Rare Diseases: The urgency of access to health

February 2018
ABOUT THE COMPANY

INTERFARMA is the Pharmaceutical Research Industry Association, a non-profit sectorial entity that represents 51 associates, companies and researchers, which seek to promote and encourage research, development and innovation focused on the production of pharmaceutical inputs, raw materials, medicines and products for human health. In order to be part of the entity, one must implement researches, development and innovation, adhering to the Association Code of Conduct.
“Action is key for every success”

Pablo Picasso
Presentation

Five years after the publication of the first study related to the construction of a National Policy for Rare Diseases in Brazil, INTERFARMA - the Pharmaceutical Research Industry Association - maintains its vigilance and effort towards the endeavor, collaborating intensely with authorities, scientists, patients and others interested in the cause.

At the request of INTERFARMA, IMS Health, current IQVIA, and Prospectiva Consultoria have done a due diligence to identify the traits, experiences, priorities, and advances that occurred in the period. To do so, they delved into primary and secondary data from a variety of sources, bills, and interviews with relevant agents, such as patient associations. The effort has led to this document, with two major biases.

The first one is the result achieved in the last five years. The cause of rare diseases has gained pace and strength, filling an important space on the agenda of the National Health Surveillance Agency (ANVISA), the Ministry of Health and the National Congress. In addition, it is necessary to emphasize, in particular, Ordinance 199/14, that brought the breath for a fight begun decades ago.

On the other hand, the study also fulfills the role of identifying and showing the path that still needs to be taken in order to adopt a strong and expressive National Policy. However, the barriers ahead are insignificant in the face of the capacity for achievement, obtained through the joint action of the protagonists of that history, namely patients, governments, scientists, industry, among other agents. The mobilizing power of society, willing to assert its rights, will be fundamental for advancing the discussions and decisions in 2018, but like every election year, attention should be more dispersed after June.

In view of this, INTERFARMA reinforces its commitment to the adoption of a National Policy for Rare Diseases, being attentive and active in several forums, seeking to clarify and contribute with governmental authorities, parliamentarians, scientists and patients to broaden access to treatments.

Enjoy your reading!
Care for Brazilians’ health is for us, INTERFARMA, much more than a commitment written on a sheet of paper. It is a daily exercise of empathy and resilience to understand the reality of the various actors and to co-create a solution.

The urgency of the issue is indisputable: Justice is the only way out for a good part of the 13 million Brazilians with rare diseases for access to treatment. Between 2010 and 2017, the total expenses of the Union with lawsuits were over R$ 5.2 billion. This amount becomes ridiculous in face of the social cost imposed by the diseases not only to the patient, but also to their relatives.

It is this painful reality that we want to contribute to change. Some challenges may be old acquaintances of those who follow the question, but we always look for a new look at the dilemmas, which can be seen by our intense content production.

Since 2012, INTERFARMA has invested in world studies, which are adapted to Brazilian legislation and reality. In this endeavor, which portrays the national reality, we establish partnerships, identify synergies and seek dialogues with different actors, in different instances. We travel between ANVISA and the National Commission of Justice, between the Ministry of Health and the National Congress, between our house and that of patients, albeit indirectly. With information, ethics and transparency, we seek to create the most difficult bond of all: trust.

This study that comes to your hands is part of this effort to pave the way towards a National Full Care Policy for People with Rare Diseases. The breakthroughs may be small yet, but, one by one, the barriers to expanding health care and pharmaceuticals for 13 million patients are falling; expanded by a collective, consistent and tireless effort, their voices are finally being heard.

Maria José Delgado Fagundes
Director – INTERFARMA
Introduction

On January 30, 2014, the Ministry of Health published Ordinance 199, which instituted the Integral Attention Policy to People with Rare Diseases in the Unified Health System (SUS or UHS). The measure was an important step in expanding specific and differentiated care for rare disease patients in Brazil. It was also a recognition of the work carried out by various agents of society to increase interest in the study, diagnosis and treatment of diseases that affect about 13 million people in the country.

For a long time, the issue was restricted to small circles and became part of the government’s agenda only from the 1980s. With the promulgation of the Orphan Drug Act in 1983, the United States pioneered the creation of access policies, followed by Japan (1993), Canada (1996), Australia (1998) and China (1999). In Brazil, the need to include programs that benefited these patients began to be discussed around 2000. Four years later, the Ministry of Health created a working group to systematize a proposal, which was avenged in 2009. Received with hope by patients, The National Attention Policy to Clinical Genetics in SUS did not take into account the diversity and specificities of the universe of rare diseases, failing to occupy a more relevant position in the national public health agenda.

This game began to change with the publication of Ordinance 199 in 2014, when the country started to have its own concept of rare disease, the outline of a network of services to adequately serve patients and more space for civil society’s, academia and decision-makers’ engagement. The advances, achieved even in a troubled political-economic environment, are recognized by the patient associations and can contribute, as the Ordinance proposes, for the reduction of mortality, decrease of morbimortality and secondary manifestations and for the improvement of people’s quality of life.

However, one may observe that some structural bottlenecks remain and need to be addressed to ensure full care, such as the structuring of the network of specialized centers, the evolution in the process of elaboration and publication of clinical protocols that define the treatment of rare diseases as a priority, and overcoming regulatory challenges related to orphan drugs, which increase judicialization and cause harmful social and economic costs to families and the country.

Given the delicacy and urgency of the matter, it is important to listen to those who suffer from this situation. Therefore, patients’ vision, through the voice of their representations (patient associations), is highlighted throughout this document. Five patient associations have been heard and their experiences will be told in short excerpts. The preservation of their respective identities does not hinder the significant testimony.

It is also important to note that the experience of other countries casts light on some challenges and can help speed up the discussions. The promulgation of the 14 bills under the National Congress, along with the improvement of the protocols and guidelines for
a national program for treating rare diseases by SUS, are fundamental to guarantee the full care of patients.

**Ordinance 199/14**

Since 2014, Brazil has its own definition of rare diseases. Illnesses with a prevalence of up to 65 people per 100,000 inhabitants are given this name.

