.

### Number of prescribing doctors

Seven hundred prescribing physicians who prescribed MVNDs at least once were identified in the 2,321 MVND applications, 29 of them had prescribed this type of medication more than ten times. Doctors with the highest number of prescriptions of MVNDs (above 20) were associated with the specialty of clinical genetics (n=30; 1.4%), followed by human genetics (n=26; 1.3%), immunology-allergology (n=24; 1.2%) and internal medicine-hematology (n=22; 1.1%).

### Most frequent diagnoses

This analysis was performed on 2,100 applications (2,071 applications for specific patient and clinical emergency, and 29 applications for multiple patients for which the pathology in which the medicine would be used was reported). A total of 368 different diagnoses were identified, and the ten most frequently declared, corresponding to 38.6% (n=810) of the applications, are described in Table 3. The most frequent pathology was acute lymphoblastic leukemia (ICD-10: C910), for which a wide range of medicines belonging to the therapeutic subgroup L01X-*other antineoplastic agents*, such as pegylated asparaginase, asparaginase Erwinia and Blinatumomab were requested, besides other medicines belonging to the therapeutic subgroup L01A-*alkylating agents*, such as Thiotepa and Busulfan, which, unlike the former, are not expensive. The second most frequent pathology was muscular dystro-

**Table 1.** Most requested therapeutic subgroups according to the ATC.

ATC	Description	2016	2017	Total
L01X	Other antineoplastic agents	323	212	535 (23.0%)
J05A	Direct-acting antivirals	134	74	208 (8.9%)
M09A	Other drugs for disorders of the musculo-skeletal system	71	41	112 (4.8%)
C01E	Other cardiac preparations	44	64	108 (4.6%)
A16A	Other Alimentary Tract and Metabolism Products	53	49	102 (4.4%)
L01A	Alkylating agents	67	33	100 (4.3%)
L04A	Immunosuppressants	73	16	89 (3.8%)
B06A	Other hematological agents	31	43	74 (3.2%)
C03X	Other diuretics	44	19	63 (2.7%)
C05B	Antivaricose therapy	33	18	51 (2.2%)
C02D	Agents acting on arteriolar smooth muscle	30	21	51 (2.2%)
Total				1,493 (64%)

Source: Authors' elaboration.

**Table 2.** Most requested medicines by type of application.

Specific patient				Clinical emergency exclusive use				More than one patient						
ATC	Active ingredient	ILM VND*	No. of applications (%)	ATC	Active ingredient	ILM VND*	No. of applications (%)	ATC	Active ingredient	ILM VND*	No. of applications (%)	2016	2017	Total
J05AX15	Sofosbuvir	No	78 (8.6%)	L01XX02	Pegylated asparaginase	Yes	55 (16.8%)	V01AA20	Allergenic extracts	Yes	65 (13.0%)	10	17	27
M09AX03	Ataluren	No	65 (7.2%)	L01XE31	Nintedanib	No	46 (14.1%)	V03AF03	Calcium folinate	Yes	56 (11.2%)	10	5	15
C01EB09	Ubiquinol liposomal	No	26 (2.9%)	B06AC01	C1 Esterase inhibitor	No	16 (4.9%)	L01AB01	Busulfan	Yes	41 (8.2%)	25	5	30
C03XA01	Tolvaptan	No	44 (4.9%)	J05AX15	Sofosbuvir	No	26 (8.0%)	L01AC01	Thiotepa	Yes	29 (5.8%)	3	9	12
L01XX02	Pegylated asparaginase	Yes	44 (4.9%)	L01XC17	Nivolumab	No	28 (8.6%)	L01XX02	Pegylated asparaginase	Yes	28 (5.6%)	-	2	2
C02DA01	Diazoxide	Yes	29 (3.2%)	L04AX06	Pomalidomide	No	20 (6.1%)	M03CA01	Dantrolene sodium	Yes	25 (5.0%)	5	5	10
C05BA04	Pentosan polysulfate	Yes	32 (3.5%)	L01XC19	Blinatumomab	No	17 (5.2%)	B02BB01	Coagulable fibrinogen	Yes	23 (4.6%)	6	2	8
L01XX23	Mitotane	Yes	24 (2.7%)	L01DB02	Daunorubicin (liposomal)	No	12 (3.7%)	V08DA01	Nanocolloid human serum albumin	Yes	21 (4.2%)	9	2	11
C10AX12	Lomitapide	No	43 (4.8%)	L01XC24	Daratumumab	No	4 (1.2%)	J06BB03	Human immunoglobulin against varicella-zoster	Yes	18 (3.6%)	14	4	18
L04AX05	Pirfenidone	No	41 (4.5%)	J05AB12	Cidofovir	No	5 (1.5%)	J05AD01	Foscarnet	Yes	16 (3.2%)	11	3	14
Total			426 (47.1%)	Total			229 (70.0%)	Total			322 (64.5%)	93 (54.1%)	86 (61.4%)	147 (58.8%)

