CIRS R&D Briefing 90

Challenges and Opportunities for Orphan Medicines' Availability in Mexico

CIRS Centre for Innovation in Regulatory Science

Introduction

The document '*Estrategia sobre Certidumbre Regulatoria para el Sector Farmacéutico*' (Strategy of Regulatory Certitude for the Pharmaceutical Sector)[1], published last January by COFEPRIS describes important working projects the agency will support from 2022 to 2030 to alleviate regulatory obstacles affecting therapeutics access for the Mexican population.

Among these, the strategy stresses the importance for COFEPRIS to comply with their commitments to international regulatory standards, including those promulgated by the ICH and PIC/S to benefit from increasing regulatory harmonisation and regulatory reliance, especially for biologic therapeutics. This includes advancing with the implementation of Good Regulatory Practices and the parameters of the WHO Global Benchmarking Tool.

Considering this recently published strategy, this CIRS R&D Briefing brings attention to a particular group of therapeutics, orphan drugs, which are designed to help patients affected by rare diseases and how their availability can be optimised for the Mexican population. Based on estimates by the Mexican ministry of health and the World Economic Forum (WEF), orphan diseases affect from 8 to 13 million Mexicans [2,3].

Around the world, availability of and access to orphan products is a complex and multifactor phenomenon. These therapeutics are designed to address diseases that each have a very low incidence in the general population. Typically, these drugs address serious conditions with high unmet medical needs where there are few therapeutic alternatives. These products result from complicated discovery programmes, require sophisticated manufacturing facilities, challenging clinical development programmes, and special expertise to develop. The availability of these products, however, is made even more challenging when there is a lack of a clear and detailed regulatory pathway to facilitate the registration and availability of these unique therapeutics.

This R&D Briefing focuses on how therapeutic options for orphan diseases in Mexico face barriers to their availability and presents opportunities to optimise the regulatory environment. Please note the work for this Briefing was undertaken in 2021-2022.

Contents

What is an Orphan Disease?

When a patient presents a set of unique and difficult-to-diagnose symptoms, both the physician and patient face a perplexing situation. Do the symptoms represent a variant expression of a common disease or are the symptoms a manifestation of a rarely observed, yet debilitating or potentially life-threatening disease? Through the exclusion of common disorders and today with the widespread use of genetic testing, patients with challenging presentations may be diagnosed with a rare/orphan disease that usually is genetically based. Many rare diseases or conditions can be difficult to diagnose and manage because in their early stages, symptoms may be absent or masked, misunderstood, or confused with other diseases [4].

It is estimated that there are about 7,000 known rare diseases worldwide and the Global Genes Project (https://globalgenes.org/) estimates approximately 300 million people worldwide are affected by a rare disease. Achieving accurate estimations of the prevalence and/or incidence of any disease is a strategically important goal of public health policy, because this information allows for planning and possible procurement of goods and services to attend to the potentially affected population. In the case of rare diseases, estimation challenges are complex because of their low incidence and the difficulties in measuring and compiling treatment and diagnostic information.

There is no single, widely accepted definition for rare diseases. Typically, a rare disease is any disease that affects a small percentage of the population, usually life-threatening or chronically debilitating, of such low prevalence that special combined efforts are needed to address them. There also is no single name utilised in Latin America to refer to this category of diseases. Some countries call them rare or orphan diseases, others simply call them low prevalence (baja prevalencia) or infrequent diseases (poco frecuentes). There are some differences in the definitions, but a constant is always the low incidence. In this Briefing we will refer to these as 'orphan diseases'.

World Relevance of Orphan Drugs

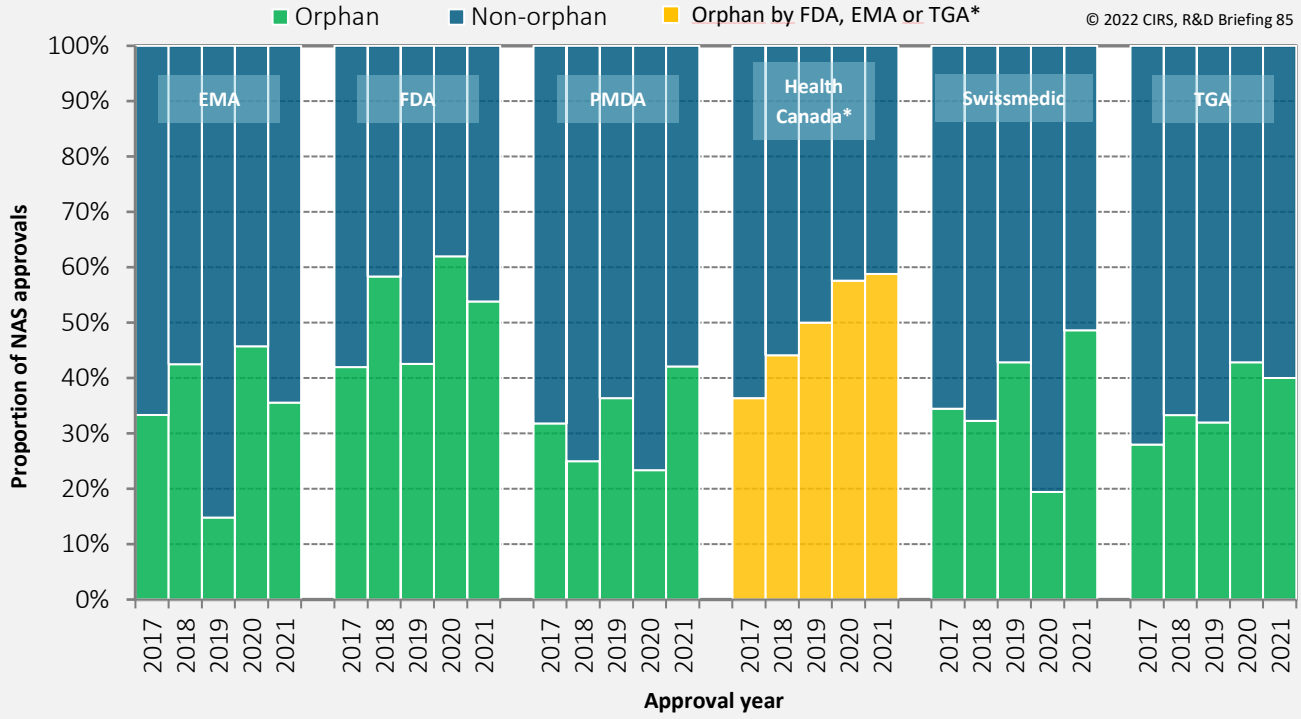
Researchers have recognised that treating rare diseases almost always requires sophisticated diagnostic approaches and specially designed therapeutic approaches using targeted "orphan drugs" (ODs). Because new rare diseases are constantly being discovered, so too are novel therapeutics to address these typically unmet medical needs. Unfortunately, only about 400 rare diseases have therapies according to the Rare Genomics Institute (https://www.raregenomics.org/). However, because about 80% of orphan diseases have a genetic basis, developing targeted therapies using sophisticated genomic approaches has opened the way to addressing the critical unmet medical needs that can be filled by targeted OD therapies.

In the United States, the Orphan Drug Act (ODA) of 1983 created financial incentives for drug and biologics manufacturers, including tax credits for costs of clinical research, government grant funding, assistance for clinical research, and a seven-year period of exclusive marketing given to the first sponsor of an orphan-designated product who obtains market approval from the Food and

Drug Administration (FDA) [5]. At the same time, federal programmes at the FDA and the National Institutes of Health began encouraging product development, as well as clinical research for products targeting rare diseases. Commercialisation of ODs requires large investments in research, which is conducted by large companies and smaller disease-focused entities. In 2018, the top twenty multinational companies accounted for 69% of the $130.6bn in global sales of orphan products; by 2024, the market for these products is expected to grow rapidly to $242.5bn.

Since 1983, the ODA has resulted in the development of more than 250 ODs, which are now available to treat a potential patient population of more than 13 million Americans alone. In contrast, the decade before 1983 saw fewer than 10 such products developed. As a result of the ODA, more treatments are available to people with rare diseases who once had no hope for survival.