The objectives of the Ordinance are:

- Ensuring universality, completeness and equity of health actions and services in relation to people with rare diseases, with a consequent reduction of morbidity and mortality;
- Establishing care guidelines for people with rare diseases, at all levels of SUS care;
- Providing comprehensive health care for people with rare diseases in the Health Care Network (RAS);
- Broadening universal and regulated access for people with rare diseases to SAR;
- Making sure that people with rare diseases, in a timely manner, have access to the diagnostic and therapeutic resources available to them;
- Qualifying care for people with rare diseases.

**Rare Diseases According to Some Countries**

- **USA**
  
  Up to 66 people/100,000 individuals

- **European Union**
  
  Up to 50 people/100,000 individuals

- **Brazil**
  
  Up to 65 people/100,000 individuals

These names are given to those diseases with a low prevalence in a population. The quantity may vary according to the legislation in force, in each country. With a universal public health system, Brazil opted for a broad definition: up to 65 people per 100,000 inhabitants, a conception different from that adopted by, for example, the United States and the European Union.

This apparently irrelevant data is the main guideline for defining the scope and amplitude of official policies for these diseases. More in-depth discussions about the need to adopt specific rules regarding sanitary registration, price fixing and incorporation of technologies into the health system may facilitate or hinder, in the case of Brazil.
Rare diseases in figures

- **75%** Children and youngsters
- **6-8%** Population
  - 420-560 million individuals
- **80%** with a genetic origin
- **20%** infectious, viral and degenerative causes
- **7-8k** Rare diseases in the world

13 million Brazilians

More than the population of the city of São Paulo, twice that of Rio de Janeiro, four times that of Salvador and nine times that of Porto Alegre
Universalizing care for patients with rare diseases inevitably requires a policy that addresses both care and treatment and the expansion of the supply of orphan drugs. The effects of Ordinance 199/14 are, to date, restricted to one of the strands, as numerous regulatory obstacles continue to make it difficult for medicines to enter the SUS and patients’ access.

### Service Networks

Ordinance 199/14 proposed the creation of two types of services: Specialized Care in Rare Diseases and Reference in Rare Diseases, which differ in relation to the treatment offered, staff and defrayal.

Each service must be accredited by local managers before being authorized by the federal manager. The average time between stages is around 1 year and 2 months. The maintenance of the services offered has a direct dependence on government transfers.

### SPECIALIZED CARE AND REFERENCE SERVICES FOR RARE DISEASES IN SUS

<table>
<thead>
<tr>
<th>Category</th>
<th>Specialized care service in rare diseases</th>
<th>Reference service in rare diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>One or more rare diseases</td>
<td>At least two groups from the axis of rare diseases of a genetic origin; or at least two groups from the rare disease axis of non-genetic origin; or at least one group for each axis.</td>
</tr>
<tr>
<td>Minimum Team</td>
<td>At least one nurse, one nursing technician, physician and/or medical technician</td>
<td>At least one nurse, a nursing technician, a geneticist, a medical specialist, a neurologist, a pediatrician, a general practitioner, a psychologist, a nutritionist, a social worker, a medical technician</td>
</tr>
<tr>
<td>Defrayal (month/month)</td>
<td>R$ 11,650.00 + R$ 5,750.00 (per additional service within the same establishment)</td>
<td>At most R$ 41,480.00</td>
</tr>
<tr>
<td>Accredited Units</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Authorized Units</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

Source: Ordinance 199/2014, Federal Official Gazette (DOU) and report of state entities (CIB) and municipalities (Health Departments) to accredit centers.
Since the publication of Ordinance 199/14, there has been a clear geographical limitation of the Reference Services. There are only seven hospitals, located in the states of São Paulo, Pernambuco, Goiás, Rio de Janeiro, Paraná and Rio Grande do Sul, as well as the Federal District. In addition to not understanding all the regions of the country, the qualified institutions are not, in some cases, in the capital of that state, which makes it difficult for patients to access them.

Source: Federal Official Gazette (DOU) and report of state entities (CIB) and municipal agencies (Health Secretariats) to accredit centers.
## HOSPITALS ENHANCED AS REFERENCE SERVICES IN RARE DISEASES

<table>
<thead>
<tr>
<th>Location</th>
<th>Association</th>
<th>Specialty</th>
<th>Patients</th>
<th>Accreditation</th>
<th>Authorized on</th>
<th>Timing (in months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curitiba, PR</td>
<td>Pequeno Príncipe Hospital</td>
<td>- Congenital anomalies&lt;br&gt;- Intellectual Disability&lt;br&gt;- Inborn Errors of Metabolism&lt;br&gt;- Genetic counseling</td>
<td>2,640/year</td>
<td>01/29/2016</td>
<td>10/17/2016</td>
<td>9</td>
</tr>
<tr>
<td>Recife, PE</td>
<td>Association of Assistance to Disabled Children - AACD</td>
<td>- Inborn Errors of Metabolism&lt;br&gt;- Rare Inflammatory Diseases&lt;br&gt;- Infectious Rare Diseases</td>
<td>1,670/year</td>
<td>03/18/2015</td>
<td>10/19/2016</td>
<td>19</td>
</tr>
<tr>
<td>Anápolis, GO</td>
<td>Association of Parents and Friends of Exceptional Children</td>
<td>- Congenital anomalies or late manifestation&lt;br&gt;- Intellectual Disability Associated with Rare Diseases&lt;br&gt;- Inborn Errors of Metabolism&lt;br&gt;- Infectious Rare Diseases</td>
<td>130 currently registered</td>
<td>12/04/2014</td>
<td>10/19/2016</td>
<td>22</td>
</tr>
<tr>
<td>Santo André (SP)</td>
<td>Specialty Ambulatory of FUABC/ABC/Santo André Medical School</td>
<td>- Intellectual Disability associated with Rare Diseases&lt;br&gt;- Inborn Error of Metabolism (IEM)&lt;br&gt;- Rare Inflammatory Diseases&lt;br&gt;- Self-immune Rare Diseases</td>
<td>1,680/year</td>
<td>02/19/2016</td>
<td>11/29/2016</td>
<td>9</td>
</tr>
<tr>
<td>Rio de Janeiro (RJ)</td>
<td>National Institute of Women, Children and Adolescents’ Health, Fernandes Figueira (IFF)</td>
<td>- Congenital anomalies or late manifestation&lt;br&gt;- Intellectual Disability associated with Rare Diseases&lt;br&gt;- Inborn Error of Metabolism (IEM)</td>
<td>Data unavailable</td>
<td>10/23/2015</td>
<td>12/28/2016</td>
<td>14</td>
</tr>
<tr>
<td>Brasília (DF)</td>
<td>Support Hospital of Brasilia</td>
<td>- Congenital anomalies or late manifestation&lt;br&gt;- Intellectual Disability associated with Rare Diseases&lt;br&gt;- Inborn Error of Metabolism (IEM)&lt;br&gt;- Rare Inflammatory Diseases&lt;br&gt;- Self-immune Rare Diseases</td>
<td>1,400/year</td>
<td>05/24/2016</td>
<td>12/29/2016</td>
<td>7</td>
</tr>
<tr>
<td>Porto Alegre (RS)</td>
<td>Hospital das Clínicas from Porto Alegre</td>
<td>- Congenital anomalies or late manifestation&lt;br&gt;- Intellectual Disability associated with Rare Diseases&lt;br&gt;- Inborn Error of Metabolism (IEM)</td>
<td>Data unavailable</td>
<td>05/08/2015</td>
<td>12/29/2016</td>
<td>19</td>
</tr>
</tbody>
</table>