Source: Author's elaboration.

phy (ICD-10: G710). In the registered applications, most of the requested medications belong to the therapeutic subgroup M09A-*Other drugs for disorders of the musculo-skeletal system*, such as Ataluren and other medications like Creatine Monohydrate and Liposomal Ubiquinol. For Chronic Type C Viral Hepatitis (ICD-10: B182), the most requested drugs correspond to the therapeutic subgroup J05A-*direct-acting antivirals*, mainly Sofosbuvir, Sofosbuvir + Ledipasvir, and Elbasvir.

#### Costs in the SGSSS associated with reimbursements applications of MVNDs granted by lawsuits

Once the information provided by the ADRES had been analyzed, 1,254 reimbursement applications of MVND granted by lawsuits were identified during the two years of study, which would cost the SGSSS US\$ 8,577,583 in total. Of these, in 2016, a reimbursement was requested for 710 (56.6%) that totaled US\$ 5,088,419, and in 2017 for 544 (43.4%) that amounted to US\$ 3,489,164. For 1,154 lawsuits (92%), the judicial decision was taken before 2016. Therefore, the database included lawsuits with court rulings from 1999 onwards and filed for reimbursement during 2016 and 2017. The years that concentrated lawsuits the most were 2008 (n=130, 10.4%), 2013 (n=136, 10.8%), 2014 (n=202, 16.1%), and 2015 (n=165, 13.2%), and 2016 and 2017 included 93 and 7 lawsuits, respectively, since the EPS application to request reimbursement takes a certain time. Based on the information provided by ADRES, in the 2016-2017 period, an equivalence of the amount requested in the UPC was

made. We found that the 2016 costs were equivalent to 24,680 UPCs, while 2017 totaled 13,803 UPCs. (Mean of 33,993 UPCs).

#### Reported diagnoses vs. recovered value

The description of the MVNDs from which the reimbursement was requested was not found in the database provided by ADRES, so we could not identify the medicines applied for. However, we managed to infer some of the medications involved from the diagnoses related to the reimbursement. A total of 176 diagnoses were identified, and the most reported was Morquio Syndrome or Mucopolysaccharidosis (n=72; 5.7%) with a total cost of 22.6% (US\$ 1,957,682) of what was demanded in the two years (Table 4). Ten of the diagnoses concentrated a large part of the percentage of reimbursements (77.9%) (Table 4), and the remaining 166 were associated with only 22.1% of the value.

#### Discussion

Ensuring a mechanism that would allow a sufficient supply of medicines that are difficult to obtain, which due to low frequency of use and low profitability in their sale were not of sufficient interest for research, development, production, and marketing in Colombia<sup>12</sup> was what motivated the enactment of Decree 481/2004. However, once the base of the applications is reviewed, it is evident that the term MVND is not limited to low prevalence medicines. It has also been used for medicines in a situation of shortage that had a marketing authorization at one time and, in