The number of new drugs with an orphan designation has increased across the European Medicines Association (EMA), the US FDA, the Pharmaceuticals and Medical Devices Agency (PMDA), Swissmedic and the Australian Therapeutic Goods Administration (TGA), from 31% between 2011 and 2015 to 38% between 2016 and 2020. In 2021, 26 of the Center for Drug Evaluation and Research's 50 novel drug approvals — more than half — were for orphan diseases [4]. In 2021, the proportion of approved new active substances (NASs) with an orphan designation was high across six key agencies [6]. Figure 1 shows the proportion of NAS approvals with orphan designation in the EMA, the US FDA, PMDA, Health Canada, Swissmedic and TGA [7].



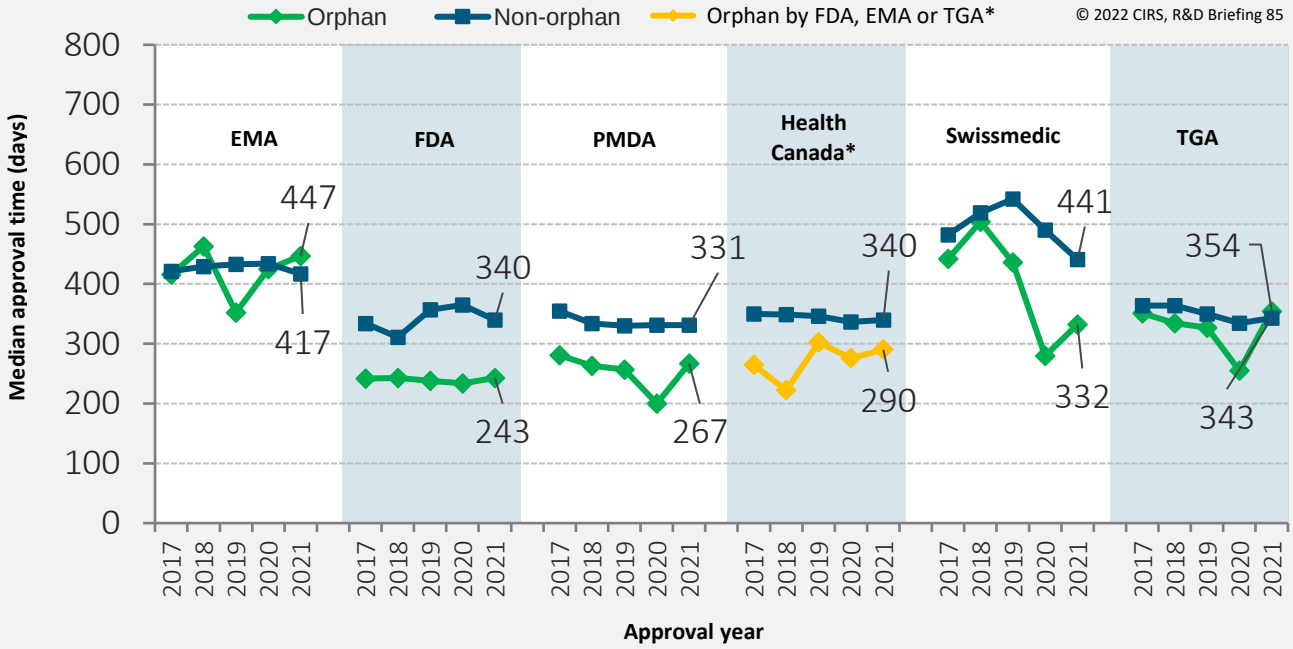
**Health Canada does not currently have an orphan policy; this data shows the number of medicines that were approved by Health Canada that were classified as orphan by either FDA, EMA or TGA.*

Figure 1 – Proportion of NAS approvals by orphan designation for six regulatory authorities between 2017 and 2021

Source: https://cirsci.org/publications/cirs-rd-briefing-85-new-drug-approvals-in-six-major-authorities-2012-2021/

From 2017 to 2021, the proportion of orphan designations varied year-on-year but has generally increased across these agencies. This may be because of disease stratification and companies' growing R&D pipelines and is consistent with increased commitment from agencies to tackle unmet medical needs. In 2021, ODs accounted for 40% of approvals for TGA, 36% for EMA, 42% for PMDA, 49% for Swissmedic and 54% for the US FDA [6]. Although Health Canada does not currently have an orphan policy, 59% of the NASs approved by the agency in 2021 were classified as orphan by either the FDA, EMA or TGA.

Figure 2 shows the median approval time for the six selected agencies considering orphans and non-orphans. Having appropriate OD-specific pathways may therefore accelerate the regulatory review times of these critical therapeutics. Approval timelines for orphans and non-orphans have been compared across six key agencies between 2017 and 2021 [6,7].



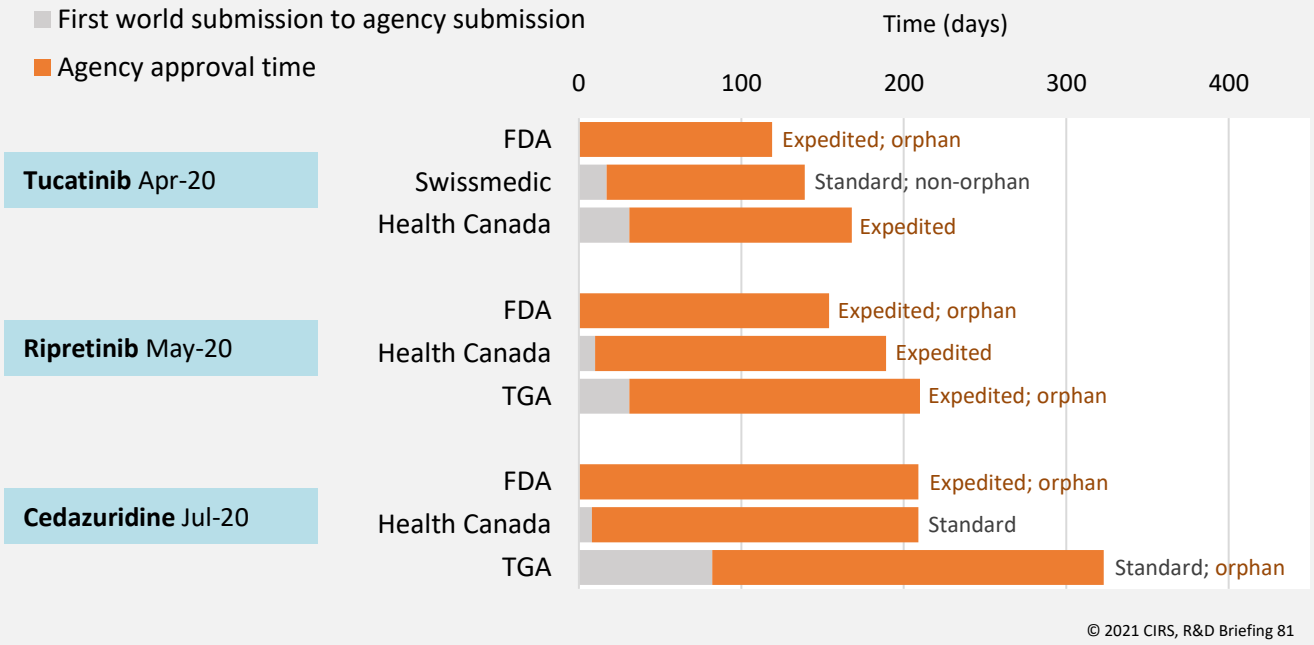
Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time.
**Health Canada does not currently have an orphan policy; this data shows the number of medicines that were approved by Health Canada that were classified as orphan by either FDA, EMA or TGA.*

Figure 2 – NAS median approval time by orphan designation for six regulatory authorities between 2017 and 2021

Source: https://cirsci.org/publications/cirs-rd-briefing-85-new-drug-approvals-in-six-major-authorities-2012-2021/

The US FDA had the fastest median approval time for orphans in 2021 (243 days), as most of these products were approved through an expedited review pathway. PMDA had the second fastest median approval time for orphans in 2021 (267 days). All new OD approved in Japan benefitted from an expedited review pathway, owing to an incentive from PMDA to address unmet needs. At the EMA, orphan medicines are eligible for conditional marketing authorisation and in some cases can be administered under compassionate use [8].

