

Interfarma

Pharmaceutical Research Industry Association

innovations for life

*Rare Diseases:
Contributions for a
National Policy*

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ABOUT INTERFARMA

Interfarma –The Pharmaceutical Research Industry Association

Interfarma is a non-profit industry group, representing national and foreign companies and researchers responsible for promoting and encouraging the development of scientific and technological research in Brazil, focused on production of pharmaceutical raw materials, inputs, medications and health products. Founded in 1990, Interfarma currently has 46 member companies which collectively account for 1,389 years

of presence in Brazil. Today, these laboratories are responsible, in the pharmaceutical chain, for sales of 80% of the leading market medications and also for 39% of generics, produced by companies controlled by member laboratories.

Interfarma sees research and innovation as factors in economic development and ethics as a fundamental principle of its activities. The organization encourages debates on topics of interest to society such as clinical research, healthcare funding

and access, combating informality, as well as biotechnology and regulatory system. Among the institutional actions are interaction and closer relations with the various agents, through a frank and open dialogue, especially with health authorities, industry leaders, opinion makers and other stakeholders who can assist in creating a new healthcare scenario, with the main objectives of increasing access and strengthening innovation in Brazil.

*To fight for equality whenever
differences discriminate us and
fight for differences whenever
equality mischaracterizes us*

BOAVENTURA DE SOUSA CAMPOS

Introduction

Interfarma, the Pharmaceutical Research Industry Association, presents to authorities, physicians, patients and other interested parties the findings of a two-year work in defense of a National Policy for Rare Diseases in Brazil.

Along with many other initiatives, together with authorities and society to contribute to the improvement of healthcare conditions and access, Interfarma has placed special attention on so-called rare diseases.

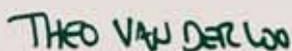
The first step was formation of a technical group in the organization. This measure was followed by the decision to seek out external consultants (IMS Health Consulting and Prospectiva) to study the size of the problem, to gather successful examples from other countries and to objectively define the peculiarities and priorities of our country.

Among the many important contributions for these studies, one is fundamental: the fact that Brazil today does not have an articulated policy for rare diseases. Without this policy, good intentions are plentiful and there is a lack of planning and articulated, realistic and successful activities. What is missing is a National Policy. And in its absence, we are left with prejudices and misconceptions. From governments, the supposition is that they can examine an issue like this only from a cost perspective. And, worse, basing examination on information that does not correspond to reality. From society, there is the assumption that governments neglect these issue only due to lack of sensitivity or respect for the suffering of patients with rare diseases and their families. And from both the government and society, there exists the idea that the solution to the issue will come through the courts, which only amplifies uncertainty and insecurity.

As a result of all of this, Interfarma's defense in favor of the adoption of a National Policy for Rare Diseases, which expresses the commitment of everyone with definitions that are sensible, clear, gradual and aligned to the duty of expanding access to treatment in a fair and sustainable manner.

In addition to publishing this summary text, we will follow up this effort with a series of activities and events, including seminars and discussions with officials from the Federal Government, parliamentarians, scientists and patients. Our goals are to contribute to the debate, collaborate for policy adoption and help to expand access to treatments. We hope these goals are achieved.

Happy reading!



Theo van der Loo
President of the Board



Antônio Britto
Executive President

Preface

Until the early 1980s, patients with rare diseases were not included on the agenda of government authorities. Patient organizations and social movements around the world gave not only a voice to the needs of these individuals, but also contributed to consideration of rare diseases as a public health problem.

This new approach led to the creation of numerous official programs directed at assisting these patients and the advent of economic and regulatory incentives for the development of medications intended to treat rare diseases – orphan drugs.

To a greater or lesser extent, the treatment of rare diseases has progressed in Brazil and abroad as a result of these measures, with medical innovations and greater awareness among society, governments, institutions, businesses, patients and families. But this context also raised a number of new issues regarding the definition of rare diseases, from the cost of medications to their impact on the healthcare system.

The main challenge, long known to public managers, is a binomial equation: balancing the need to adequately meet the demands of patients with the rising costs in the industry due to scientific and technological advancement.

Brazil is no exception to the general rule: despite advances, the road ahead is still long. There is no effective and safe treatment for many rare diseases and several barriers hinder patient access to specialized treatments and drugs. There is insufficient research and information about these diseases, and professionals in the area are in need of training and education, compromising and delaying diagnosis, with the health system itself also not offering a means of timeliness.

Within this complex scenario – a true challenge for health authorities and all segments involved in rare diseases issues – Interfarma offers in this document a contribution so that the topic may gain its deserving place on the national agenda, as well as means of reflection for Executive and parliamentary officials linked to the cause – important requirements for Brazil to advance needed care for individuals with rare diseases.



Maria José Delgado Fagundes
Director – Interfarma

1. Introduction

Interest in rare diseases has increased in recent years, alongside the recognition that they pose a public health problem. The last decade has witnessed development of most of the official programs for rare diseases in various parts of the world, at a time when many countries, including emerging countries, created policies specifically directed at the issue.

Although they have different definitions and approaches regarding the topic, public policies developed around the world have presented a range of solutions to expand patients' access to care. The challenge is considerable, considering that 95% of rare disease treatments do not depend on a network of palliative care to guarantee or ensure the quality of patients' lives.

At the other end of the spectrum is a small percentage of rare disease treatments with medical treatments capable of interfering in progression - the so-called orphan drugs - but the high cost of drugs has required governments to make decisions on specific policies and procedures to ensure their continual supply. Among one group and another, there are certain forms of rare diseases that can be treated surgically

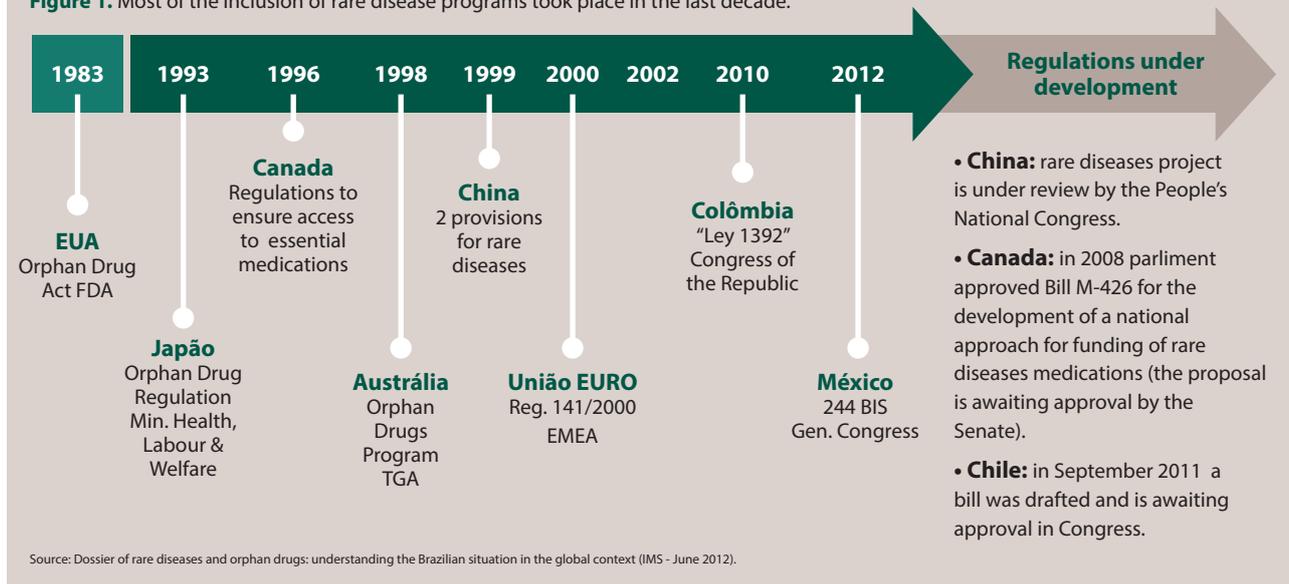
or with regular medication that only helps alleviate symptoms.