To date, the structure of the centers has not been satisfactorily implemented by some factors:

(a) delays in the development and publication of clinical protocols (PCDT to define rare diseases considered to be a priority.

(b) delay in the accreditation of centers, preventing the transfer of funds for operation.

There are at least ten accredited hospitals between November 2015 and December 2017 waiting for authorizations from the Ministry of Health: two in Bahia, two in Rio de Janeiro,
one in Ceará, one in Goiás and four in São Paulo - two of which are located in the Capital.

The territorial extension of the country, the difficulty in specialized care, the delay in treatment, the worsening of clinical conditions with greater use of hospital services, social security expenditures, delays in training, capability and accreditation of services generate financial costs and emotional exhaustion, culminating in the obtainment of medicines by judicial means.

For patient associations, Ordinance 199/2014 represented a breakthrough in the theory, as it presents, in practice, failures in the effective deployment of the measures, such as delays in the protocols, delays in the certifications of reference hospitals due to bureaucratic problems, delays in the training of teams and lack of specialists, including geneticists. These groups that provide relevant assistance to patients and their families call for training of evaluation and control teams, as well as more transparency in decisions. They also highlight the variety of factors that can influence, positively or negatively, in this process.

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**SERVICES AWAITING TO BE ALLOWED BY THE MINISTRY OF HEALTH**

<table>
<thead>
<tr>
<th>City</th>
<th>Hospital</th>
<th>Entity</th>
<th>Accreditation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvador</td>
<td>University Hospital Professor Edgard Santos – HUPES</td>
<td>Bipartite Intermanagement Commission of Bahia</td>
<td>11/19/2015</td>
</tr>
<tr>
<td>Salvador</td>
<td>Association of Parents and Friends of Exceptional Persons - APAE</td>
<td>Bipartite Intermanagement Commission of Bahia</td>
<td>02/17/2016</td>
</tr>
<tr>
<td>São Paulo</td>
<td>Hospital das Clinicas at FMUSP</td>
<td>Municipal Health Department of São Paulo</td>
<td>03/18/2016</td>
</tr>
<tr>
<td>São Paulo</td>
<td>Heart Institute/ Hospital das Clinicas at FMUSP</td>
<td>Bipartite Intermanagement Commission of the State of São Paulo</td>
<td>04/27/2016</td>
</tr>
<tr>
<td>Rio de Janeiro</td>
<td>University Hospital Clementino Fraga Filho</td>
<td>Bipartite Intermanagement Committee of the State of Rio de Janeiro</td>
<td>05/30/2016</td>
</tr>
<tr>
<td>Goiânia</td>
<td>General Hospital of Goiânia Dr. Alberto Rassi</td>
<td>Bipartite Intermanagement Commission of the State of Goiás</td>
<td>06/24/2016</td>
</tr>
<tr>
<td>Ribeirão Preto</td>
<td>Hospital das Clinicas from the Ribeirão Preto College, at the University of São Paulo</td>
<td>Bipartite Intermanagement Commission of the State of São Paulo</td>
<td>07/14/2016</td>
</tr>
<tr>
<td>Campinas</td>
<td>Hospital das Clinicas from UNICAMP</td>
<td>Bipartite Intermanagement Commission of the State of São Paulo</td>
<td>12/16/2016</td>
</tr>
<tr>
<td>Fortaleza</td>
<td>University Hospital Walter Cantidio from UFC</td>
<td>Bipartite Intermanagement Commission of the State of Ceará</td>
<td>07/07/2017</td>
</tr>
<tr>
<td>Rio de Janeiro</td>
<td>University Hospital Gaffrée and Guinle, from UNIRIO</td>
<td>Bipartite Intermanagement Commission of the State of Ceará</td>
<td>11/09/2017</td>
</tr>
</tbody>
</table>

Source: Reports of state entities (CIBs) and municipal entities (Health Secretariats) to accredit centers.
The average cost of each child treated in European public centers, organized from national plans, corresponds to 33% of the cost of treatment in a non-integrated program.