Worksharing agreements are being used increasingly frequently to authorise orphan products. In 2020, TGA authorised Isatuximab and tafamidis (both granted orphan status at TGA) through the collaborative efforts of the ACCESS consortium. Similarly, ORBIS (Figure 3) has also provided an important opportunity to accelerate the authorisation of orphan products around the world [9].



Submission gap is calculated as the time from date of submission at the first regulatory agency to the date of regulatory submission to the target agency. 'Expedited review' refers to Health Canada/TGA 'Priority Review' and Swissmedic 'Fast Track'. Health Canada does not currently have an orphan policy. Approval time is calculated from the date of submission to the date of approval by the agency.

Figure 3 – Project ORBIS; submission lag and approval times for NASs approved in 2020 (by month-year of approval by the US FDA)

Key International Regulations for Orphan Drugs

Key to facilitating access to these innovative medicines, including ODs, is the regulatory flexibility that agencies have put in place to address this need. In addition to expedited review routes, worksharing and collaborative projects described above, a variety of facilitated regulatory pathways (FRPs) are now available in various agencies, including the Breakthrough Therapy designation (FDA) and Sakigake (PMDA), along accelerated/conditional approval pathways in many countries.

Nevertheless, there remain important differences and gaps in the availability of ODs across the world. One analysis found that health plans in the United States apply fewer restrictions for orphan than non-orphan drugs (30% vs 47%). This analysis also found considerable variation (11% to 65%) in OD coverage restrictions across insurance plans. Interestingly, United States insurance plans were more likely to restrict access to those ODs with larger budget impacts [10].

Legislation, government strategy and an encouraging regulatory environment are key for the development, authorisation, and availability of any medicinal product. In the case of ODs, these

aspects are even more relevant considering the low prevalence and the challenges to justify the business case to develop and launch a product.

As mentioned before, the first worldwide official recognition and publication of legislative/regulatory considerations was in 1983 when the United States enacted the United States Orphan Drug Act. Australia and some Asian countries then launched legislation/regulation during the nineties. The European Union, however, launched its first regulation on ODs in 2000, 17 years later than the United States, with the publication of the regulation EC 141/2000.

Key Latin American Regulations for Orphan Drugs

It was not until the first decade of the 21st century that Latin American countries published their first laws/regulations on ODs. Table 1 compares the instruments and details of OD legislations in the United States, the European Union and the five largest Latin American countries [11–19].

Table 1 – Year and name of first legislation/regulation related to Orphan Drugs for selected countries

Country	Legislation/Regulation	Year
United States	Orphan Drug Act	1983
European Union	EU Regulation EC 141/2000	2000
Colombia	Ley 1392	2010
Argentina	Ley Nacional 26689	2011
Mexico	Article 224, General Health Law	2012
Brazil	Rare Diseases National Attention Policy, Ordinance 199; RDC 205	2014; 2017
Chile	Ley 20850, Luis Ricarte Soto Law	2015

The scope and characteristics of the legislation/regulation of OD in Latin America have evolved. New decrees, resolutions or instruments have been published detailing treatment in each country, however, only Brazil has on focused regulations dealing with these products.

There are many relevant regulatory/legal issues that influence the availability and access to ODs. Among the most important elements are:

- the official definition of what can be considered a rare/orphan disease.
- OD designation procedure, and
- the market authorisation paths and their possible inclusion of incentives for development and market authorisation.

A common element considered to define a rare disease refers to the number of people living with a disease (Table 2). Some countries consider other factors such as the existence of adequate treatments, the degree of unmet medical need, or the severity of the disease.

Official definitions of rare/orphan disease

In general, the definition of a rare disease in most Latin American countries is comparable with the European parameter, implying a prevalence of not more than five for every 10,000 individuals. Brazil's definition, however, is 6.5 persons per every 10,000 population and it is close to the United States definition which implies a maximum of 200,000 individuals for the country. Considering a total United States population of 332.7 million (United States Bureau of Census estimate for January 2022), the United States definition is equivalent to about six per every 10,000 persons.

Table 2 – Definitions of rare disease in different countries

Country	Patient ratio as defined	Patient ratio standardised for comparison
Brazil	65 in 100,000	1 in 1,538
United States	<200,000 in population	1 in 1,659
Argentina	1 in 2,000	1 in 2,000
Australia	5 in 10,000	1 in 2,000
Chile	5 in 10,000	1 in 2,000
Colombia	1 in 2,000	1 in 2,000
European Union	5 in 10,000	1 in 2,000
Mexico	5 in 10,000	1 in 2,000
Norway	5 in 10,000	1 in 2,000
Panama	1 in 2,000	1 in 2,000
Singapore	1 in 2,000	1 in 2,000
Switzerland	5 in 10,000	1 in 2,000
United Kingdom	1 in 2,000	1 in 2,000
Japan	<50,000 in population	1 in 2,507
Russian Federation	10 in 100,000	1 in 10,000
Peru*	1 in 100,000	1 in 100,000
• * Ministerial Resolution 230-2020-Minsa lists more than 500 rare diseases.		

Source: Rare disease - Wikipedia

Often, the terms "low prevalence" or "ultra-rare" are used for diseases with a prevalence of fewer than 1 in 2,000 people.

Rare/orphan diseases designation procedure

The orphan designation procedure is a process independent of the market authorisation and it is particularly important in countries where new drugs are being researched and developed. Generally, this process allows sponsors to benefit from various incentives when developing a therapeutic for the designated disease. The US FDA and the EMA require OD sponsors to apply for orphan designation status. The designation requires complying with criteria related to prevalence, morbidity of the disease and lack of therapeutics. Canada does not have a statutory definition of ODs, consequently it does not have a designation procedure for orphan diseases.

The Pan American Health Organization (PAHO) regional reference Latin American countries do not have a procedure like the FDA and EMA for orphan designation of a drug. Mexico and Chile do not have a process to assign orphan status to a drug. Instead, they require proof of the designation as orphan by a reference agency. In the case of Brazil, the orphan designation is a requirement to utilise the expedited orphan review process by Resolution RDC 205/2017 [18]. Characteristics of OD pathways are compared in Table 3.

Table 3 – Selected characteristics of the regulatory environment in the Americas and Europe

Country	Regulatory Authority	OD legislation or regulation	OD designation procedure	Market authorisation path
United States	FDA	Yes	Yes	Fast Track, Priority, Accelerated
Europe	EMA	Yes	Yes	Centralised accelerated procedure
Canada	Health Canada	No	No	Accelerated available, not specific
Argentina	ANMAT	Yes	No	Under special conditions
Brazil	ANVISA	Yes	No	Special procedure
Mexico	COFEPRIS	No	No	Recognition letter, 2 years
Chile	ISP	Yes	No	General abbreviated registration
Colombia	INVIMA	Yes	No	Simplified procedure for Vital drugs not available

Special Market Authorisation Regulatory Pathways

Among the most important factors affecting a decision to submit for a new OD registration to a country are the characteristics of the specific-regulatory-pathway for market authorisation for such medicines. The US FDA and the EMA have established specific pathways that aim to facilitate development and access to ODs and these can also benefit from the use of a Priority Pathway, Fast Track and Accelerated procedure. Each of the PAHO regional reference Latin American authorities have their own particulars with respect to market authorisation of ODs and/or rare diseases.

Argentina

In Argentina, the first official publication on ODs/rare diseases was Law 26,689 published in 2011 [15]. This law stressed the need to promote comprehensive care for persons with “low frequency diseases” and created a multidisciplinary societal committee responsible for managing incentives for research, training, social involvement, etc. This law defined these low frequency diseases,

implying an incidence equal or below 2 persons for every 2,000 individuals. The regulation to this law, published in 2015, created an Honorary Consulting Council for the development of proposals on how to apply the 2011 mentioned law. The main impact of the law and its regulation was the establishment of a definition of rare disease for Argentina.