In Brazil, the subject is not a new one for health authorities. Although the country lacks specific policies for rare diseases, it has been the subject of discussions since the early 2000s – yet, it has chosen to discuss them from the perspective of genetic diseases. In 2004, the Ministry of Health created a work group in order to systematize the proposal for a National Policy for Clinical Genetics in the SUS (National Health System). The proposal was developed, but it did not move forward.

About five years later, the National Policy for Complete Attention for Clinical Genetics was instituted, whose results, though seen as a breakthrough, are considered insufficient by industry experts.

The lack of a broad perspective that takes into account specificities and responds to different needs in the rare diseases universe - those without treatment; those that benefit from treatment of symptoms; and those with orphan drug treatments - has been a barrier that makes it difficult and sometimes even prevents patients from gaining access to appropriate assistance.

Figure 1. Most of the inclusion of rare disease programs took place in the last decade.



2. Rare diseases, neglected diseases and orphan drugs

When it comes to rare diseases, there is no unanimity even in terms of its concept. The only commonality is the definition that the diseases affect a small portion of the population. In general, analyzing the various concepts adopted around the world, it is possible to locate rare diseases with a range of maximum prevalence variable from 0.5 to 7 per 10,000 inhabitants. This data, which apparently may seem irrelevant, is essential to define the scope and breadth of official policies developed by each country.

Compared with other countries, Brazil lags behind: just as it lacks an official policy specific to rare diseases, it lacks an official concept to define them. In an attempt to move forward on this issue, some bills related to rare diseases and orphan drugs are currently under consideration in Congress. Besides establishing guidelines for a national program for the treatment of rare diseases under the National Health System (SUS), such action seeks to define rare disease prevalence, placing it at 6.5 per 10,000 inhabitants, the same parameters as Europe.

The concept of rare disease is frequently confused with neglected disease, even by health legislation in some countries. At the root of this misconception might be the indistinct use of the term “orphan” to describe treatment of both rare diseases and neglected diseases.

While rare diseases have this name due to its low prevalence in the population, neglected diseases refer to so-called tropical diseases common in developing countries or regions, that typically affect low-income populations. This is the case of leishmaniasis, Chagas disease, leprosy and other endemic diseases caused by infectious and parasitic agents.

The adoption of the term “neglected” is based on lack of incentives for research activities. Although such

illnesses are responsible for almost half of diseases in developing countries, investments in R & D do not prioritize this area. The same criterion is used to define the “orphan drug”. Due to a lack of a sufficient market to absorb them, there is no stimulus for research, development and production of drugs and vaccines to prevent or treat them.

Epidemiological Profile

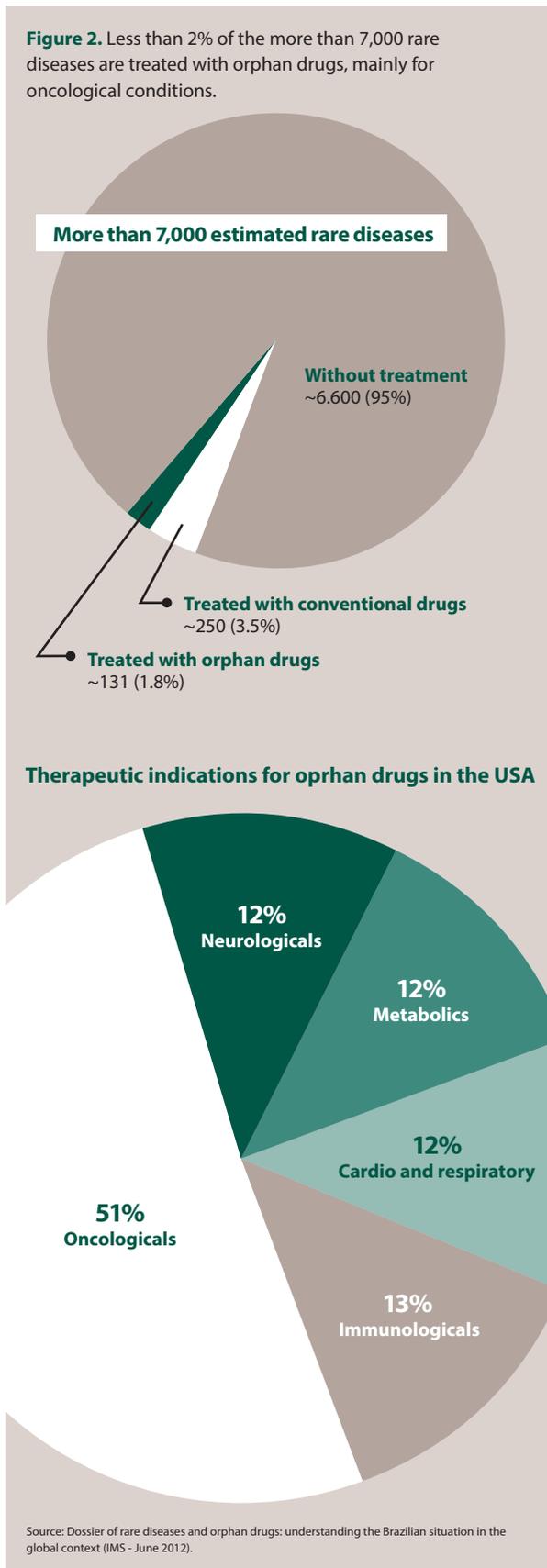
It is estimated that there are approximately 7,000 rare diseases in the world. If these diseases individually reach a limited number of people, together they affect a considerable proportion of the world population - between 6% and 8%, or 420 million to 560 million people. Of this total, approximately 13 million such individuals are in Brazil, according to these estimates.

Around 80% of rare diseases have a genetic origin. The remainder are the result of bacterial and viral infections, allergies or degenerative causes. Most rare diseases (75%) are manifested early in life and affect children from 0-5 years of age. They also contribute significantly to morbidity and mortality in the first 18 years of life.

Such disturbing indicators make it necessary to consider a care policy to ensure a better future and social inclusion for these children and for their caregivers - usually family members, who abandon all activities to exclusively take on this role.

In the complex world of rare diseases, there are at least three different situations that should be considered for any healthcare policy: 95% have no treatment and require specialized services for rehabilitation that promote improved quality of life. Around 2% of rare diseases can benefit from orphan drugs that interfere with progression of the disease. The other 3% have already established treatments for other diseases, which help alleviate symptoms. In such cases, medication, despite being given to a patient with a rare disease, is not considered an orphan drug.

Figure 2. Less than 2% of the more than 7,000 rare diseases are treated with orphan drugs, mainly for oncological conditions.



3. The Scenario in Brazil

Providing adequate care for patients with rare diseases means formulating a policy which is able to combine the two main facets of the issue: care and treatment on the one hand, and the offer of orphan drugs on the other.

In practice, this binomial equation requires the organization of a network of services that merge treatments and high-technology medications with low complexity procedures and can meet the main needs of patients: early and accurate diagnosis - one of the major problems faced by these people. There is a lack of qualified professionals, a shortage of medical and scientific knowledge about these diseases, infrastructure for different health needs of patients, and access to medications and monitoring of administered treatments.

The fact that Brazil does not have an official policy specifically for rare diseases does not mean, however, that patients do not receive care and treatment. They eventually secure medication, mostly through the courts. And the SUS, one way or another, meets the needs of these people - but in a piecemeal fashion, without planning, with great waste of public resources and harm to patients.