The international experience reinforces that the structuring of the network of specialized services is an important evolution, but also highlights the Brazilian fragility and slowness in the care of rare diseases. In 2001, Italy established a national network of free care centers for the prevention, diagnosis and treatment of rare diseases. Four years later, France approved a national plan for structuring reference centers in school hospitals, totaling 131 units distributed throughout the country. Germany has 16 research centers, while Norway, Denmark and Sweden invest in multidisciplinary clinics. According to the 2009 EURORDIS report, which brings together patient associations from 49 countries and representatives of 544 rare diseases, the average cost of each child treated in European public centers, organized from national plans, corresponds to 33% of the cost of treatment in a non-integrated program.
Access to Orphan Drugs

According to the Ministry of Health, there are currently 26 clinical protocols linked to rare diseases, of which 18 have been elaborated under the National Full Attention Policy to Clinical Genetics (PNAIGC). They offer access to 45 medicines, clinical and surgical treatments, 70,000 appointments and more than 560 laboratory procedures for diagnosis and treatment at an annual cost of more than 4 million reais.

According to the “Dossier of Rare Diseases and Orphan Drugs: Understanding the Brazilian Situation in the Global Context”, published by the IMS (current IQVIA), through June 2012, of the 18 diseases with a treatment protocol, only one, Gaucher Disease, incorporated orphan drugs. The remainder use symptomatic pharmacological drugs.

In 2017, nine rare disease drugs were incorporated, three of which are considered orphan by the FDA (North American Agency for Health Surveillance) - laronidase (Mucopolysaccharidosis Type I), idursulfase (Mucop-
polysaccharidosis Type II), and somatropin. Recently, in January 2018, the drug named Tafamidis (Familial Amyloid Polyneuropathy - PAF) was also added to this list.

According to patient associations, many PCDTS are shelved; others were discarded for lack of clear information or alternative treatment capable of justifying the protocol.

A Patient's voice

"Many of the protocols were not returned by the specialists responsible for the work. Some were returned with no conclusions."

It is also important to highlight that, even after the inclusion of a drug in SUS, access to the treatment can run into problems of management and logistics, which often affect the supply of the health network and compromise the treatment of patients. In recent years, the aggravation of the country’s economic crisis and the constant changes within the Ministry of Health have affected periodicity and the volume of purchases, impacting the availability of medicines for patients.

Sanitary Regulation

In Brazil, medicines can only be marketed after obtaining an ANVISA registration that certifies their safety, quality and efficacy and after obtaining the price registration at the CMED. Ordinance 199/14 did not provide a definition or set forth specific rules for orphan drugs. However, in December 2017, a resolution of the Agency’s Collegiate Board of Directors (RDC 205/17) established a special procedure for Rare Diseases, involving the approval of clinical trials, the certification of good manufacturing practices and registration of new drugs for treatment, diagnosis or prevention of rare diseases. And drugs registered through such criteria will be prioritized, with a deadline of up to 365 days to be marketed. The resolution, which is expected to come into force by March 2018, significantly reduces regulatory approval time.

As shown, there are currently 19 rare diseases with orphan drugs registered with ANVISA not yet incorporated into official treatment lines. The main justification, the cost of treatment, loses ground for the reality of the increase in the number of actions and the involvement of the Judiciary to access medicines or treatments.

Financial Regulation

The pharmaceutical sector in Brazil is regulated by the Medicine Market Regulation Chamber (MMRC), which establishes the entry prices and the maximum prices that can be practiced in the national market. For certain medicines, a Price Adjustment Coefficient (PAC), created by the CMED with the aim of standardizing the process of public procurement of medicines and making universal and egalitarian access a fundamental principle of the Unified Health System. In practice, the application of PAC is justified for medicines purchased by the public administration, mainly through centralized purchases, allowing a higher price discount according to the quantity of the product obtained.

It is noteworthy that the strategies for gain of scale are impaired in the acquisition of orphan drugs, which treat diseases that reach a small portion of patients. This prerogative also applies to the compulsory discount, which does not consider the specificities of such a particu-
lar niche market. It is worth mentioning that, in order for an orphan drug to be available in the health system for the population, it must undergo an incorporation process, as explained below.

**Mechanisms for Evaluating Technologies in Health**

Because they cover much smaller groups of users, the production costs of orphan drugs are considerably higher, jeopardizing effectiveness tests, which do not show any significant results.

The cost-effectiveness methodology, adopted by the International Commission for the Incorporation of Technologies in SUS (CONITEC), also does not apply to orphan drugs. Traditional technology assessment tools emphasize price by comparing new treatments with those already available through SUS. In view of the limited number of patients, the results of the clinical studies are not at all robust when compared to drugs for higher prevalence diseases. In addition, this methodology disregards the impact on the social value of rare diseases, as explained in the item on social costs.

**Clinic Protocols**

Although the drug is incorporated in the health system, it is necessary to define its role in the patient care strategy. This is the objective of the so-called Clinical Protocols and Therapeutic Guidelines (PCDT), established in Ordinance 199/14. In the same year of publication of this Ordinance, CONITEC opened a public consultation to prioritize the rare diseases that would be part of the new PCDTs. Hence, 834 contributions were registered, 91% of which were referred by patients, relatives, friends and patient groups. In May 2015, the final prioritization report listed 42 diseases, whose PCDTs were to be published by 2018. The initiative, received with enthusiasm by patients and other stakeholders, did not evolve as it ran into changes in the Ministry of Health, with the replacement of ministers and teams.

It is important to note that, since 2014, 22 rare disease PCDTs have been published. None of these, however, were included in the final list of prioritization produced by CONITEC. The body, which leads this process, is currently involved in the development of five rare disease PCDTs, three of which are in advanced stages and are only awaiting the signature of the secretary of the Ministry of Science, Technology and Strategic Inputs (SCTIE) to be published. They are: Mucopolysaccharidosis type I (MPS I), Wilson’s Disease and Sickle Cell Disease. The other two PCDTs are under review after public consultation, with a favorable opinion by CONITEC. They are: Mucopolysaccharidosis type II (MPS II) and Self-immune Hepatitis. Of the five protocols, only two (MPS I and MPS II) are included in CONITEC’s prioritization list.
Judicial power

With the increase of the judiciary, the National Justice Council (CNJ) adopted a support position for magistrates and created the National Judicialization Forum for Health, a multidisciplinary work that allows interaction between the Ministry of Health, ANVISA, National Health and State and Municipal Health Councils (CONASS and CONASEMS).