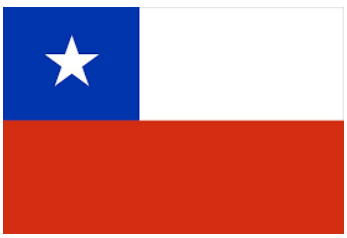
In 2012, ANMAT issued Regulation No. 4,622/2012 explicitly created the Commission and Assignation and Evaluation of Medicines responsible for determining whether a medicine can be authorised under the so-called registration "under special conditions" applying to therapeutic products for the prevention, diagnosis and/or treatment of low frequency diseases (rare diseases) and other serious illnesses for which there are not sufficient therapeutic products available. This regulatory framework is based on Rare Disease status, defined by Law 26,689 and Annex I of regulation No 4622. In a succinct manner, Annex 1 defined a simplified procedure requiring full presentation of early phases of clinical studies and other available clinical trials, complete evidence that the drug has been classified as an OD, a risk assessment plan to closely monitor safety, quality and efficacy of the product, including registration of patients and medical guidance, an intensive pharmacovigilance plan, periodic reports on monitoring the results of the treatment, and a written informed consent of the possible risks and benefits of the drug.

Brazil

Brazil did not have any specific comprehensive regulation for ODs until recently. The ANVISA Resolution RDC No. 205, published in December 2017 [18], provides for a special procedure for approval of clinical trials, good manufacturing practices certification and most importantly for a registration path of new drugs for rare diseases.

The initial applicable regulation, RDC 60/2014 [17], was general for all drug registrations and did prioritise the assessment of orphan therapies. To access the RDC 205 expedited pathway, the sponsor must have an initial pre-submission meeting with ANVISA within 60 days after the first submission to another regulatory agency to express interest in using this pathway. Thereafter, companies have a 30-day time limit to submit a full formal application to ANVISA for registration and the authority is committed to a maximum of 60 days for a resolution. By this process, ANVISA encourages manufacturers to submit in Brazil at approximately the same time as other major regulatory agencies, like the US FDA or the EMA.

Chile



In Chile, there is no law that defines what is considered an orphan or rare disease; however, the Instituto de Salud Publica (ISP) issued Resolution 411 in 2015 [19] which defines ODs and rare or orphan diseases, and lists requirements and general conditions for market approval. The sponsors must provide proof that the product has been previously approved by the US FDA or the EMA and certification that such agencies have classified the drug as an OD. The resolution indicates submissions must comply

with normal requirements for registration, except the possibility of having limited clinical trials. Finally, the sponsors must present updated public safety reports, special pharmacovigilance provisions and a comprehensive risk management plan. The resolution indicates that market approval would be subject to an abbreviated procedure, implying a time limit of 5 months from submission to final decision.

Colombia

Decree 481 of Colombia, published in 2004, regulate the so-called "Vital Drugs not Available". The Decree defines these drugs as essential medicines without substitutes aiming to preserve a life or reduce suffering and not sufficiently available in the country because of its low market profitability. Decree 481 also indicates that it is the responsibility of the Specialized Chamber of Medicines and Biological Products of the Reviewing Commission (Comisión Revisora) to determine whether a drug can be listed as "Vital Non-Available". If a drug is determined as Vital Non-Available, then it qualifies for a simplified import procedure and is not subject to registration. In 2010, the Congress of Colombia published Law 1392 [14], a general law that recognises and defines orphan diseases and outlines general principles, commitments of the government for research, treatment, drug procurement and for the creation of a national registration of patients. This law briefly discusses drugs for treatment of orphan diseases.

Mexico

In Mexico, there is no regulation specific to the assessment and approval of ODs. The main official references include a 2006 description in the Mexican Pharmacopeia defining general characteristics of ODs and a General Health Law amendment of 2012 which defined and recognised rare diseases [16].

The approval process of ODs seems to be managed by internal procedures of COFEPRIS. In 2020, the agency organised a virtual seminar to explain the authorisation procedure. Accordingly, submissions for approval have to be presented and organised in a Common Technical Document (CTD) format and requested via a formal letter with application form EL87 which is available on the COFEPRIS website. During this seminar it was also indicated that module 1 of the submission should include a copy of an authorisation letter from the national pharmacovigilance committee, proof of recognition as orphan by reference authorities like the US FDA, EMA or Swissmedic, and also recent studies about the disease prevalence in Mexico and internationally. Submissions are not currently required to go through COFEPRIS's New Molecules Committee. The authorisation is granted not as a registration but as a "Recognition Letter" with a validity of two years.

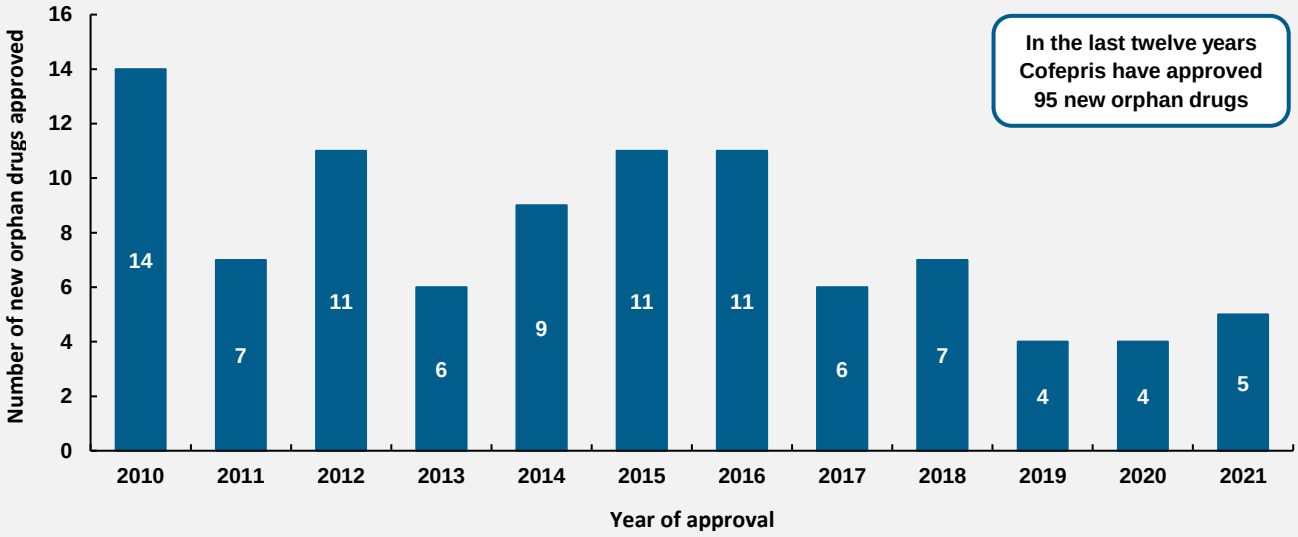
In 2017, Mexico created a multidisciplinary commission responsible for the analysis, evaluation, registration, and monitoring of conditions with respect to the listed rare diseases. Until recently, this commission had officially listed only 20 rare diseases. However, last June 29, 2023, Mexico

issued a new regulation which abrogated the 2017 norm that created the above commission and instead recognize the 5500 rare diseases listed in the International Classification of Diseases of the World Health Organization.

Availability of Orphan Drugs in Mexico

Official statistics

Agencies strive to ensure that the most effective, safe, quality medicines are made available to their populations. Yet patients suffering from rare diseases, who often require treatment with ODs, may find themselves with a limited range of treatment options. This holds true across much of Latin America, including Mexico. To better understand the challenges of optimising the availability of ODs in Mexico, we assessed those from various perspectives.Figure 4 shows the total number of OD approvals in Mexico from 2010 to 2021 (published by COFEPRIS) [20, 21]. During this period, COFEPRIS approved a total of 95 products targeted for rare diseases. The graph clearly shows a sharp decline in approvals over the past five years.



Note: Nine ODs were excluded from this analysis since their active substances were approved previously

Figure 4 – New orphan drugs approved by COFEPRIS, 2010–2021

Source: https://www.gob.mx/cofepris/documentos/registros-sanitarios-medicamentos. Last time visited 29/12/2021. Using data derived from publicly available resources.