Public policy for clinical protocol

The Ministry of Health reports that there are currently 26 clinical protocols related to rare diseases within the SUS - 18 developed under the aegis of the new National Policy for Complete Attention for Clinical Genetics. Through these protocols - the official entryway to care for rare diseases in the public system - 45 drugs and surgical and clinical treatments were offered, 70,000 office visits and more than 560 laboratory procedures for treatment and diagnosis were carried out, with investment of more than R\$ 4 million per year. However, although cited by the Health Ministry, some diseases such as Pompe, Homocys-

tinuria, Fabry and all forms of Mucopolysaccharidose – have not been included in any clinical protocol since the policy was created.

Additionally, of the 18 most recent protocols, only one - for the treatment of Gaucher's Disease - incorporates orphan drugs. The others include only conventional drugs, which lessen symptoms of disease but not interfere in its progression.

Currently, almost all rare diseases registered with ANVISA that use orphan drugs remain outside protocols, which represents a considerable barrier for accessing these drugs through the SUS. According to the study conducted by Interfarma, 14 diseases are in this situation: they rely on drugs approved by ANVISA and marketed in the country, but are excluded from the government's agenda.

The study also shows that the official policy for rare diseases itself – based on clinical protocols for disease - helps perpetuate inadequate care in terms of diag-

Figure 3. 18 diseases theoretically covered in the National Policy of 2009 with treatment protocol granted*

Diseases

Addison's Disease
 Congenital Adrenal hyperplasia
 Congenital Hypothyroidism
 Crohn's Disease
 Cystic Fibrosis of the Pancreas
 Pulmonary Cystic Fibrosis
 Gaucher's Disease
 Hereditary Angioedema
 Hereditary ichthyosis
 Hypoparathyroidism
 Hypopituitarism
 Myasthenia Gravis
 Multiple Sclerosis
 Phenylketonuria
 Sickle Cell Disease
 Turner's Syndrome
 Wilson's disease

* 17 protocols do not use medications that interfere in the progression of disease (orphan drugs), treating only symptoms.

Source: Dossier of rare diseases and orphan drugs: understanding the Brazilian situation in the global context (IMS - June 2012).

Figure 4. 14 remaining diseases have a pharmacological treatment that is marketed in Brazil.

Maintained Diseases	Drug marketed in Brazil (brand; active ingredient; company)
Pompe Disease	Myozyme; alfa-galactosidase; Genzyme
Homocystinuria	Biotine: various low-cost options
Fabry's Disease	Replagal; alfa-galactosidase; Shire • Fabrazyme; beta-galactosidase; Genzyme
Mucopolysaccharidosis I	Aldurazyme; laronidase; Genzyme / BioMarin
Mucopolysaccharidosis II	Elaprase; idursulfase; Shire
Mucopolysaccharidosis VI	Naglazyme; galsulfase; BioMarin
Niemann-Pick Type C	Zavesca; miglustate; Actelion
Pulmonary Arterial Hypertension	Tracleer; bosentan; Actelion
Acute Myeloid Leukemia	Evomid; idarubicina; Evolabis • Zavedos; idarubicina; Pfizer
Amyotrophic Lateral Sclerosis	Rilutek; riluzol; Sanofi-Aventis
Gaucher's Disease	Zavesca; miglustate; Actelion • Cerezyme; imiglucerase; Genzyme • Vpriv; alfa-galactosidase; Shire
Hereditary Angioedema	Firazzy; icatibant acetate; Shire
Acromegaly	Somavert; pegvisomant; Pfizer
Familial Amyloid Polyneuropathy	Vyndaquel; tafamidis meglumine; Pfizer

Source: Dossier of rare diseases and orphan drugs: understanding the Brazilian situation in the global context (IMS - June 2012).

nosis, infrastructure and professional training. To reduce bottlenecks, it would be desirable to consider rare diseases in a general context and to structure a support network capable of responding to different categories of care required by patients.

Incorporation of drugs vs judicialization

The supply of orphan drugs from the SUS depends on incorporation in a clinical protocol which, in turn, depends on an assessment of technical and economic viability. However, the criteria employed by the government to assess the availability of orphan drugs in the public system is based on cost-effectiveness and in most cases this excludes patients from the possibility of obtaining this kind of treatment.

Brazilian law establishes that medications for diseases of low prevalence be analyzed by the same parameters used for those of high prevalence for the purpose of incorporation in the SUS. Taken into account are issues such efficacy of treatment and cost impact, compared with other measurements of the same nature.

If these parameters are in theory justified for planning and prioritizing public spending, in practice they have functioned as a major obstacle to patients with rare diseases. The low prevalence of the disease does not allow clinical trials for effectiveness of orphan drugs to have the same duration and number of patients involved than those of high prevalence.

Since it is intended for few individuals and it does incur cost of development diluted between large population groups, orphan drugs end up being more expensive than conventional ones. Moreover, most of these drugs do not rely on another drug with the same function which allows the realization of a comparative analysis of cost-effectiveness, as required by law.

To try to break this vicious circle that impedes access to orphan drugs, many patients have resorted to the courts, with considerable financial impact to the public. A measure of the problem lies in the fact that the Ministry of Health disbursed, in 2011, R\$ 167 million

for the 433 lawsuits that ruled in favor of the purchase of medications for individuals with rare diseases.

According to Interfarma's study, in order to facilitate patient access to orphan drugs and avoid the heavy costs of lawsuits, adjusting the analysis parameters to the particularities of rare diseases would be necessary, replacing the criteria of cost-effectiveness for other more appropriate ones, such as clinical effectiveness.

4. Barriers to care in Brazil

The lack of an official policy for rare diseases has transformed the lives of patients into an excruciating obstacle course, whether in regards to care and treatment or in relation to medications, the latter subject to numerous regulatory barriers that impede their entries into the market and the SUS.

Lack of access to care and treatment

Late diagnosis

The first major difficulty that people face is making people aware that they are suffering from a rare disease. There are two main causes of the problem: the lack of trained professionals to make the clinical diagnosis and the fact that the SUS does not include genetic tests in its list of procedures needed to confirm the diagnosis. It is estimated that patients take an average of two to four years of seeing health services and professionals in various specialties until the disease is identified.

The result could not be worse for everyone. Late diagnosis results in disease developing rapidly and reaching disabling and chronic stages, making the treatment more of a sacrifice and less effective for the patient. The public system, in turn, is required to



PHOTO: AGENCIA CLAMBA

“It is unfortunate that some patients jump from office to office and take so long to receive a diagnosis”.

Interview with Congressman Romário

One of the most active supporters of the Parliamentary Front to Combat Rare Diseases (House of Representatives) and an organizer of meetings and debates on the topic, Congressman Romário advocates the need for the country to adopt an official program specific to these diseases.

Romário says that patients are being poorly treated and proposes a series of initiatives to improve care and expand access to orphan drugs. To facilitate this process, he highlights the need for the Government to assume responsibility for individuals with rare diseases.

P: How do you evaluate the care currently given to patients with Rare Diseases in Brazil?

R: People affected by rare diseases are poorly cared for by the Government, even due to the complexity of the problem. There are more than 8,000 types of rare diseases. These diseases are still poorly known to science, and many without treatment. I estimate that Brazilian public health is crawling in terms of serving these people.

P: What is necessary for the country to advance in this area?

R: The country should advance in genetic research, expand the network of genetic counseling. According to Government's own data, there are just 80 hospitals across the country that offer some kind of treatment linked to the specialty. Expanding this network would help, especially for low-income people and those who live far from major centers. This portion of the population suffers the most and faces the greatest difficulty in obtaining an early diagnosis.

P: What is your position regarding the possible development of a national policy for rare diseases under the SUS?

R: I'm totally in favor. Today there exist many projects in the House of Representatives which present a series of Government obligations to better serve people with rare diseases. I support all those initiatives that, among other determinations, provide medical, pharmaceutical and full rehabilitation care to patients with rare diseases.

P: What, in your view, are the priorities that a policy of this nature should include?

R: In terms of care and treatment, early diagnosis is a primary posture that will slow, in some cases, the progress of the diseases. But it also involves the training of professionals. It is unfortunate that some patients jump from office to office and take so long to receive a diagnosis.