Other initiatives have emerged, such as the Technical Chamber of Rare Diseases, created by the Federal Medical Council in 2015. It brings together patient associations, representatives from the pharmaceutical industry, government agencies and medical societies.

In 2017, the Board approved a course that aims to make doctors who are not experts in genetics apt to recognize it. With this, these professionals will be able to adequately refer cases that require expert evaluation and offer, in basic health care, medical care to people with genetic diseases. The first trainings were held in November 2017 and had the participation of 5,200 doctors.

The University of São Paulo (USP) also joined the State Health Department of the State of São Paulo, defending the elaboration by researchers of reports and opinions that instruct the magistrate about the effectiveness of medicines claimed in court, besides the existence of alternative treatments available in SUS. In one way or another, all discussions deal with models of care that enable the right to health as guaranteed by Articles 196 of the Federal Constitution and No. 16 of the Organic Act of SUS (Act 8080/1990).

In December 2017, the National Justice Council (CNJ) held another round of discussion. For more than 10 hours, 30 representatives from various segments of society and government presented their perspectives on judicialization. According to the President of the Federal Supreme Court (FCJ) and the CNJ, Minister Carmen Lúcia, measures will be taken to deal with the “collection of lawsuits”, such as technical and scientific support to the judge.

Although relevant, the initiatives were not enough to contain the strong growth of lawsuits. According to Ministry of Health estimates, they have grown 490% since 2011. In 2016 alone, the Union’s expenses with lawsuits reached R$ 1.3 billion, an increase of 23% over the previous year. In July 2017, the federal government had already accumulated R$ 705.1 million in expenses with judicial products.

The share of orphan drugs in judicial Union spending already accounts for 90% of the total. By 2016, 10 of the 20 most-demanded drugs were linked to rare diseases. This movement intensified in 2017, and up to June, 13 of the 20 most judicialized medicines were intended for rare diseases.

In addition to draining financial resources, lawsuits affect both the Union, States and Municipalities due to the lack of predictability in the allocation of resources due to the lack of programming for the purchase of medicines, the reduction of the negotiation power of the public administration and the lack of control as patients, who are at risk of discontinuity in treatment. Throughout 2017, an attempt was made by federal entities to improve purchasing management through a series of initiatives. Among them, the core of lawsuits of the Ministry of Health, which also offered to the state and municipal administrations a software (S-CODES) to control purchases.

One could also observe last year some government initiatives to reduce the supply of drugs by lawsuits. In March 2017, patients received enough for 45 days of treatment, not for six months as was usual. The situation was only reversed after mobilizing patient groups and
UNION TOTAL EXPENSES WITH JUDICIAL REQUESTS (2010-2017*) – IN MILLIONS OF REAIS

* Expenditures until July/2017    Source: Prospective with data from the Ministry of Health, 2016, 2017

UNION EXPENDITURE WITH THE 20 MOST JUDICIALIZED DRUGS (2011-2017 **) - IN MILLIONS OF REAIS

* Data from 2016 were made available until November   ** Data for 2017 were made available up to June
Source: Prospective with data from the Department of Logistics in Health (MS), 2016

THE 20 MOST JUDICIALIZED MEDICATIONS BY THE UNION (2011-2017**)

* Data from 2016 were made available until November   ** Data for 2017 were made available up to June
Source: Prospective with data from the Department of Logistics in Health (MS), 2016
members of the Legislative power. The Ministry decided to extend the deadline to 150 days.

It is important to note that possible delays in court decisions punish patients, given the risk of affecting the continuity of treatment. Patient associations corroborate this view, emphasizing that access to the main treatments is still very uneven. Judicialization arises from the absence or de-updating of protocols, as well as the lack of definition regarding the role and obligations of private payers. In addition, the call to justice to guarantee access to medicines is now limited to a small part of the population that is aware of or have contact with more prepared entities.

Legislative Power

Rare diseases are the focus of several discussions in the National Congress, either through bills that guarantee the need for adequate care, or by creating a regulatory environment compatible with the reality of treatments. In total, there are 14 projects in process, which should not be faced as ready answers prepared by the congressmen, but as an opportunity to raise the discussion and engage more social actors in the process.

Between 2014 and 2017, the Social Security and Family Commission (CSSF) of the Chamber of Deputies held 154 public hearings (23, 52, 28, 51, per year, respectively), of which 102 were on health; of these, 8 were on rare diseases, an expressive number facing the number of topics in the sector.

It is important to emphasize that, in the midst of the institutional crisis, the Chamber and the Senate have served as the stage for important discussions on the subject.

AT THE FCJ’S AGENDA...

Two appeals related to Rare Diseases have awaited, since 2016, a decision by the Federal Supreme Justice (FCJ). They refer to the State’s obligation to provide high-cost medicines to people who do not have any financial capacities to buy them (RE 566.471) and to provide medicines that are not registered with ANVISA (RE 657.718). Paralyzed after the death of Minister Teori Zavascki, the appeals judgment has three votes, which point out that the judicialization must, in the long-term, be restricted to patients unable to afford the treatment costs, as well as the strengthening of technical instances of the Unified Health Service, such as ANVISA and CONITEC, in decisions related to registration and incorporation. The appeals will also be analyzed by the other eight ministers.

The president of the FCJ, Minister Carmen Lúcia, already got involved with the issue and endorsed, in November 2017, the decision of the Court of Justice of Rio de Janeiro (TJ-RJ) that imposes on the Municipal Health Foundation of Niterói (RJ) (MKD) the supply of the drug for treating the Mevalonate Kinase Deficiency (MKD) of a person with the disease, noting that “the suspension of the effects of the contested decision could cause a more serious situation (including the death of the patient) than that which is intended to be combated”.