Figure 5 presents a comparison of the total number of new OD approvals in Mexico with those of the US FDA and the EMA over the period 2010–2021. Recent years have shown an opposite trend between the number of ODs approved by the FDA and the EMA (increasing numbers) and the approvals in Mexico (lower than most other years). In 2020 and 2021 there were only 4 and 5 new ODs authorised in Mexico, respectively, compared with 31 and 28 products for the FDA in those years and 16 for the EMA in each year.

The lower authorisations of Mexico compared with the US FDA and the EMA may be impacted by Mexico's lack of a specific ODs regulation and/or of a specific pathway for these types of therapeutics, as well as company strategy in submitting to the various markets.

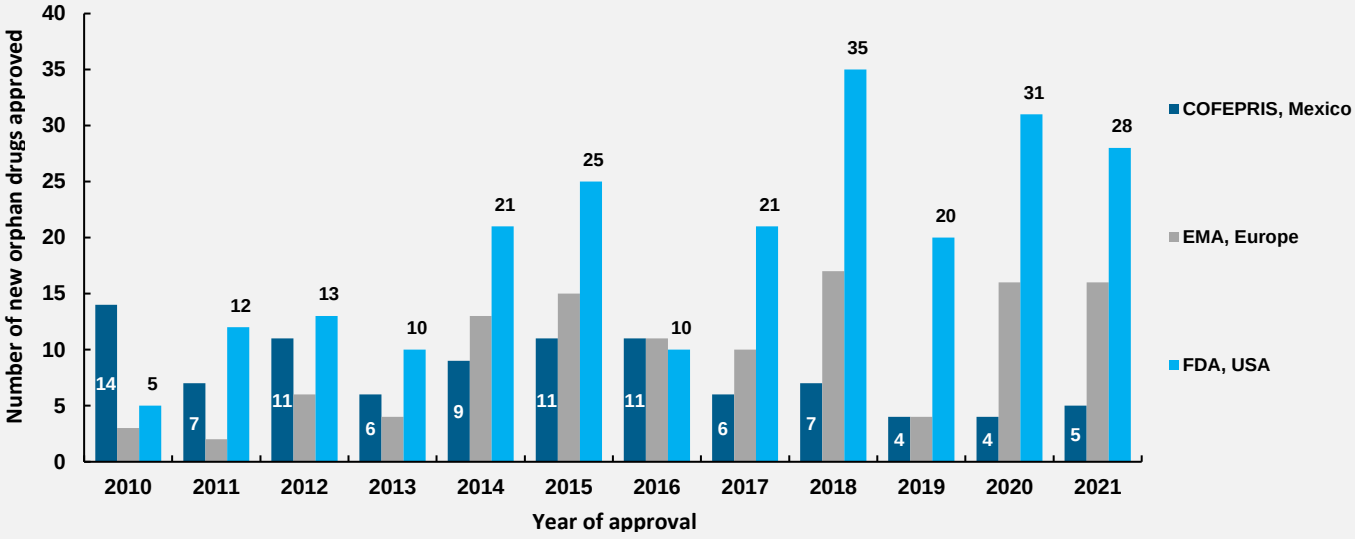


Figure 5 – Comparison of total new orphan drugs approved by COFEPRIS, the US FDA and the EMA, 2010–2021

Sources: 1. https://www.gob.mx/cofepris/documentos/registros-sanitarios-medicamentos. Last time visited 29/12/2021. 2. CIRS Regulatory Review times Database 2022 (RRTD 2022).

Approval time is a key consideration for patients who are waiting for these important medicines. Figure 6 compares the overall approval time for ODs by the US FDA, EMA and Mexico for the period 2010–2021. Because of the regulatory agilities built into their systems, the US FDA and EMA consistently show shorter approval time than Mexico. This situation became more evident in Mexico in the past two years. For 2020 and 2021, total approval time in Mexico is about twice as long as the EMA and four times longer than for the United States. Those years registered the longest approval times in Mexico for the 12 years of analysis.

The overall results for Mexico in 2020 show the differences in the number of authorisations and length of registration times are widening in those years compared to the US FDA and the EMA.

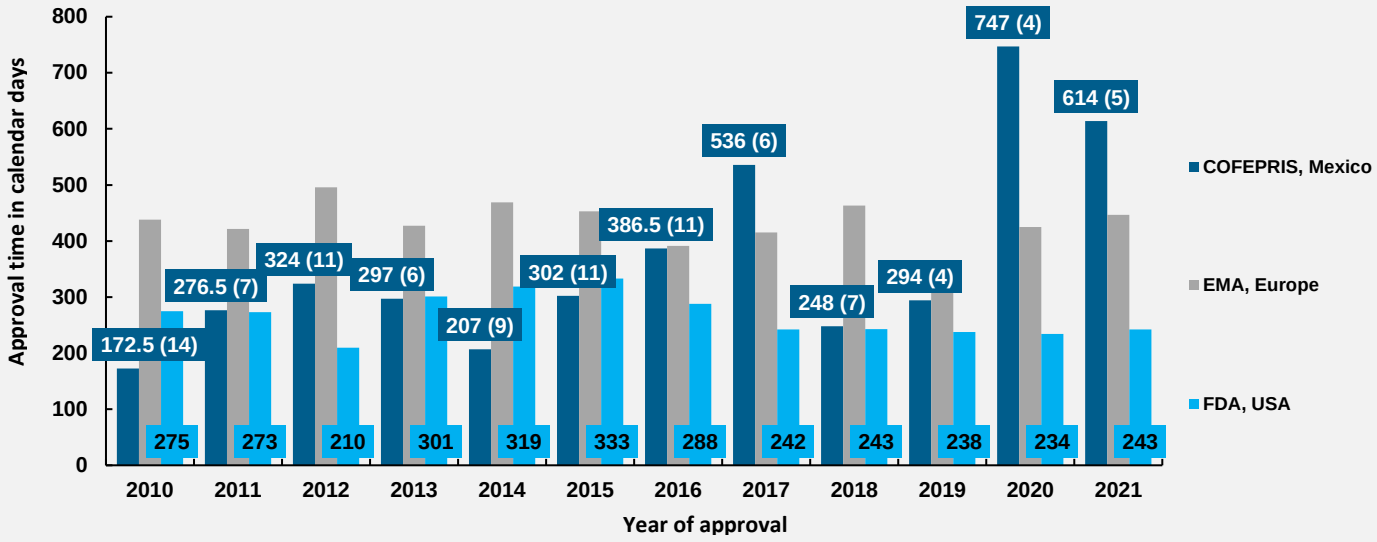


Figure 6 – Comparison of median approval time for total new orphan drugs by COFEPRIS, the US FDA and the EMA, 2010–2021

Sources: 1. https://www.gob.mx/cofepris/documentos/registros-sanitarios-medicamentos. Last time visited 29/12/2023. 2. CIRS Regulatory Review times Database 2022 (RRTD 2022).