P: And in relation to the availability of orphan drugs?

R: Agility in the analysis for granting registration of medications should be a priority. This is a frequent complaint of patients with rare diseases. The delay in the release of a drug may mean the time between the life and death of a person.

P: Today the incorporation of orphan drugs in the SUS is subject to many barriers. What would be necessary to improve access to this type of treatment for individuals with rare diseases?

R: The Government should subsidize research and production of orphan drugs. A portion of the population cannot remain without help because these drugs aren't profitable. It is very important that Brazil assumes this social responsibility.

meet the more complex situations generated by the progression of diseases - such as hospitalization and medication - which entail higher costs.

There are still a number of patients who continue orbiting in the health system without ever receiving diagnosis, making clear the need to intensify efforts in care and assistance as in research.

Lack of trained professionals

Around 80% of rare diseases have genetic origins and must be accompanied by medical geneticists. Currently, in Brazil there are about 200 specialized doctors that are registered with the Brazilian Society of Medical Genetics - equivalent to one geneticist for every 1.25 million Brazilians. To understand this gap, the World Health Organization (WHO) recommends that there be a geneticist for every 100,000 inhabitants. By this criterion, Brazil has a current deficit of approximately 1,800 professionals.

Insufficiency and regional concentration of reference centers.

In addition to a shortage of professionals, professionals are heavily concentrated in the South and Southeast, where leading centers of reference in medical genetics are located. Although linked to universities, including hospitals, the centers are not formally integrated into the SUS and financed by research funding agencies or the pharmaceutical industry.

Given the general lack of support for patients with rare diseases, these centers end up offering informal and individualized care, using part of the money that should be allocated to research part of the resources of the SUS itself, which pays for some tests.

Yet patients who cannot access treatment centers are fully funded by the SUS. In general, they do not have qualified professionals to conduct appropriate treatment and receive fragmented and insufficient care.

Direct and indirect social costs

The concentration of reference centers in South and Southeast generates an influx of patients and caregivers to these regions. Given the severity of most of these diseases and the fact that they occur more frequently during childhood, require action by families and loved ones, most who devote themselves exclusively to the care of patients. This is a cost that also ends up falling on hands of the government, since family members stop working and start relying on public welfare, with virtually no prospects of resuming their previous activities.

Orphan drugs

Delay in granting registration

According to Brazilian law, the sale of drugs in the domestic market depends on obtaining registration with ANVISA (National Health Surveillance Agency). Granting such registration, in turn, is linked to the proof of fulfillment of requirements such as product safety and efficacy, and this is where one of the bottlenecks in the process is found.

The verification of those requirements by the regulatory agency and the granting of registration, which should be carried out within a 90-day period has been delayed, on average, by two years. A considerable number of registration requests for medications are currently waiting, delaying market entry for products that are important to the health of the population, including those for rare diseases.

Public relevance

Brazil counts with legislation, Law no. 9.782/99, which enables ANVISA to expedite the granting of registration of medications and pharmaceutical supplies. It also has a standard, the Resolution of the Board of Directors (RDC. 28/07), which provides companies the ability to make priority requests for products considered of public relevance. In such cases, the period



PHOTO: CONTRIBUTED PHOTO

“Although rare diseases affect the lives of about thirteen million people, Brazil still does not possess a positive policy for this specific population, nor a organized structure for care”.

Interview with Senator Eduardo Suplicy

In late 2011, Senator Eduardo Suplicy presented to the Senate Bill no. 711, establishing the National Policy on Protection of Rights of People with Rare Disease. The bill is pending before the Economic Affairs Committee and awaits the opinion of the rapporteur, Senator Paulo Bauer. Suplicy also advocates creation of a National Fund for Rare Diseases, and about a year ago presented another bill to make it possible

“I’m fully in favor of creation of a National Policy on Rare Diseases under the auspices of the SUS. Although rare diseases affect the lives of about thirteen million people, Brazil still does not possess a positive policy for this specific population, nor a organized structure for care. Moreover, the country is unaware of the magnitude of the problem and does not have a mapping of their specificities and needs.”

People with rare diseases today face gigantic social difficulties. The barriers are many times insurmountable. Prejudice is frequent, as well perception that these individuals are a burden rather than an integral part of society. Many end up socially isolated, due to lack of adequate infrastructure to meet their specific needs in schools, universities, and in the workplace and in leisure activities. The vast majority of people with rare diseases do not have the conditions necessary to reach their full potential.

I consider change in the social culture for dealing with rare diseases to be necessary in our country. The approval of legislation, as is the case of PLS 711/2011, which establishes national guidelines for the conduct of public policies on the rights of people with rare diseases, is an important step in that direction.

I understand it would be very important to also create a National Fund for Rare Diseases, in order to support research projects and related projects in the area of rare and neglected diseases. I presented on May 7, 2012, Senate Bill no. 23 of 2012, that establishes this fund. “

of analysis and granting of registration can be shortened to 75 days.

However, since the standard does not define what rare diseases are, orphan drugs cannot be prioritized nor considered of public relevance. Although they are often the only treatment option, they may take years to reach patients, who are thus deprived of this benefit.

Delay in setting prices

Besides health registration, the marketing of a drug depends on the pricing set by the CMED (Medication Market Regulation Chamber). This process can be very slow, taking from one to two years. Some drugs can take up to five years to reach the market when considering the two steps together – registration and

pricing. The bureaucratic obstacles, coupled with difficulties in establishing prices that enable companies to recover large investments in employee development and production of orphan drugs eventually becomes a disincentive for introduction of products in the country, further damaging patient care.

Clinical research

Clinical studies conducted to verify the safety and efficacy of medications are an important possible means for the country to receive investments and deliver innovative treatments to patients. However, government bureaucracy has hampered Brazil's participation in multicenter research protocols, in which research groups from different countries conduct simultaneous clinical trials for a given drug.

While the global average for approval of clinical trials varies from three to four months, in Brazil it is necessary to wait three times as long. For this reason, the country has lost important opportunities to integrate multicenter protocols and as a consequence, it has narrowed patient access to orphan drugs as well as monitoring by a clinical body of excellence. In the case of rare diseases, studies involving multiple countries and centers carry great weight, as patients are recruited in different parts of the world as a result of the disease's low prevalence.

But this is not the only disincentive in the country for the sponsors of research and development of orphan drugs. By virtue of a resolution of the National Health Council, sponsors of clinical studies should continue to provide patients the treatment being tested for the rest of their lives when there is some benefit to the patient, even without approval from ANVISA. Given the low incidence of rare diseases, this is a problematic issue, since the sponsor will need to provide the drug free of charge to almost all of its consumer market.

5. International experiences

The analysis of international experiences related to rare diseases can offer important contributions to the discussion and development of a public policy that addresses these diseases in Brazil. While most countries that have official programs specific to rare diseases are developed, in some emerging – such as China, Colombia and Chile –, there are expanding efforts to increase patient access to treatments. The United States, Mexico, the 27 members of the European Union, Australia, Japan, Singapore, South Korea and Taiwan are examples of countries that have developed specific policies for rare diseases and show how this concern is widespread throughout the world.

As a backdrop to these initiatives are the recognition of rare diseases as a public health problem, the expansion of public-private partnerships, the improvement of patient recruitment for clinical trials through the internationalization of these studies, the strengthening of patient advocacy groups and the increase in industry interest in certain niche markets, including rare diseases.

In general, international experience is focused on two main areas: the first refers to how some countries structure differentiated services to meet the needs of patients with rare diseases. The second relates to strategies to offer orphan drugs in national markets and to incorporate them into health systems.

Care

In relation to care and treatment, the countries of the European Union – which adopt a single definition for rare diseases – are the most advanced. They base care at multidisciplinary clinics and prioritize integrated care. France was the first country in Europe to adopt a national plan for rare diseases in 2005. The main measure taken to ensure diagnosis, care and treatment and access to orphan medications was the structuring of reference centers, which operate within hospitals.