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...AS WELL AS AT THE SCJ’S

The Superior Court of Justice is also a decisive actor for the judicialization of medicines. In May 2017, the First Panel suspended all lawsuits in progress and underscored the State’s obligation to provide high and low cost drugs not incorporated into the SUS. The decision has generated a great repercussion. According to Minister Benjamin Gonçalves, rector of the appeal, the supply can occur as long as there is, cumulatively, a medical report on the indispensability of the medication, a proof of financial insufficiency by the patient and the drug registration in ANVISA.

The trial was interrupted after the request for minister Assusete Magalhães to assess it. The other nine ministers who make up the 1st Section should assess the appeal, whose decision must be rendered within one year. It should not affect the FCJ work, but the outcome of the FCJ’s judgment may create an exception and, in the case of high-cost drugs, in a final decision by the SCJ.
A similar scenario is observed in the Senate’s Committee on Social Affairs (CAS). Between 2014 and 2017, the commission held 70 public hearings, 37 of which were about health. Of the health audiences, 13 treated rare diseases, five of which were carried out in 2017, the year when the Special Subcommittee on Rare Diseases (CASRARAS) was created, chaired by Senator Waldemir Moka, with the participation of patient associations, representatives of government, doctors and the pharmaceutical industry.

**SUMMARY OF LAW PROJECTS BEING PROCESSED**

<table>
<thead>
<tr>
<th>Project</th>
<th>Author (Party)</th>
<th>Theme</th>
<th>Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL 3,167/2008</td>
<td>Deputy Luiz Carlos Hauly (PSDB/PR)</td>
<td>Access to drugs</td>
<td>It requires the supply of medicines for patients with chronic diseases of low prevalence or rare to patients of the public health network and determines the participation of all federal entities in the financing of medicines.</td>
</tr>
<tr>
<td>PLC 56/2016 (1,606/2011)</td>
<td>Ex-Deputy Marçal Filho (PMDB/MS)</td>
<td>Access to drugs</td>
<td>It deals with the dispensation of medicines for rare and severe diseases, which are not included in the lists of exceptional medicines standardized by the SUS.</td>
</tr>
<tr>
<td>PL 4,815/2012</td>
<td>Deputy Mara Gabrielli (PSDB/SP)</td>
<td>Specialized care</td>
<td>It establishes the Specialized Support Service for Activities of the Daily Life, intended to people with severe deficiencies or rare diseases, with great restriction of movements, aiming at guaranteeing their autonomy and personal independence.</td>
</tr>
<tr>
<td>PL 6,566/2013</td>
<td>Former senator Eduardo Suplicy (PT/SP)</td>
<td>R&amp;D for technologies in rare diseases</td>
<td>It obligates the transfer of 30% of the resources from the Health Research Promotion Program, in activities aimed at the technological development of medicines, immunobiological products, health products etc. for the treatment of rare or neglected diseases.</td>
</tr>
<tr>
<td>PL 8,188/2014</td>
<td>Former senator Eduardo Suplicy (PT/SP)</td>
<td>Awareness</td>
<td>It provides for the institution of the National Day of Rare Diseases.</td>
</tr>
<tr>
<td>PL 2,657/2015</td>
<td>Former senator Vital do Rêgo (PMDB/PB)</td>
<td>Regulatory environment</td>
<td>It provides for the registration and import by individuals of an orphan medicinal product, and provides for a differentiated criterion for the evaluation and incorporation of these medicinal products; it also specifies that in the definition and adjustment of prices of such medicinal products, comparing prices must be restricted to that category.</td>
</tr>
<tr>
<td>PL 3,302/2015</td>
<td>Deputy Pedro Cunha Lima (PSDB/PB)</td>
<td>R&amp;D for technologies in rare diseases</td>
<td>It provides for the minimum application of resources for the research and development of diagnostics, medicines and other health products intended for the treatment of rare diseases, and allocates part of the resources recovered in actions for reimbursement to the Union purse, for the actions of full attention to people with rare diseases at the SUS.</td>
</tr>
<tr>
<td>PL 2,654/2015</td>
<td>Deputy Diego Garcia (PHS/PR)</td>
<td>Tax exemption</td>
<td>It includes expenses for the acquisition of medicines, in order to treat rare diseases in the event of deduction of the basis of calculation from income tax for individuals.</td>
</tr>
<tr>
<td>PLS 31/2015</td>
<td>Senator Álvaro Dias (PSDB/PR)</td>
<td>Regulatory environment</td>
<td>It typifies and defines orphan drugs for legal purposes, in addition to enumerating in which cases and under what conditions its import will be allowed. It also determines that the registration of these drugs is endowed with agile and unbureaucratized procedures.</td>
</tr>
<tr>
<td>PL 4,345/2016</td>
<td>Deputy Atila A. Nunes (PSL/RJ)</td>
<td>Access to treatments</td>
<td>It creates centers for treating rare diseases in all the states of the federation and makes other provisions.</td>
</tr>
<tr>
<td>PL 4,818/2016</td>
<td>Deputy Mariana Cavalho (PSDB/RO)</td>
<td>Access to treatments</td>
<td>It authorizes the use of drugs, chemical substances, biological and related products still experimental and not registered, by patients with severe or rare diseases.</td>
</tr>
</tbody>
</table>
### SUMMARY OF LAW PROJECTS BEING PROCESSED (TO BE CONTINUED)

<table>
<thead>
<tr>
<th>Project</th>
<th>Author (Party)</th>
<th>Theme</th>
<th>Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL 5,017/2016</td>
<td>Deputy Leandre (P/I/PR)</td>
<td>Access to treatments</td>
<td>It deals with the compassionate use of experimental drugs by patients with severe or rare disease.</td>
</tr>
<tr>
<td>PL 5,998/2016</td>
<td>Deputy Mariana Carvalho (PSDB/RO)</td>
<td>Regulatory environment</td>
<td>It sets forth differentiated criteria for the evaluation and incorporation of orphan medicinal products for treating rare diseases.</td>
</tr>
<tr>
<td>PLS 415/2015</td>
<td>Senator Cássio Cunha Lima (PSDB/PB)</td>
<td>Regulatory environment</td>
<td>It makes the definition in regulation and the disclosure of the indicator or parameter of cost-effectiveness used in the analysis of applications of incorporation of technology mandatory, and determines the randomness and publicity in the distribution of the processes to the bodies responsible for this analysis.</td>
</tr>
</tbody>
</table>


- **Health**: 66%
- **Other**: 18%
- **Social Security**: 13%
- **Social**: 3%


- **Health**: 53%
- **Other**: 18%
- **Social Security**: 3%
- **Social**: 26%
In my opinion, it would be more important to educate doctors at the Basic Unit.