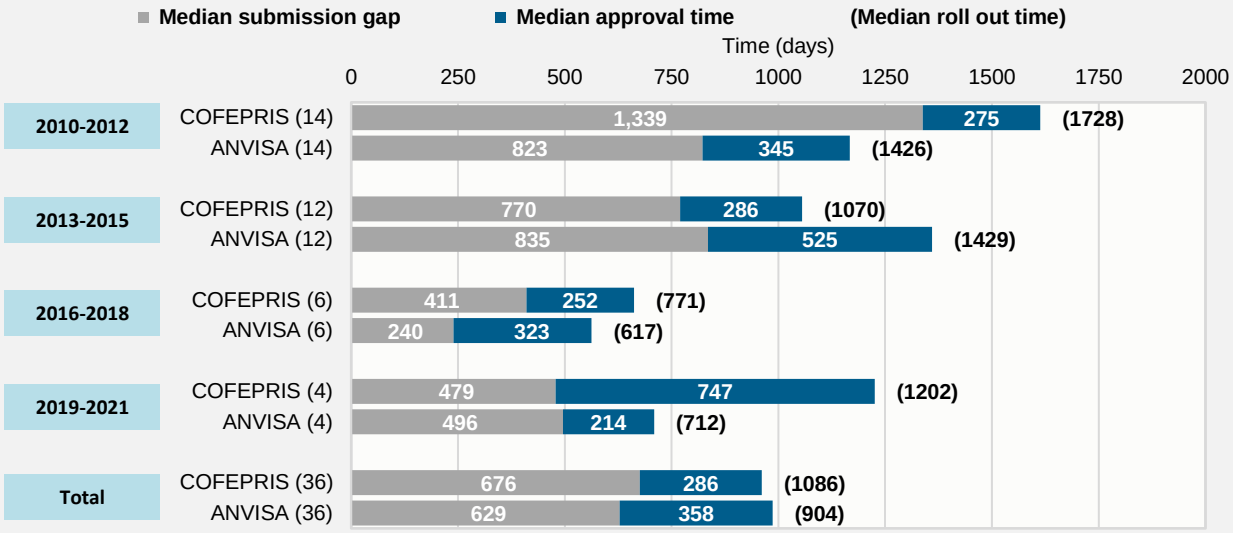
Company survey statistics

Because of the previous observations, it was considered relevant to examine Mexico's approval time with respect to a similar Latin American country: Brazil. CIRS conducted a survey of 11 multinational pharmaceutical companies, all of which are active in Mexico in the OD arena, as described in further detail on page 17, in order to obtain additional detail on the COFEPRIS submission timeline.

The agencies of both countries (COFEPRIS and ANVISA) are PIC/S and ICH members, and their countries are the most populated and largest economies in Latin America. A cohort of 36 ODs that were approved by both COFEPRIS and ANVISA were analysed over the period 2010–2021. For this cohort, the approval time, the submission gap time and the total roll out time were measured.

The **approval time** for a therapeutic in an agency is defined as the difference between the submission date and the approval date and includes both agency and company time. The **submission gap** for a drug in a specific agency is the difference between the first-in-the-world submission date and the submission date to that agency.

Figure 7 compares the median approval time, the submission gap and the total roll out time of the same cohort of ODs approved Brazil and Mexico for the full period 2010–2021 and examines four consecutive 3-year periods during those years.



Notes: The surveyed pharmaceutical companies mentioned that between 2010 and 2021 they received 39 new orphan drug approvals from COFEPRIS. Research on the approval time, submission gap and roll out time was done using the submission dates described by the surveyed companies, the approval dates described in open-source publications from COFEPRIS, and the first in the world submission dates extracted from the CIRS Regulatory Review Time Database 2022. The approval time is the difference between the approval date and the submission date in COFEPRIS. The submission gap is the difference between the first in the world submission date (CIRS RRTD 2022) and the submission date in COFEPRIS. The roll out time is the difference between the first in the world submission date (CIRS RRTD 2022) and the approval date in COFEPRIS.

Figure 7 – Submission gap, approval time, and roll out time of a same cohort of 36 new orphan drugs approved by COFEPRIS and ANVISA

Sources: CIRS Industry Survey Results 2021, CIRS Regulatory Review Time Database, https://www.gob.mx/cofepris/documentos/registros-sanitarios-medicamentos. Last time visited 01/07/2022, and Open data portal of Brazil https://dados.gov.br/dataset/medicamentos-registrados-no-brasil, https://dados.gov.br/dataset/cico-de-via-de-analise-de-peticodes-de-registro-de-medicamentos. Last time visited 18/07/2022.

When observing the full period (2010–2021), the two countries seem relatively aligned with a total difference for the full period in the median approval time of 72 days in favour of COFEPRIS. However, when comparing period by period, considerable differences and variations in approval time, submission gap and total roll out time were noted. Considering only approval time, in the case of Mexico, the median during the first three periods (covering from 2010 to 2018), ranged between 252 and 286 days, comparatively shorter than Brazil and a relatively "reasonable" time. However, Mexico's median approval time for the four products approved during the period 2019–2021 increased to 747 days. In contrast, Brazil had a median approval time for the period 2019–2021 of 214 days, an improvement with respect to its own previous experience and less than one-third of Mexico's similar approval time.

Comparing the submission gap, largely owing to company decisions, differences among the two countries were also observed. The comparison of 2010–12 and 2016–18 show more than 60% longer time for submission to Mexico compared with Brazil. For the other cohorts (2013–15 and 2019–21), the difference is no more than 8% lower in Mexico than in Brazil.

The approval time and submission gap have direct and considerable impact on the total time to availability of medicines. In the most recent period analysed (2019–2021), the total roll out time shows that it took slightly less than two years for a new drug from its first world submission to the Brazilian authorisation. A similar measure for Mexico indicates it would take about three years and four months to become available in the market.

Comparison with Latin America

The trends for ODs in Mexico were also compared with other jurisdictions considering a similar cohort of drugs. First, a cohort of 43 ODs approved in both the US FDA and the EMA from 2016 to 2020 was identified and these were analysed to determine whether those drugs were approved in Mexico and other Latin American jurisdictions. The comparator countries were Argentina, Canada, Brazil, Colombia, Chile and Mexico (Table 4). The information for approvals was obtained from the websites of the relevant agencies or by interviews directly with the regulators.

For this cohort, Mexico authorised only five of the ODs, equivalent to about 11% of the total ODs. In comparison, Canada and Brazil showed high levels of registrations for this cohort, 77% and 65% respectively, while Argentina granted approval to 44% of the products. Colombia had the smallest number of approvals (9%).

It is relevant to mention that the lower percentage of approvals of those ODs in Mexico, Chile and Colombia could have resulted from a variety of factors, including reduced market interest of companies or regulatory barriers.

Table 4 – Number of products approved by jurisdiction for a cohort of 43 new orphan drugs approved by both the US FDA and the EMA

Country	Regulatory Authority/Agency	Number of approved products
Canada	Health Canada	33
Brazil	ANVISA	28
Argentina	ANMAT	19
Chile	ISP	10
Mexico	COFEPRIS	5
Colombia	INVIMA	4

Source: This information was obtained from the websites of the relevant agencies or directly from the regulators.

Industry Perception Study

CIRS conducted a survey of 11 multinational pharmaceutical companies, all of which are active in Mexico in the OD arena. The authorisations originating from those 11 companies represented 50 of the 95 (53%) total orphan products approved in Mexico during the period 2010–2021. The survey was conducted between October and November 2021 and was designed to understand the industry's perception of the Mexican regulatory environment for ODs and how it compares with

other Latin American regulatory environments. The companies surveyed were active in other Latin American countries as follows: all (11) had a presence in Brazil, 10 were active in Colombia and Chile, and 9 companies in Perú and Argentina.

The respondent's general perception of Mexico's regulatory process for ODs shows that four companies rated the process as poor (approximately 36%), four considered the process as acceptable (approximately 36%) and three companies as good (approximately 27%). This response indicates there is no consensus within the industry on the existence of significant regulatory problems. However, when asked for details regarding their answers, the responses indicated some barriers existed, including:

- Lack of a formal OD regulation
- Legal uncertainty
- Lack of clear procedures for authorisation
- Influence of the individual reviewer's criteria in authorisations and renewals for ODs.

The main positive aspects mentioned were:

- A good level of communication with the agency and reviewers
- The existence of a focused area of expertise within the agency for orphan products, despite the lack of a specific OD pathway.

The survey also reflected the company's perception that approval times for ODs by COFEPRIS took longer than for other countries (Figure 8).