**Table 3.** Most reported dDiagnoses reported in the applications.

ICD-10	Diagnosis	2016	2017	Total
C910	Acute lymphoblastic leukemia	101 (7.5%)	60 (6.1%)	161 (6.9%)
G710	Muscular dystrophy	78 (5.8%)	55 (5.6%)	133 (5.7%)
B182	Chronic viral hepatitis C	71 (5.2%)	50 (5.1%)	121 (5.2%)
T783	Angioneurotic edema	33 (2.5%)	56 (5.7%)	89 (3.8%)
J841	Other interstitial pulmonary diseases with fibrosis	56 (4.2%)	12 (1.2%)	68 (2.9%)
C900	Multiple myeloma	30 (2.2%)	23 (2.3%)	53 (2.2%)
E780	Pure hypercholesterolemia	48 (3.6%)	3 (0.3%)	51 (2.2%)
C919	Lymphoid leukemia, unspecified	45 (3.4%)	3 (0.3%)	48 (2.0%)
J849	Interstitial pulmonary disease, unspecified	38 (2.8%)	6 (0.6%)	44 (1.8%)
N301	Interstitial cystitis (chronic)	30 (2.2%)	12 (1.2%)	42 (1.8%)
	Total	530 (42.9%)	280 (32.3%)	810 (38.6%)

Source: Authors' elaboration.

other cases, for new drugs that wish to be included for use in the country without having the marketing authorization, bypassing procedures required by law that demand a more extended study time, which is corroborated by the delay in the registration in Colombia compared to the FDA and the EMA.

The behavior of the import applications for MVND varied in the two years of study. Filing for specific patients and clinical emergencies decreased against the previous year, and the applications for several patients increased. According to the provisions of Decree N° 481/2004, the import authorization requests for multiple patients allow importing the same medicine for different patients by making a single payment in the application that, under the requirements established in Article 10 of the Decree mentioned above does not require the presentation of medical information (medical records and medicine prescription), facilitating filing the procedure but increasing the difficulties for the INVIMA to monitor the authorized medications. In the case of requests for specific patients and clinical emergencies, the interested party presents the medical records of the patient but not a certificate of analysis or batch number; that is, the quality of the imported medicine cannot be verified through a certificate of analysis or traceability to the imported product with the batch number.

Considering that most of the applications (76%; n=1,754) submitted to INVIMA were au-

thorized, it can be inferred that access to medicines is part of the right to health, and well-being in Colombia, as well as in other South American countries<sup>19</sup>. However, when observing that at least 2% of the authorizations were granted through the courts, it is clear that the import requests possibly obey more administrative and non-health criteria, considering that judges decide the need and relevance of the medicine in these requests, without considering effective and safe therapeutic alternatives, influencing a profitable business of interest to the pharmaceutical industry and with little benefit to the health of patients. Likewise, the use of this mechanism underestimates the capacity of the health authorities by ignoring or omitting the technical criteria that justify the non-supply of the medicine<sup>20</sup>, mismatching the role of each entity within the State organization.

On the other hand, the characterization of the number of applications per applicant showed that the market for unavailable vital medicines behaves like an oligopoly because while the Decree establishes that any natural or legal person can make the request, in practice, marketing and access still depend on a few suppliers<sup>21</sup>. Likewise, the fact that at least 1% of the applicants reported the main activity was unrelated to selling or importing medicines shows that imports can be made by any person or company, whether competent or not.

Concerning the most requested groups of medicines, the fact that there are “other antineoplastic

**Table 4.** Most reported diagnoses vs. recovered reimbursement value requested.

ICD-10	Description	Number of judicialization actions			Recovered Value	%
		2016	2017	Total		
E762	Other mucopolysaccharidoses	42	30	72 (5.7%)	\$ 5,777,745,272	22.8%
E763	Mucopolysaccharidosis, unspecified	28	9	37 (3.0%)	\$ 3,525,649,266	13.9%
E780	Pure hypercholesterolemia	6	15	21 (1.7%)	\$ 3,124,132,336	12.3%
T783	Angioneurotic edema	1	25	26 (2.1%)	\$ 2,440,880,985	9.6%
E760	Mucopolysaccharidosis, type I	15	5	20 (1.6%)	\$ 1,584,066,210	6.3%
M353	Polymyalgia rheumatica	4	4	8 (0.6%)	\$ 937,389,110	3.7%
C910	Acute lymphoblastic leukemia	4	5	9 (0.7%)	\$ 778,403,633	3.1%
K732	Chronic active hepatitis, not elsewhere classified	12		12 (1.0%)	\$ 606,386,816	2.4%
E770	Defects in post-translational modification of lysosomal enzymes	44	19	63 (5.0%)	\$ 597,336,363	2.4%
Z000	Encounter for general adult medical examination	3		3 (0.2%)	\$ 362,668,152	1.4%
Total		159	112	271 (21.6%)	\$ 19,734,658,143	77.9%