Enacted in December 2016, Constitutional Amendment (CA) No. 95 limited the federal government spending limit for 20 years. In its first year of validity, health and education were the least affected areas in comparison to other bodies and Powers of the Republic. The CA 95 spared two key sectors from cuts larger than last year's spending, coupled with the IPCA variation, and allowed the Ministry of Health to continue to receive extra resources from cuts made to other ministries. Although the constitutional transfers made to states and municipalities have not been affected, the transfer of funds from the National Health Fund (NHF) to the budgets of states and municipalities should be affected, as they are part of the Ministry of Health budget. They will exclusively finance public health programs and services, which are already at risk from the fiscal crisis and from the drop in collections. This situation reinforces the importance of the current agenda for increasing management efficiency and reducing spending by the Ministry of Health - including judicialization.

Costs related to lost productivity alone represent up to 56% of the total cost of diseases.

There are no significant studies in Brazil about the nature of the data generated by rare diseases. The loss of productivity by patients and their relatives due to physical and/or emotional malaise is unquestionable though, as well as patient and family absenteeism caused by the need for medical appointments, examinations and other care, early retirement or invalidity pension as a result of the worsening of the disease, the emotional costs related to the pains and sufferings caused by the disease and the absolute lack of perspective of cure and difficulty of access to the treatment.

Some international initiatives help to tangibilize the economic and social impacts related to these diseases. This is the case of the European project entitled “Socioeconomic Cost and Quality of Life related to Rare Diseases” (BURQOL RD. 2008), which evaluates the overall costs (medical and non-medical) and identifies the relevance and economic and social magnitude related to 10 rare diseases in eight countries (Germany, Bulgaria, Spain, France, Hungary, Italy, United Kingdom and Sweden). The results indicate the significant impact of indirect costs. Costs related to loss of productivity alone represent up to 56% of the total cost of the disease. Although there are local peculiarities, the results can direct efforts and support decision-making.
Clinic Researches

The scenario for the development of clinical research in Brazil is also not favorable. Bureaucracy and the delay in the approval process of research protocols make it difficult to develop innovative therapies and to adopt patient-centered measures, as in other countries.

The global average of clinical trial approval, for example, ranges from 3 to 4 months, well below that of Brazil, which may exceed one year. This delay makes it impossible for Brazil to participate in multicenter researches (which occur simultaneously in several countries). In addition, the Resolution by the National Health Council (NHC) No. 466/2012, which requires a mandatory supply of the drug for the rest of the life of the research participants, is another factor affecting the national clinical research environment. With regard to ultraraphic diseases, it is also worth mentioning Resolution 563, published in November 17, intended exclusively for diseases with an incidence lower than or equal to one case for every 50 thousand inhabitants. This Resolution makes sponsors responsible for the free access for all the research participants to the prophylactic, diagnostic and therapeutic methods considered most effective, for a five-year period, after obtaining the registration in ANVISA.

These experiences reinforce the importance of the internationalization of clinical trials, public-private partnerships, the structuring of differentiated care services and the reduction of bureaucracy to the availability of orphan drugs, incorporating them into health systems.

Some countries have adopted strategies to streamline patient access to the orphan drug, such as a rapid review of documentation and the reduction of technical requirements when assessing parameters and other facilities. Policies differ according to the characteristics of the health system, whether public or private. Another differentiated solution that could serve as inspiration is the temporary authorization of medicines for patients with rare diseases, in cases of risk of life or in the absence of an alternative therapy, as in France and Spain.

<table>
<thead>
<tr>
<th>Country</th>
<th>Disease</th>
<th>Total Cost</th>
<th>Direct Cost</th>
<th>% total</th>
<th>Indirect Cost</th>
<th>% total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hungary</td>
<td>Systemic Sclerosis</td>
<td>€ 12,032.00</td>
<td>€ 5,350.00</td>
<td>44.4%</td>
<td>€ 6,742.00</td>
<td>56.6%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Histiocytosis</td>
<td>£ 49,947.00</td>
<td>£ 34,962.00</td>
<td>70%</td>
<td>£ 14,984.00</td>
<td>30%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Cystic fibrosis</td>
<td>€ 48,603.00</td>
<td>€ 42,381.00</td>
<td>87.2%</td>
<td>€ 6,221.00</td>
<td>12.8%</td>
</tr>
<tr>
<td>France</td>
<td>Systemic Sclerosis</td>
<td>€ 22,459.00</td>
<td>€ 11,933.00</td>
<td>53.1%</td>
<td>€ 10,526.00</td>
<td>46.9%</td>
</tr>
</tbody>
</table>

Source: Prospective with data from Angelis et al (2015); Angelis et al. (2014); Chevreul et al. (2014); Cavazza et al (2016).
The role of Patients

Many organizations have a key role for patients and for the environment development: on one hand, they offer support and counseling services, playing a role that would belong to the health system itself; on the other hand, they give visibility to the issue and pressure the Executive, Legislative and Judiciary powers to find solutions to guarantee access to treatments. This mobilization is also essential to combat the lack of information, which is still one of the main obstacles to early diagnosis and appropriate treatment of rare diseases.

Currently, the activities of Patient Associations are focused on:

- Patient and family support with regard to knowledge, support and guidance in access to treatment and improvement of quality of life;
- Promoting lectures and other activities to increase the visibility of the theme among different audiences;
- Participating with public agents for policy development and awareness raising;
- Collaborating with other smaller entities;
- Elaborating projects to raise funds.