In the first four years of the plan, 131 centers were created in the country. Italy pursued a similar path with reference centers and instituted, in 2001, a national network of prevention, observation, diagnosis and treatment of rare diseases was introduced into the existing public system, in addition to free care. The network has centers in all regions of the country and intends to share information between them.

In Germany, the National League of Action for People with Rare Diseases - under the Ministry of Health – is discussing the implementation of the reference centers. The country currently has 16 research centers on rare diseases.

Norway, Denmark and Sweden have adopted multidisciplinary clinics for rare diseases based on the concept of reference centers. The treatment optimization and cost reduction are the main drivers of the initiative.

According to a 2009 report from EURORDIS – an alliance of patient organizations from 49 countries representing 544 rare diseases – the average cost per child treated in centers corresponds to only 33% of the cost of treatment in programs that are not integrated into these institutions.

Orphan drugs

To expedite patient access to medications, some countries have adopted strategies to facilitate registration – a prerequisite for marketing. Accelerated review of documentation and reduction of demands in relation to clinical studies are some of the most common practices. In some cases, the designation of orphan drugs in other countries may be sufficient for a drug's approval. Many countries still grant incentives to manufacturers, such as reduced rates and market exclusivity in relation to competition.

The policy model adopted by each country in relation to orphan drugs varies according to the particularities of the health system – whether it is public or private and who is paying for the majority of these costs. The United States, a pioneer with the enactment in 1983 of a specific policy for orphan drugs – the Orphan Drug

Act –, followed the path of providing support and facilities for the pharmaceutical industry, in order to encourage research and development of these drugs.

Marketing exclusivity for seven years, exemption from taxes, flexible criteria for approval of the drug by the FDA (Food and Drug Administration) are some of the incentives offered in the country, where the private system predominates. Besides being available in the market, most medications are covered by private health insurance and the public system. Access is rarely denied, but is subject to reimbursement mechanisms and co-payment.

Meanwhile, the European Union has implemented measures to encourage research and development of orphan drugs common to all member countries. However, the policy of access to medications is a decision made by each country. Some also adopt the system of co-payments but, unlike the U.S., the contribution of the patient is small.

Most countries use a cost-effectiveness assessment to determine the incorporation of orphan drugs into the national health system, but with some adjustments. Germany, for example, is more flexible in terms of the analysis criteria. England is now studying a differentiated system of evaluation.

The priority of the governments of Australia and Canada is to expedite patient access to orphan drugs. As a means to facilitate the registration process of these drugs, the Australian health authority, the TGA, utilizes the assessment made by the American FDA, adding a criterion of clinical efficacy (it does not adopt the criteria of cost-effectiveness).

In Canada, there are various mechanisms and programs that patients can use to obtain funding by the State for a medication that is not on the general reimbursement list of the country. The government's decision regarding if there will be full payment of the medication or some degree of co-payment is evaluated on a case-by-case basis. The population is making some claims for the adoption of a specific policy guaranteeing reimbursement for orphan drugs through the public health system.

Figure 5. Although practices differ from country to country, some points can be used in the Brazilian case.

Items analyzed	Learnings
Clinical studies: requirements and obstacles	Clinical studies are generally facilitated for orphan drugs. Some of the tools to allow this scenario are: combination of stages (e.g., II and III), requirement of small group of patients (less than 100) and "case-by-case" analysis. Patient organizations (advocacy groups) play an important role in promoting drug approval in the countries analyzed.
Clinical evidence to secure approval	Requirement of efficacy profile of drugs is less demanding than that of common drugs: in some countries, the increased rate of survival is the main criterion considered.
Economic evidence	Europe's approach is less restrictive in that sense, exempting drugs from an economic analysis/budget impact in some countries.
Pricing/discounts	Discount policies are not a common practice. Orphan drugs are likely to follow the same rules of common drugs (e.g. compulsory discounts).
Reimbursement ^(a)	Most countries reimburse/provide free orphan drugs, supported by its innovative profile and the pressure of local POs.
Special financing	In Europe, additional funding for highly innovative medications are granted to orphan drugs. In some countries, a portion of total healthcare funding is dedicated exclusively to orphan drugs In the U.S., NORD offers patient assistance programs that go beyond access to medications, especially for the uninsured (in general, low-income populations).
Fast track approval	A análise de via rápida de aprovação é realizada caso a caso em alguns países da Europa

(a) the term reimbursement used throughout this document refers to the furnishment of drugs by the government.

Source: Dossier of rare diseases and orphan drugs: understanding the Brazilian situation in the global context (IMS - June 2012).

Among Latin American countries, the situation in Mexico, Chile and Colombia is equivalent to that of Brazil; there is a concern about adopting specific policies for patients with rare diseases, but the process is still ongoing.

Mexico, for example, recently passed a law that requires the government to make efforts to provide medications and foster their development. However, the legislation does not specify how this should be done.

In Chile, a number of different bills related to rare diseases are pending. In Colombia, where the public health system is not universal – unlike Brazil, Mexico and Chile – the law guarantees full assistance to patients, but does not provide access to orphan drugs.

In the context of the BRICS (Brazil, Russia, India and China), the closest situation to that of Brazil is Russia. Some drugs are reimbursed by the state and the judicial process is often used to obtain others.

In India, most of the population uses the private health system. With a strong tradition of drug research and development, the main demand is to adopt

a policy similar to the U.S., with a predominance of incentives for businesses.

China, on the other hand, has a public health plan that benefits a small portion of the population and does not reach the majority of those living in rural areas. Still, the country has mechanisms to ensure rapid approval of drugs to accelerate commercialization.

From analysis of international experiences adopted by these countries, the combination of two equally important perspectives is evident: on the one hand, facilitating the entry of orphan drugs in the market, and secondly, the feasibility of patient access to these drugs through the public health system and, in the case of diseases that have no specific treatment, offering a range of appropriate healthcare services.

Australia is the country that has advanced the most in initiatives, enabling orphan drugs to reach the market quickly and to be incorporated and available to patients through the use of different mechanisms of evaluation. It is a model that can be of great inspiration to Brazil, but not without considering the characteristics and particularities of the SUS.

Figure 6. The main characteristics of the public health system and access programs for orphan drugs.