Source: Authors' elaboration.

agents” and “direct-acting antivirals” is consistent with the information provided by the Ministry of Health, which indicates that cancer is the most critical public health problem in Colombia<sup>22</sup>. On the other hand, chronic infection by the hepatitis C virus is one of the leading causes of chronic liver disease, liver cirrhosis, and hepatocellular carcinoma globally<sup>23</sup>. In Colombia, the National Institute of Health reported 287 cases in 2016<sup>24</sup>.

The most requested medicine for exclusive use in clinical emergencies, pegylated asparaginase (n=124; 7.9%), obtained its health registry in 2017<sup>25</sup>. However, this product obtained approval in 1994<sup>26</sup> in countries such as the U.S. The 23-year difference is staggering considering the advantage of this medicine over other types of asparaginase (produced by *Escherichia coli* and that produced by *Erwinia chrysanthemi*)<sup>27</sup>. The EMA Committee for Medicinal Products for Human Use (CHMP) recommended its marketing authorization in 2015<sup>28</sup>. Sofosbuvir (n=65; 13.0%), the most requested medicine for a specific patient, obtained a marketing authorization in 2017 (25), four years after it was approved by the U.S.<sup>29</sup> and three years after the EMA (30). These delays in the application for marketing authorization could be related to the fact that the exemption of registration of the MVNDs does not allow adequate control of their prices since it does not have the Unique Code of Medicines-CUM<sup>31</sup> with which sale in the country is monitored, including the report on purchase and sale prices, the number bought and sold, and reimbursement in the ADRES, through the Medicines Price Information System-SISMED, information that is key to the application of price control regulation<sup>32</sup>.

The most requested medications for multiple patients during the two years of study were allergenic extracts, which are indicated for different allergic conditions such as hypersensitivity to insect bites, allergic asthma, rhinitis, and conjunctivitis<sup>33</sup>. Therefore, we have several extracts with different components, which hinders identifying the authorization date in each country. However, this type of product not having a marketing authorization in Colombia to date causes a stir.

On the other hand, access to MVNDs seems to be related to the SGSSS regime in which the patient is insured, since most of the patients registered in the import applications belong to the contributory regime, showing inequality in insurance coverage<sup>34</sup> and the need to resort to the Judiciary to guarantee access to medicines<sup>5</sup>.

Regarding the prescribing doctors involved, medical specialties that request medicines the

most correspond to those that treat genetic disorders, typically considered rare diseases, which could show that the implementation of Decree N° 481/2004 is fulfilling its objective. On the other hand, the results suggest that health professionals know new and alternative treatments to attend to specific pathologies, without these having a marketing authorization at INVIMA, even long before they are included in the list of unavailable vital medicines. This could be related to the fact that there is an influence of the pharmaceutical industry in medical practice with the involuntary or voluntary participation in the sale of new drugs<sup>35</sup>, and advertising is one of the primary sources of information for newly-marketed medicines<sup>36</sup>.

Based on the data of the reimbursement applications for MVND requested by lawsuits presented to ADRES 2016 and 2017, we observed that they are mostly not lawsuits issued during the same year. The analysis identified that requests for reimbursements were made for lawsuits resolved since 1999; that means in these cases, the medicines have been reimbursed since the date when the lawsuits was ruled.

Regarding the diagnoses and treatments, as indicated above, we could not access to the data of the medications that were effectively reimbursed. However, with the diagnoses reported in the ADRES database, we could infer some of the possible medications involved in the lawsuits. Product Vimizim® Elosulfase alfa was included in the MVND list in 2015<sup>37</sup> for the Morquio Syndrome or Mucopolysaccharidosis. It obtained marketing authorization in 2016<sup>25</sup>, at which time it lost its MVND status. This medicine has been considered a high-priced one, with a mean price per vial of US\$ 941. In 2016, for treating people with a diagnosis of hypercholesterolemia, Lomitapide was authorized as MVND, which obtained a marketing authorization for the three concentrations requested in 2016<sup>25</sup>, losing the status of unavailable vital medicine. The importation of C1 Esterase Inhibitor and Conestat alfa is authorized as unavailable vital medicines for angioneurotic edema during the study years until now, and neither of them has a marketing authorization.