The projects defended as a priority:

- Awareness and incorporation of the “Neonatal Hell Prick”;
- Stipulating a deadline, by law, for CONITEC to incorporate drugs into the SUS soon after registration;
- Immediate implementing a rare disease policy;
- Disclosing the theme on national TV channels.

It is also essential to point out the increase in the role of associations in recent years, which started to act in advocacy, strongly acting to increase awareness and change public policies, extending care to patients and their families.

Education and Professional Capability

Awareness of health professionals, including primary care, is a known hindrance to the system. To foster interest and strengthen capability, one must work on:

- the lack of knowledge and understanding of diseases by all agents involved in the regulation and control of the policies;
the awareness of physicians and nurses to identify and effectively diagnose illnesses;
- the high turnover of professionals in SUS units, which impairs close control and patient follow-up;
- the development of the centers, with adequate equipment and teams.

A Patient’s voice
“Sometimes it is not the doctors. Our biggest scouts are, in fact, the nurses.”
Impact Budgeting

In INTERFARMA’s estimation, the budget increase would be directly proportional to the number of patients benefited by protocols, early and accurate diagnoses, adequate treatments, specific medication and supervision of specialized teams.

On the other hand, the costs of the judiciary, which significantly impact the federal, state and municipal budgets, would fall, since they include expenses with medication, judicial processes and social security, as well as the social security benefits to which patients and their caregivers are entitled. In addition, there is a drop in expenses with unnecessary and incorrect treatments and their possible and frequent complications that require hospital admissions, generating more costs.

<table>
<thead>
<tr>
<th>Indication/Rare Diseases</th>
<th>Estimated in Brazil</th>
<th>Patients treated</th>
<th>Total cost/year (R$ MM)</th>
<th>%Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Currently</td>
<td>Estimated with the protocol</td>
<td>Currently</td>
<td>Estimated with the protocol</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>1,770</td>
<td>115</td>
<td>553</td>
<td>8.9</td>
</tr>
<tr>
<td>Cushing</td>
<td>8,300</td>
<td>0</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>Fabry</td>
<td>1,769</td>
<td>612</td>
<td>772</td>
<td>269.9</td>
</tr>
<tr>
<td>Gaucher</td>
<td>2,588</td>
<td>734</td>
<td>1,000</td>
<td>465.5</td>
</tr>
<tr>
<td>HAE</td>
<td>3,100</td>
<td>300</td>
<td>300</td>
<td>182.2</td>
</tr>
<tr>
<td>HAP</td>
<td>8,243</td>
<td>63</td>
<td>450</td>
<td>7.8</td>
</tr>
<tr>
<td>H PTEC</td>
<td>1,973</td>
<td>70</td>
<td>387</td>
<td>13.5</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>26,255</td>
<td>904</td>
<td>2,327</td>
<td>45.3</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>2,000</td>
<td>105</td>
<td>163</td>
<td>23.6</td>
</tr>
<tr>
<td>MPS VI</td>
<td>250</td>
<td>155</td>
<td>162</td>
<td>194.2</td>
</tr>
<tr>
<td>Nienmann-Pick</td>
<td>1,725</td>
<td>22</td>
<td>100</td>
<td>9.3</td>
</tr>
<tr>
<td>Pompe</td>
<td>3,450</td>
<td>106</td>
<td>120</td>
<td>119.5</td>
</tr>
<tr>
<td>Neuroendocrine Tumor</td>
<td>100,000</td>
<td>44</td>
<td>69</td>
<td>5.1</td>
</tr>
<tr>
<td>Total</td>
<td>161,423</td>
<td>3,230</td>
<td>6,448</td>
<td>1,345</td>
</tr>
</tbody>
</table>

Source: Data provided by Interfarma, Datasus, published epidemiological studies, QuintilesIMS proprietary databases.

* Note: The calculations, assumptions, and estimates made by IQ for this study were based on the information readily available and without the adoption of specific methodologies or validation with specialists; they should not, thereby, be adopted as a reference and source for other purposes (e.g., studies, protocols etc.).

** For calculating the total cost in the year for these indicated, Interfarma has adopted a 0.5 factor due to the delay to start treatment.
Conclusion

Undoubtedly the advances obtained after the publication of Ordinance 199/2014, in particular the recognition of patients with rare diseases in the Country through Clinical Protocols and specialized health services. International experience corroborates this view, demonstrating that the policy of implementation of referral centers represents a significant improvement in all aspects - whether they be emotional, social, organizational, cultural or economic. However, after three years of promulgation, patients and family members have to work their frustration at seeing hospitals waiting to be licensed and delays in the publication of PCDTs.

The need for a strong and expressive national policy is present in the face of current regulations, which disregard the specificities of orphan drugs, affecting access to treatment and negatively impacting the health and quality of life of these people.

In this scenario, Judicialization continues to be one of the main forms of access to treatments, but is limited to those who are better informed or who maintain contact with more prepared associations. In addition to the lack of definition of responsibilities for private payers (National Agency for Supplementary Health), the current legislation undermines the interest of the industry and does not favor the development of clinical research.

Pressure from patient associations is essential to maintain discussion and interest. The union of these entities would strengthen the struggle. Dialogue and union with the pharmaceutical industry are also key elements in accelerating registration, pricing and negotiations with the government. With transparent objectives and control over the performance of the pharmaceutical industries, this partnership would benefit the final objective, positively putting pressure on government institutions.

In short, the path to action is the union of sectors, both public and private. Closer relationships among all agents and organizations, mirrored in successful models in other countries, can accelerate processes and change the national reality. Training and management courses, team training, ongoing training of specialists, including geneticists, and the promotion of clinical research are some initiatives for a consistent advancement of access policies. Last but not least, the creation of a Public Policy, instead of Ordinances, can reduce the bureaucracy that hinders the progress of the process at all levels.

The economic scenario and the interest of the government remain as barriers to be transposed. Limited health resources, bureaucracy, political obstacles and crises, despite the involvement of some deputies and senators, contribute to the slow progress.
COMPLIANCE NOTICE

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- Being available on the internet without restriction;
- Not having a commercial value;
- Being freely distributed.