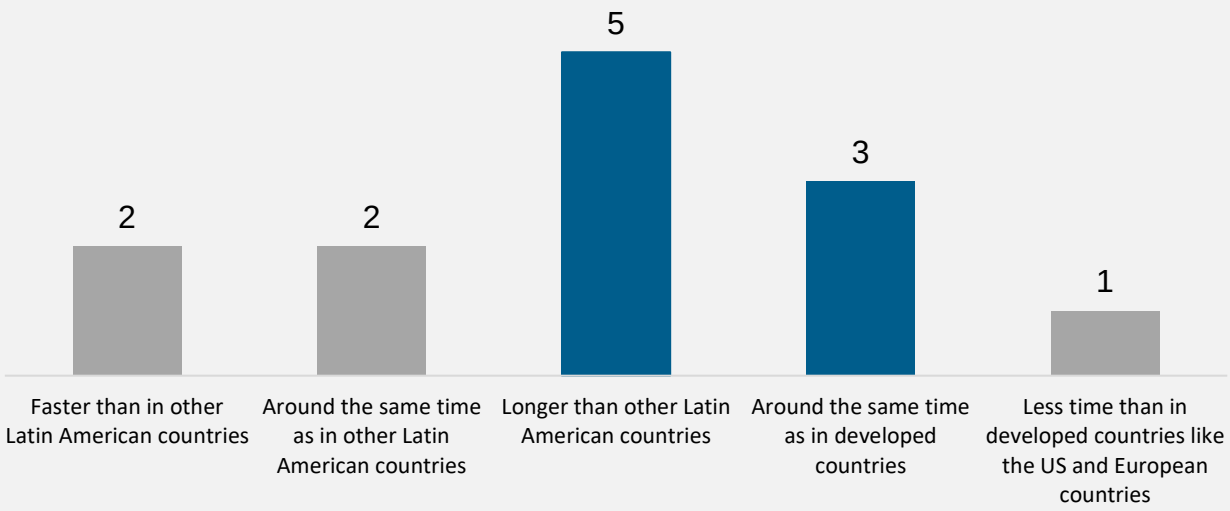


Figure 8: Company perception of COFEPRIS approval time compared with other Latin American countries and reference countries

Source: CIRS Survey

All companies agreed that when there is a previous authorisation by a mature agency, the regulatory approval process for a new OD by COFEPRIS should take no more than 6 months.

Companies perceived authorisation delays are related to an existing review backlog at the agency and to COFEPRIS' requests for additional information beyond what might be expected (Figure 9).

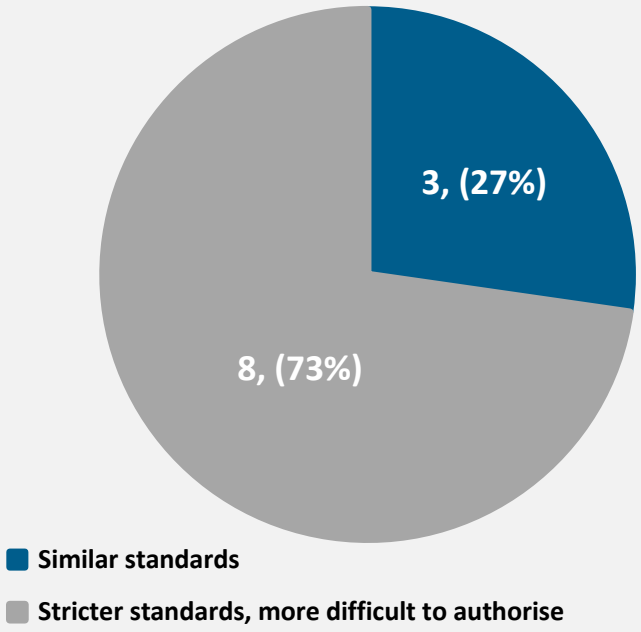


Figure 9 – Comparison of standards and requirements requested by COFEPRIS with other countries such as the United States or a European country

Source: CIRS Survey

Eight of 11 companies felt that the standards for authorisation were stricter and more difficult to address than in other countries and that these were impacted by:

1. **Lack of specific guidelines** on the requirements and the description of the homologated assessment criteria
2. **Hard-to-meet requirements as per the normal marketing authorisation** (e.g., Phase III clinical trials, stability studies batch number, commercial batch information requirement, demonstrating the prevalence of the disease in Mexico)
3. **Additional CTD information required** (e.g., traceability of batches submitted, Good Manufacturing Practice certificates issued only by agencies recognised by COFEPRIS, chromatograms, and manufacturing license for the marketing authorisation holder).

Other barriers to an efficient OD regulatory process are listed in Table 5.

Table 5 – Major challenges facing COFEPRIS in its regulatory authorisation process for new orphan drugs

Major challenges	% of surveyed companies that agree
Work overload in the agency, leading to delays in the regulatory process	100% (11)
Too much information is requested, which makes the regulatory evaluation process longer, especially in cases when the product has been previously authorised in strict regulatory agencies	91% (10)
Lack of resources with knowledge to assess regulatory requests	82% (9)
Equivalence agreements or routes of consignments (de reliance) are not actually used to benefit from the scientific evaluation previously carried out by other agencies	82% (9)
Orphan drugs are not a priority	45% (5)
The lack of clear orphan drug-specific regulations indicating what, how and when	18% (2)

Source: CIRS Survey

Finally, the role that companies could play in optimising the OD process in collaboration with COFEPRIS was explored. Although 9 of the 11 companies felt that the industry had low or no input into developing the regulatory processes and polices for ODs in Mexico, the survey respondents were eager to contribute to and improve the process. They indicated desire in:

- Supporting the development of local standards for ODs
- Raising awareness about the prevention, diagnosis, and treatment of rare diseases among the health system participants and the agency
- Contributing to the agency´s technical knowledge on new advanced technology products and process details needed for a supportive scientific review within the authorisation process.
- Creating and promoting a favourable regulatory environment that simplifies and shortens the authorisation process for a new OD.

This would help address the three main challenges indicated by the survey:

- Uncertainty in registration requirements
- Lack of reliance authorisation process
- Lack of local rare diseases prevalence information.

And could be further addressed by the:

- Development of a robust and clear OD regulatory framework
- Development of a reliance process for ODs through a specific equivalence agreement
- Improving collaboration among the agency, academic researchers and developers.

Survey of Patient Associations: The lack of treatments for rare diseases in Mexico

Rare diseases affect so few people that information about them may be difficult to find, making the situation more traumatic and stressful. In the past, support could only be found through networking with other families coping with similar diseases or through networks developed by academics and concerned doctors. Over the years, patient representative groups have worked tirelessly to draw attention to the needs of people with rare diseases, and especially to the lack of treatment options. One important role of these patient advocates is to promote legislation that encourages the authorisation of and access to life-saving OD products.

Therefore, CIRS engaged patient representative groups in Mexico to obtain their organisational perceptions of how the regulatory process for orphan products is conducted in Mexico**.** Barriers and opportunities to access ODs were explored. Four patient organisations responded to the survey providing basic insights into the complexities of the process for patients.

Their aspirations were found to be largely in line with those of other stakeholders. For example, their expectation was for a 6-month target authorisation time in Mexico. They too had divergent perceptions of the speed with which COFEPRIS addressed new products for orphan diseases with a split between being slower, similar or faster than other Latin American agencies. They recognised that COFEPRIS was burdened by its workload; coupled with a perceived lack of prioritisation of orphan products and a poor scientific understanding of these diseases, patients were left waiting for their specialty therapies. However, they felt that these obstacles could be overcome through greater opportunities for interactions with the agency, including pre-submission meetings and educational forums.

The Way Forward

Mexican patients who suffer from rare diseases have an expectation of having available to them the same innovative therapies that patients with similar afflictions can access in other countries. The availability of innovative medicines for rare and orphan diseases in Mexico is influenced by many factors. These include the relative low prevalence of the disease in Mexico, the roll-out strategy of the developer of the medicines and not least of all, the types of regulatory pathways that are available to facilitate the development and authorisation of these important medicines.

In Mexico, these factors have resulted in the relative lack of availability of innovative ODs compared not only to major economies such as the United States and Europe, but also compared with other Latin American countries. To optimise the regulatory process and facilitate the availability of innovative ODs in Mexico, our observations, together with perceptions and recommendations from multinational companies and patient groups suggest that the following activities could serve to address these issues in Mexico:

- COFEPRIS could develop a robust OD regulatory framework with clear guidelines for developers and assessment procedures for reviewers.
- COFEPRIS could encourage a reliance process for ODs through a specific equivalence agreement based on approvals by reference agencies.
- All parties (COFEPRIS, academic researchers, patient groups, and developers) could collaborate to create a learning environment for all stakeholders, including COFEPRIS assessors who wish to focus on orphan products.