Country	Health System	Policy for Rare Diseases – Access
USA	<ul style="list-style-type: none"> • Dominance of the private sector. • Access to the public system has age and income restrictions. 	<ul style="list-style-type: none"> • Focus is on encouraging R&D. There is no specific policy for access to orphan drugs, which are considered to be in the category of specialized medications. • Most orphan drugs are covered by both private health insurance as well as the public system (Medicare and Medicaid). • Access ≠ "accessible" (affordable) --> just like for other specialized medications, there are mechanisms for co-payment – which is usually high cost for specialized drugs, which can make the drug too costly for the patient, affecting use. • Medicare, the federal public health plan for seniors and disabled adults who qualify for the Social Security Disability Insurance program. Children are not covered by the public plan. • Medicaid is a state plan and it covers very low-income families. That is, much of the population relies on private health plans, which bear most of the costs of these medications.
Australia	<ul style="list-style-type: none"> • Universal Public System • Includes pharmaceutical assistance 	<ul style="list-style-type: none"> • Focus is on access to these drugs. There are no incentives for R&D. • Fast-Track in the registry: use of information from the drug approval process by the FDA as basic document • Access to medications is done via pharmaceutical assistance programs, two of them targeted at highly specialized medications and "life-saving medications", directed at medications that treat diseases of low prevalence and threaten the patient's life, but were not incorporated into the overall list of reimbursement (understanding that orphan drugs are clinically effective, but do not fit the criteria of cost-effectiveness) • There is an institutionalized mechanism to access drugs not yet registered in the country.
Canada	<ul style="list-style-type: none"> • Universal Public System • Pharmaceutical care for elderly and indigent only 	<ul style="list-style-type: none"> • Focus is on access to these drugs. • There is a list of medications funded by the government. • If the product is off the list, there are three mechanisms for access to special medications --> Orphan drugs are considered to be in the broader category of "special medications" or "specialized medications" • There is still the possibility of co-payment • The courts do not act in this sphere. • There is no government incentive for R&D
European Union		<ul style="list-style-type: none"> • There is a unified policy of incentives for R&D and drug registration. • Policies for access to orphan drugs are created individually by each country. • European Organization for Rare Diseases.
England	<ul style="list-style-type: none"> • Universal Public System • Includes pharmaceutical assistance 	<ul style="list-style-type: none"> • Access to a medication is secured via incorporation of the drug on the public system's reimbursement list. • The inclusion of a medication on the list depends on the favorable opinion of the National Institute for Health and Clinical Excellence (NICE), based on Health Technology Assessment (HTA) with criteria of cost-effectiveness. • Today, there is no specificity attributed to orphan drugs in the ATS. They are subject to the same evaluation criteria of a medication for prevalent diseases. • Adoption of different criteria for evaluating orphan drugs is being studied. • NICE has already made such a proposal to be adopted by Ministry of Health.
Germany	<ul style="list-style-type: none"> • Público Universal • Assistência farmacêutica para desempregados 	<ul style="list-style-type: none"> • The inclusion of a medication on the list depends on the favorable opinion of the G-BA, based on ATS criteria of cost-effectiveness. • Orphan drugs have more flexible criteria for entry on the list, no need to prove an additional benefit over other existing therapies (do not need cost-effectiveness studies). • If gross sales of some medication named as orphan drugs exceed 50 million euros, the G-BA may request extra data showing additional benefit, which must be arranged within three months, and the medication is subject to the same approval criteria as any other medication. • "sickness fund" can reimburse a medication that has not yet been approved.
Spain	<ul style="list-style-type: none"> • Universal Public System • Includes pharmaceutical assistance 	<ul style="list-style-type: none"> • Large number of orphan drugs are on the reimbursement list. • There may be co-payment of these drugs. • When a drug is administered in the hospital, payment comes from the Hospital budget.

Figure 6. Continue.

Country	Health System	Policy for Rare Diseases – Access
Italy	<ul style="list-style-type: none"> • Universal Public System • Counts on pharmaceutical assistance 	<ul style="list-style-type: none"> • To integrate the reimbursement list, an orphan drug passes through the same procedures as a common drug. • There is a fund to reimburse orphan drugs still awaiting marketing approval. • Has reference centers for rare diseases.
Mexico	<ul style="list-style-type: none"> • Universal Public System 	<ul style="list-style-type: none"> • The Mexican legislation is a little more advanced; in the sense of establishing laws that will make efforts to make available orphan drugs needed and try to foster their development. • The concrete ways by which these efforts are made are not yet specified.
Chile	<ul style="list-style-type: none"> • Universal Public System • Includes pharmaceutical assistance 	<ul style="list-style-type: none"> • Bills in the area that are still pending. • There are principles in the Chilean Constitution that guarantee health care by the State.
Colombia	<ul style="list-style-type: none"> • Mixed System • Access to the public system is restricted 	<ul style="list-style-type: none"> • There is legislation that provides full assistance to these patients, but does not deal with access to orphan drugs in particular.
Russia	<ul style="list-style-type: none"> • Universal Public System 	<ul style="list-style-type: none"> • Very similar situation to Brazil: only a few medications are on the reimbursement list. • The country also has an issue with the courts. • Funding to purchase these drugs relies on regional health authorities (not from the federal budget).
China	<ul style="list-style-type: none"> • Basic public plan, which covers a small part of the population. • Greater inequality between rural and urban areas 	<ul style="list-style-type: none"> • There is a mechanism for quick approval of orphan drugs. • There are government incentives for orphan drugs. • Bill in Congress which establishes mechanisms for reimbursement of orphan drugs and for patient care network.
India	<ul style="list-style-type: none"> • Universal Public System • Dominance of the private sector. 	<ul style="list-style-type: none"> • Reimbursements offered by the public sector are very low. Much of the cost is paid by the patient, which often makes use of very expensive drugs, such as orphan drugs, not feasible. • Does not have a policy for R&D of orphan drugs. • The most common demands in the country are calling for an orphan drugs policy similar to the U.S., given the potential for research and development of new medicines in the country.

Source: Proposals for a National Policy on Rare Diseases: Prospectiva Consultoria, May 2012

6. Proposals for a National Policy on Rare Diseases in the SUS

The analysis of the best practices adopted worldwide shows that the formulation of an all-encompassing National Policy for Rare Diseases must include three complementary fronts:

- The first concerns the organization of assistance, ensuring patient access to care and treatments;
- The second is related to the adoption of differentiated registration mechanisms to accelerate the entry and sale of orphan drugs in the Brazilian market;
- The third refers to the policy destined to facilitate the incorporation of orphan drugs in the SUS.

Assistance organization: access to care and treatment

A major goal on this front is to provide rapid and accurate diagnosis, by trained professionals, with rapid referral of patients to health services that best meet the needs identified – whether it be rehabilitation, palliative treatment or availability of orphan drugs. This assistance structure should provide further monitoring of these individuals, with monitoring of clinical progression and the effects of the medication, and provision of incentives for training and recognition of medical geneticists in the SUS.

The path proposed to enable this type of assistance is the constitution of a National Network for Care of Patients with Rare Diseases, built from the linkage of State Networks for Patient Care with Rare Disease. Network coordination is a model of patient care that Brazil has already adopted successfully for some diseases. This is the case with the National Policy of Blood and Blood-Related Products, which includes the treatment of hereditary coagulation disorders.

According to this model, each state network must practice both Primary Care and Specialized Care. In the case of rare diseases, first there will be the identification and tracking of individuals and families with problems related to congenital anomalies, genetic errors of metabolism, genetically determined diseases and rare diseases that are not genetic.

Specialized care, in turn, will cover the multidisciplinary approach and other specialized procedures relating to cases that have been referred by primary care. This level of assistance will consist of Units of Specialized Care and Rehabilitation and Reference Centers.

The existence of Reference Centers equipped with qualified professionals and specialists is fundamental to ensure the achievement of early and accurate diagnosis and for proper monitoring and evaluation of the clinical progression of patients.

Because treatment with orphan drug is expensive, these experts will also help to define eligible patients to receive these drugs, according to the premises established by clinical protocols for the diseases.

For this model to work properly, the centers must be present throughout the national territory and be linked and financed by the SUS. Furthermore, they must be integrated with each other and share information, to enable the creation of a National Registry of Rare Diseases. Since today reference centers are linked to genetic research groups from universities not affiliated with the public system, it is not possible to obtain official data on these diseases. Not to mention the difficulty patients face getting assistance in an integrated manner at all stages of treatment, which is exacerbated by the fact that the centers and geneticists are concentrated in the South-Southeast (see map below).

Priority for granting registration

Like some countries with specific policies for rare diseases, Brazil also has rules and laws that allow the speeding up of the process of registration of orphan drugs. The possibility of applying for priority analysis is something that already exists through the RDC

Figure 7. Location of reference centers in Brazil.