In the case of Active Chronic Hepatitis, Unclassified, it is assumed that applications for Sofosbuvir – Ledipasvir and Sofosbuvir were submitted, which have an INVIMA marketing authorization since 2017. We were unable to determine which medicines were requested by lawsuits for cases of Lymphoblastic Leukemia, defects in the post-translational modification of

lysosomal enzymes, Polymyalgia Rheumatica, and General Medical Examination. The medicines used for these pathologies have a high-profit margin due to the shorter clinical development time and the incentives related to research and development<sup>38</sup>. Thus, it is not clear whether litigation is granting the right to health or the pharmaceutical industry benefits through the life expectancy offered to patients by this mechanism, as mentioned by Vargas et al.<sup>5</sup>.

According to the report “*Structure of Health Expenditure in Colombia*”, the 2016 amount allocated for the PBS-UPC benefit plan amounted to COP\$ 39 trillion (approx. US\$ 13,214,000,000) and COP\$ 3.5 trillion (approx. USD 1,185,000,000) for all benefits not included in the benefit plan. Based on the above, the mean health expenditure (COP\$ 12,657,595,648, approx. USD 4,288,000) in MVNDs requested by lawsuits corresponds to 0.36% of the budget allocated for the set of non-PBS-UPC benefits, which, as a unique mechanism, is high, even more so when we are only talking about medicines requested by lawsuits reimbursed by the ADRES in this discussion and not about all the MVNDs reimbursed by the health system at all. This discussion is also visible when we see that the equivalence with the UPC exceeds, on average, 10,000 units, which indicates the potential impact of MVND reimbursement on the SGSSS.

It should be noted that regulating MVNDs is challenging due to the lack of marketing authorization or CUM standardization. During the study period, it was not mandatory to report them to SISMED. In 2018, an attempt has been made to standardize medicines by implementing the Unique Medicine Identifier-IUM with Resolution N° 3.311, and one of its objectives was to facilitate the regulation and surveillance of prices.

It should be assigned by INVIMA to all medicine presentations sold and used in the country, including MVNDs<sup>39,40</sup>. While the resolution established that all medicines would be reported to SISMED as of January 1, 2020<sup>39</sup>, this mechanism has not yet been effective and does not contribute to price regulation. Castillo and González<sup>41</sup> argue that the issue of IUM codes is still not sufficiently clear, and drug manufacturers do not have information.

## Conclusions

The behavior of import applications for MVNDs recognizes the effort made by Colombian legislation to ensure access to medicines. However, the import application of these medicines presented by any natural person or type of company expose the need to define criteria, which establish that this type of request must be filed by competent persons in the subject, guaranteeing the correct use. On the other hand, the medicines most requested by this mechanism reflect the existing shortcomings in the access of new technologies in the face of public health problems, such as cancer and hepatitis C. The results also showed that the implementation of Decree N° 481/2004 is not alien to the structural inequalities of access to health services and medicines of the SGSSS since most of the patients are insured with the contributory regime. Finally, without having the data on the cost of the MVND requested by lawsuits reimbursed by the SGSSS and starting only from those presented to the ADRES, it is evident that these medicines impact public health and the allocated budget, either because of the high cost of importing them or the lack of regulation of these medicines within the national market.

## Collaborations

LA Olivares, JJ López, and CM Vargas-Peláez conceptualized the study. LA Olivares, CM Vargas-Peláez, and F Rossi designed the methodology. LA Olivares, CM Vargas-Peláez, and F Rossi made the arrangements to have access to the INVIMA and ADRES databases. LA Olivares and CM Vargas-Peláez analyzed the data. LA Olivares, MF Chacón-Garzón and CM Vargas-Peláez were responsible for drafting the paper. F Rossi and JJ López contributed to the analysis of the results. All authors made a critical review and approved the final version of the manuscript, including tables and figures.

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## ERRATUM

p. 5441,

### where it reads:

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