These initiatives could contribute to the timely availability of ODs for the Mexican population.

List of acronyms

ANMAT	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica
ANVISA	Agencia Nacional de Vigilancia Sanitaria
CIRS	Centre for Innovation in Regulatory Science
COFEPRIS	Comisión Federal para la Protección contra Riesgos Sanitarios
CTD	Common Technical Document
EMA	European Medicines Agency
FDA	Food and Drug Administration
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INVIMA	Instituto Nacional de Vigilancia de Medicamentos y Alimentos
ISP	Instituto de Salud Publica
NAS	new active substances
OD	orphan drug
PAHO	Pan American Health Organization
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PMDA	Pharmaceuticals and Medical Devices Agency
TGA	Therapeutic Goods Administration
WEF	World Economic Forum
WHO	World Health Organization

References

1. COFEPRIS. Estrategia sobre Certidumbre Regulatoria para el Sector Farmacéutico. January 2023. Accessed at https://www.gob.mx/cms/uploads/attachment/file/792036/Estrategia_de_Certidumbre_Regulatoria_para_el_sector_Farmaceutico_enero_2023.pdf
2. Gobierno de México. Alrededor de 8 millones de mexicanos viven con enfermedades raras. 28 February 2018. Accessed at https://www.gob.mx/salud/articulos/alrededor-de-8-millones-de-mexicanos-viven-con-enfermedades-raras?idiom=es.
3. World Economic Forum, Global Data Access for Solving Rare Disease: A Health Economics Value Framework. 2020. Accessed at https://www3.weforum.org/docs/WEF_Global_Data_Access_for_Solving_Rare_Disease_Report_2020.pdf
4. US FDA. CDER Continues to Make Rare Diseases a Priority with Drug Approvals and Programming to Speed Therapeutic Development. 4 March 2022. Accessed at https://www.fda.gov/news-events/fda-voices/cder-continues-make-rare-diseases-priority-drug-approvals-and-programming-speed-therapeutic
5. US FDA. Rare Diseases at FDA. 13 December 2022. Accessed at https://www.fda.gov/patients/rare-diseases-fda
6. US FDA. Orphan Products: Hope for People With Rare Diseases. 1 March 2018. Accessed at https://www.fda.gov/drugs/information-consumers-and-patients-drugs/orphan-products-hope-people-rare-diseases
7. Centre for Innovation in Regulatory Science (2022) R&D Briefing 85: New drug approvals in six major authorities 2012–2021: Focus on Facilitated Regulatory Pathways and internationalisation. Centre for Innovation in Regulatory Science (CIRS), London, UK. Accessed at: https://cirsci.org/wp-content/uploads/dlm_uploads/2022/06/CIRS-RD-Briefing-85-6-agencies-v2.3.pdf
8. European Medicines Agency. Orphan designation: Overview. Accessed at https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview
9. Centre for Innovation in Regulatory Science (2020) R&D Briefing 81: New drug approvals in six major authorities 2011–2020: Focus on Facilitated Regulatory Pathways and Worksharing. Centre for Innovation in Regulatory Science (CIRS), London, UK. Accessed at https://cirsci.org/wp-content/uploads/dlm_uploads/2021/06/CIRS-RD-Briefing-81-6-agencies-v5.pdf
10. Chambers JD, Panzer AD, Kim DD, Margaretos NM, Neumann PJ: Variation in US Private Health Plans' Coverage of Orphan Drugs. Am J Manag Care. 2019;25(10):508-512. Accessed at https://www.ajmc.com/view/variation-in-us-private-health-plans-coverage-of-orphan-drugs?p=3
11. Orphan Drug Act (1983). Public Law 97–414—JAN. 4, 1983. Accessed at https://www.govinfo.gov/content/pkg/STATUTE-96/pdf/STATUTE-96-Pg2049.pdf
12. Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999. On orphan medicinal products. Accessed at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32000R0141
13. Colombia. Enfermedades huérfanas. Accessed at https://www.minsalud.gov.co/salud/publica/PENT/Paginas/enfermedades-huerfanas.aspx
14. Por medio de la cual se reconocen las enfermedades huerfanas como de especial interes y se adoptan normas tendientes a garantizar la proteccion social por parte del estado colombiano a

la población que padece de enfermedades huérfanas y sus cuidadores. Accessed at https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/DE/DIJ/ley-1392-de-2010.pdf
15. Argentina Public Health Law 26,689. Promote comprehensive health care for people with Rare Diseases. June 29, 2011. Accessed at https://www.argentina.gob.ar/normativa/nacional/185077/texto
16. Mexico. Ley General de Salud Federal Artículo 224. Accessed at https://leyes-mx.com/ley_general_de_salud/224.htm
17. Brazil National Policy for Rare Diseases (2014). Accessed at https://bvsms.saude.gov.br/bvs/saudelegis/gm/2014/prt0199_30_01_2014.html
18. Brazil RDC Resolution # 205, December 28, 2017. Accessed at https://abracro.org.br/pdfs/Resolucao-RDC205-de-27-12-17-ingles.pdf
19. Chile Resolución 411 Recomendaciones para el Registro Sanitario de Medicamentos Huérfanos, Febrero 2015. Accessed at https://www.bcn.cl/leychile/navegar?idNorma=1075139
20. Gobierno de México. Listados de Registros Sanitarios de Medicamentos. 26 September 2016. Accessed at https://www.gob.mx/cofepris/documentos/registros-sanitarios-medicamentos.
21. EducaPRiS. Medicamentos Huérfanos: oficio de reconocimiento, vigencia y prórroga. 20 January 2022. Accessed at https://www.youtube.com/watch?v=lP8c2DOoM-w.
22. US GAO: FDA Could Improve Designation Review Consistency; Rare Disease Drug Development Challenges Continue. Nov 30, 2018. Accessed at https://www.gao.gov/products/gao-19-83

Other References

Genetic and Rare Disease Information Center. Accessed at https://rarediseases.info.nih.gov/about

Arnold RJG, Bighash L, Bryón Nieto A et al. The role of globalisation in drug development and access to orphan drugs: orphan drug legislation in the US/EU and in Latin America. [v1; ref status: indexed, http://f1000r.es/3ix] F1000Research 2015, 4:57 (doi: 10.12688/f1000 research.4268.1)

PRIME: priority medicines. European Medicines Agency. Accessed at https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines.

M.L. Bouwman, J.J.S. Sousa and M.E.T. Pina, Regulatory issues for orphan medicines: A review, Health Policy and Technology, https://doi.org/10.1016/j.hlpt.2019.11.008

Arnold RJ, Bighash L, Bryón Nieto A, Tannus Branco de Araújo G, Gay-Molina JG, Augustovski F. The role of globalization in drug development and access to orphan drugs: orphan drug legislation in the US/EU and in Latin America. F1000Res. 2015 Feb 27;4:57. doi: 10.12688/f1000research.4268.1. PMID: 25844162; PMCID: PMC4367514.

Gammie T, Lu CY, Babar ZU. Access to Orphan Drugs: A Comprehensive Review of Legislations, Regulations and Policies in 35 Countries. PLoS One. 2015 Oct 9;10(10):e0140002. doi: 10.1371/journal.pone.0140002. PMID: 26451948; PMCID: PMC4599885

Khosla N, Valdez R. A compilation of national plans, policies and government actions for rare diseases in 23 countries. Intractable Rare Dis Res. 2018 Nov;7(4):213-222. doi: 10.5582/irdr.2018.01085. PMID: 30560012; PMCID: PMC6290840.

APEC Action Plan on Rare Diseases. Accessed at https://www.apec.org/docs/default-source/satellite/Rare-Diseases/APEC_ActionPlan.pdf

Rare Diseases Act of 2002. Public Law 107–280—NOV. 6, 2002. Accessed at https://www.congress.gov/107/plaws/publ280/PLAW-107publ280.pdf

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About CIRS

The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independent UK-based subsidiary of Clarivate plc. CIRS provides an international forum for industry, regulators, Health Technology Assessment (HTA) and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science and to facilitate access to pharmaceutical products. It is governed and operated by Clarivate for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities, special projects and grants.