Source: Proposals for a National Policy on Rare Diseases: Prospectiva Consultoria, May 2012

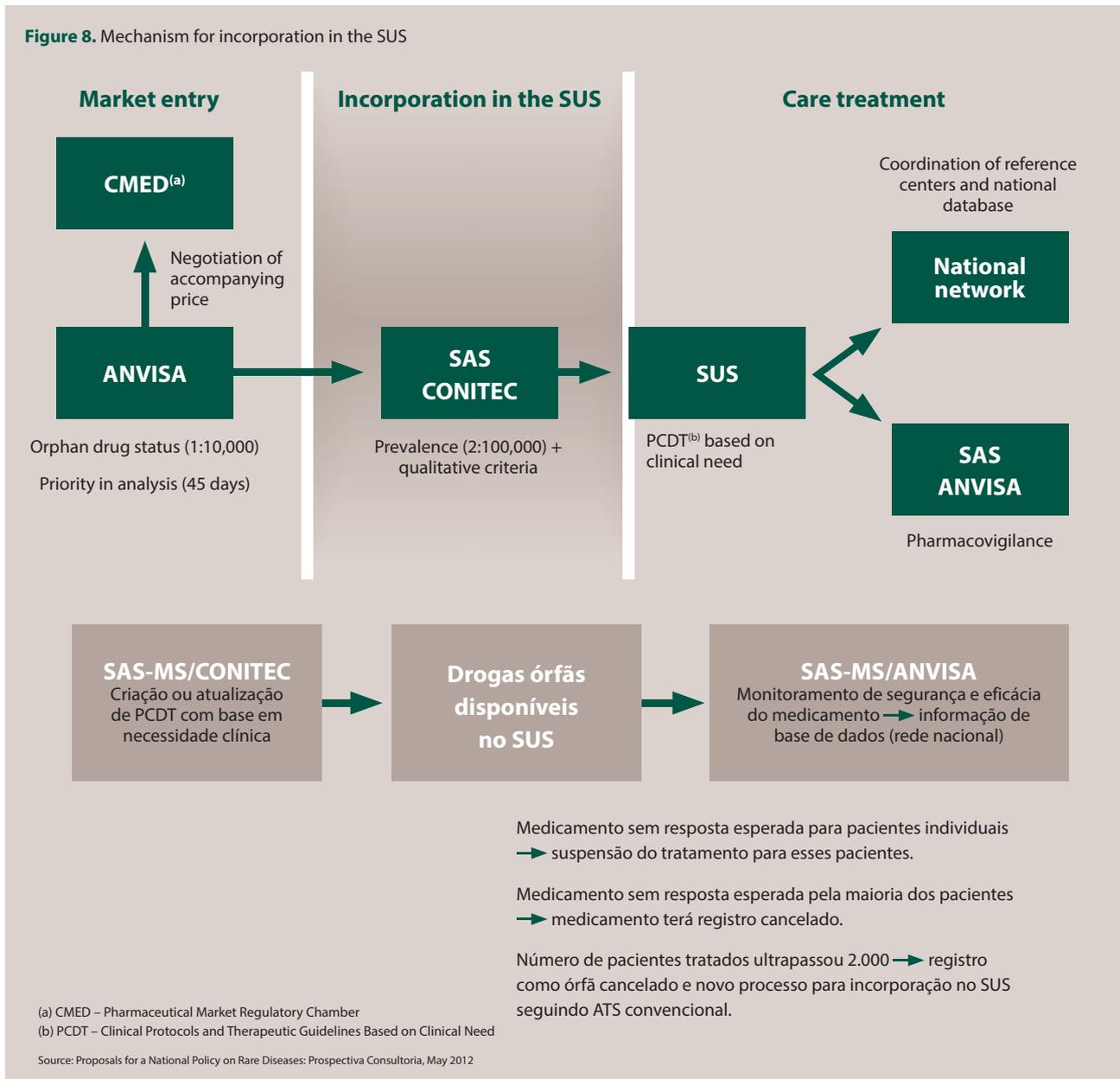
28/12, ANVISA. The norm is being revised through public consultation and it is an instrument that can be adjusted to meet the specificity of these drugs and the health needs of patients.

To benefit from priority analysis in the granting of registration, the product needs to first receive the orphan drug status from ANVISA. The manufacturer may request this status for the medication directed at treatment of diseases with a prevalence of 1 to 10,000. This condition automatically ensures priority analysis and registration concession by ANVISA within 45 days. Concomitantly, the price assignment is made with CMED, accelerating the availability of the drug on the market.

Incorporation of orphan drugs in the SUS

The proposed policy outlines a specific program and clear and differentiated criteria for the incorporation of orphan drugs in the SUS. It relies on the fact that these drugs are medically necessary for the treatment of certain rare diseases. The unique profile of these diseases – low prevalence, the small number of participants in clinical trials, no other drugs for comparison of effectiveness, high cost, among other particularities – prevents them from fitting the criteria of cost-effectiveness currently employed, and, therefore, that they be incorporated via the SUS HTA (Health Technology Assessment).

Figure 8. Mechanism for incorporation in the SUS



The option proposed to overcome this barrier is to adopt alternative parameters for the incorporation of these drugs in clinical protocols, basing analysis on clinical need. The evidence derived from clinical trials used in an initial evaluation for incorporation by the SUS may be supplemented by further assessments derived from drug-surveillance, as a way to expand the universe being studied.

The idea is to enable the implementation of this process through a differentiated channel, involving the Secretary of Health (SAS) together with CONITEC (National Committee for Incorporation of Technologies in the SUS) – the body now responsible for product and technologies evaluations.

For inclusion on the list of the SUS coverage, not all drugs designated as orphan should be evaluated by alternative criteria for registration. The suggested

parameter is to incorporate in the public system the medications for the treatment of diseases that affect no more than two per 100,000 people – approximately 4,000 patients, considering the current population. This criteria represents the average prevalence of rare diseases which are most prevalent in Brazil (as there is no official national data, globally accepted prevalence was accepted for each disease).

The ceiling of affected patients should be revised every ten years, based on demographic census. For the purposes of a national policy on rare diseases, the numerical criterion should be complemented with social and medical parameters:

- Reasonable diagnostic accuracy of disease;
- Epidemiologic evidence that the disease reduces life expectancy and that the drug improves the quality of life of the patient;
- Drug must be considered clinically effective and necessary for treatment, but without meeting the criteria of cost-effectiveness;
- No other cost-effective alternative for the treatment of disease;

- No other non-medication treatment recognized by physicians as appropriate and cost-effective for treatment;
- Medication cost must represent a significant financial burden to the patient and their family.

The continuation of treatment with the orphan drug, crucial for patients, should be based on periodical evaluations performed by reference centers. The information concerning the patients as well as responses to treatments make up a national database, which feeds a National Registry for People with Rare Diseases.

This information will be used for drug surveillance, conducted by a committee formed by members of the Department of Health Care (SAS-MS), ANVISA and by medical experts. It will be up to the committee to make an assessment on the safety and efficacy of treatment with orphan drugs and decide on its maintenance in the clinical protocol.

The intention is that the centers of reference work based on a logic similar to that of Sentinels Hospitals created by ANVISA: they will be responsible for col-

Figure 9. The Brazilian government should base its rare diseases protocol on main worldwide practices.

Items analyzed	Learnings
Official protocols	• Protocols usually include definitions and policies from other countries in order to enhance credibility.
Definitions/ requirements	• The maximum prevalence ranges from 0.5 to 7 in 10,000 people, with prevalence of 5:10,000 in the majority of countries analyzed. • Additionally, the lack of satisfactory commercially viable treatment is another parameter considered.
Eligible products	• Most countries include only drugs and biological products in the protocols. However, treatment devices may also be considered in some countries.
Market exclusivity	• About 7 to 10 years, but only for the rare disease indication (where drugs are approved for other indications). • In some countries it can be reduced if the prevalence significantly increases.
Reduction of fees	• Registration fees are any times reduced or even waived. • Accelerated review of documentation and evidence can be reduced and accepted.
Facilitation of registration	• The designation of orphan drug in other countries may be sufficient for adoption. • Specific care and consultation can be provided for the processes of approval for marketing.
R&D Incentives	• Tax credits for some types of loans to support R & D and clinical trials varies.

lecting and recording the reactions to the medication and any other events that may result from its use.

7. Financing

The study carried out by Interfarma points to five relevant cost parameters that should be analyzed when considering the implementation of a National Policy for Rare Diseases in Brazil: costs of diagnosis; cost of professionals (doctors, nurses and support staff); cost of drugs; related costs (hospitalizations and auxiliary treatments, for example) and costs not covered by the health budget, such as transportation and caregivers, among others.

Diagnosis

Accurately determining the existence of a rare disease requires, generally, a combination of low-cost testing, such as blood testing, with more sophisticated and more expensive analysis, such as genetic mapping. Currently, most of these resources come from research budgets.

Interfarma's study reveals that the adoption of a national policy for rare diseases does not lead to higher government spending with diagnosis. Although an increase in the number of patients diagnosed is expected, a system prepared with trained professionals to meet the demand would promote a reduction in the occurrence of erroneous or inaccurate diagnoses and, as a consequence, the performance of unnecessary procedures.

It is important to remember that even today, the government already pays for the costs of the large volume of tests and consultations conducted during the passage – of patients through the health system in search of a diagnosis, which can take up to four years. This is without considering the sacrifice imposed by this situation.

Professionals

The lack of an effective structure for attending patients with rare diseases is already overwhelming the healthcare system to some extent. Doctors, nurses, physiotherapists and other health professionals act in the treatment of rare diseases complications and during the diagnosis period. But these efforts take place in a disconnected and occasional way. The introduction of an official policy would optimize the work of these teams which, through the programs' well-established directives, would make teamwork more focused and generate a higher degree of results.

Medications

In the long term, orphan drugs represent the largest part of total costs related to the treatment of rare diseases. With the establishment of an official public policy, it is expected that medication costs should rise. However, certain circumstances exist which tend to limit the abrupt rise of costs.

One of them is related to clinical protocols, which will define parameters for identification of patient eligibility for the use of orphan drugs. Additionally, medical, social and economic criteria may also be used to define a scale of drug priorities: predominance of the disease and number of people who may benefit from it; cure rates vs. increase in survival; impacts on patients productivity; indirect social costs of the mobilization of relatives who take care of patients; and increase in accurate diagnosis, which helps avoid the situation of ineligible patients submitted for treatment.

With access to more precise information, the Government can plan and secure better deals for purchasing of medications, based on volume. From the private sector's point of view, having a more precise notion of demand also allows for more flexible commercial practices.

Still, there are inherent limitations to the precariousness of the current assistance structure. Even if unwanted, these limitations should, at the first moment, stop an explosion of demand and costs for orphan drugs. One of the main problems is the lack of

treatment centers and the incapacity of the system to manage the patients' full time treatment.

Another factor is deficient and poorly distributed professional training across the country, as there are few doctors able to diagnose and treat most of the known rare diseases. The way around this obstacle is to promote training of healthcare teams, but this process takes time to generate significant impact on the system as a whole.

Other related costs

By Interfarma's estimations, hospitalization and auxiliary treatment costs should decrease with the adoption of a policy for rare diseases. If patients were diagnosed accurately and treatment protocols followed, then the hope is that the frequency of complications

Figure 10. Analysis of relevant cost parameters.

Cost parameters	Expected financial impact
Drug	↑
Cost parameters	Expected financial impact
Diagnosis	↔
Other related costs (hospitalization fees, joint treatments, etc.)	↓
Personal	↔
Costs outside healthcare budget	↓

Source: Dossier of rare diseases and orphan drugs: understanding the Brazilian situation in the global context (IMS - June 2012)

Figure 11. Estimate of financial amount applied to medications.

Diseases ¹	Estimated number of patients in Brazil ⁴	# of suitable patients ²		Total cost/year (R\$ MM)		Variation	
		Currently treated	Estimated: introduction of policy	Currently	Estimated with policy ³	Patients treated	Total estimated cost
MPS I	343 (if)	93	130	34.8	38.6	40%	11%
MPS II	200 (if)	100	140	73.8	93	40%	26%
MPS VI	200 (if)	155	162	97.2	101.6	5%	5%
Niemann-Pick Tipo C	200 (eu)	58	100	12.4	15,6	72%	26%
HAP	8,245 (br)	4,000	7,500	70	131	88%	87%
Hereditary angioedema	3,840 (if)	100	150	1.7	2.3	50%	35%
Fabry (2 drugs)	648 (if)	203	332	60.2	89.4	64%	49%
Gaucher's	1,000 (EU)	650	1,000	60	100	54%	67%
Acromegaly ⁵	10,450 (if)	1,667	2,425	82.2	129.2	45%	57%
PAF	1,900 (if)	—	300	—	97.1	—	—

Considering the adoption of the policy for this group of diseases:

- More than 5,000 patients benefit → increase of ~75%
- Additional amount ~R\$300M → increase of ~60%
- Total purchase specialized programs is ~ R\$ 3.5 B / year. Thus, the financial impact would be ~ 8.5% of the total budget.

(1) Cost estimate was made based on data from Interfarma. Diseases for which data are available were considered.
 (2) Number of patients who were properly diagnosed, received appropriate treatment and had access to specific drugs were estimated.
 (3) The discount in drugs as given by the industry varies from 4% to 40%.
 (4) Source of prevalence: (IF) - Interfarma, (EU) - European Union (BR) - Brazilian protocols.

related to the disease should decrease, alongside reduction of hospitalization fees and occurrence of associated diseases. This would also be accompanied by a reduction of public costs for medications and examinations.

Non-contemplated costs in the health budget

Currently, besides the costs with health, the public power handles at least two other costs which impact significantly on federal, state and municipal budgets: the costs coming from the increase in court cases filed by patients to obtain treatment and medication; and the costs with social security and the benefits to which patients and their caretakers have the right to – in general their families, who are forced to abandon their professional activities.

According to Interfarma, these costs, currently relevant, tend to decrease with the introduction of a public policy for rare diseases, relieving concomitantly the public coffers, judicial system and the social security sector.

8. Conclusions

International experience, especially in Europe, shows that Reference Centers for patients with rare diseases that offer multi-disciplinary and integrated treatment promote significant savings when compared to conventional, occasional and piecemeal treatment. The adoption of a system with an implementation and a consolidation phase tends to promote a major improvement in care for individuals with rare diseases and considerable savings through optimization of Government expenses.

Data from EURODISIS (a patient alliance in 49 European countries), for example, shows that treatment in reference centers is, on average, 1/3 of the value spent on care outside of these programs, with incomparably better results.

Regarding orphan drugs – which represent highest costs in treatment of rare diseases – Interfarma's study concludes that there should be an increase in public expenses as a result of implementation of an official policy. However, in perceptual terms, this growth will be smaller than the potential growth in the number of patients requiring treatment.

Taking as an example the group of rare diseases with the most organized data - Mucopolysaccharidosis I, II and VI, Gaucher's, Niemann-Pick Type C, Pulmonary Arterial Hypertension, Fabry, hereditary Angioedema, Acromegaly and Family Polyneuropathy-amyloid – Interfarma predicts that the establishment of an official program would provide medication to more than 5,000 patients. This estimate represents 75% growth compared with the population assisted today.

On the other hand, the additional costs estimated to make this aspect of the program viable, according to the association, would be R\$ 300 million – a 60% increase compared to current Government expenses. If taking into consideration the total universe of federal expenses for purchasing of medications for specialized programs (the category in which rare diseases fall), the impact on public accounts would be only 8.5% of the total.

However, regarding public expenses with all types of medication – currently around R\$ 11.5 billion – orphan drugs would represent a little over 2.5% of the total, with the potential to considerably increase the number of attended patients and to promote great benefits to them.

Given the complexity of the topic and the countless challenges to be considered, it is important that the implementation of a national policy for rare diseases occurs in a progressive manner. According to Interfarma, this would be the most appropriate path, so that parameters could be monitored and adjusted throughout the process, in order to obtain best use of public resources, with the best results for the patient health.





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