The Impact of Recent Regulatory Developments on the Mexican Therapeutic Landscape

Access to innovative medicines is key to improving overall population health, reducing hospitalisation time and decreasing morbidity and mortality. An efficient regulatory process can be reflected in measurable positive health impacts; conversely, activities that slow or impede regulatory efficiency and predictability can be detrimental. Recent developments in the Mexican regulatory system for the assessments of innovative new products have had a negative impact on Mexican public health.

This Briefing addresses the impact of suspending the activities of the New Molecules Committee (NMC) on the Mexican therapeutic landscape. First, we compared the way that "new medicines" are defined within the context of the Mexican regulatory system, with definitions used by comparable regulators and health organisations. We have also investigated the extent to which new drugs approved by the US FDA have also been approved by other important jurisdictions, specifically Mexico, Brazil, Europe, and Canada. In this manner, we expect to gain a better understanding of the impact the absence of NMC evaluation sessions is having on the availability of new medicines for Mexican patients.

NMC's regulations require that all new innovative products (including innovative biologics and biosimilars) considered for the Mexican market be assessed by this committee prior to formal submission for market authorisation. The last time this committee held a session was in May 2019. Since that time COFEPRIS has not received any new submissions for the registration of innovative products.

Our findings indicate the regulatory approval system that had been in place prior to the NMC ceasing its activities provided an opportunity for innovative products to obtain regulatory approval, despite recognised long timelines and process inefficiencies. The current situation has severely curtailed the availability of innovative products; this landscape could be improved by the reinstitution of the NMC, the more effective use of accelerated pathways and by prioritising the assessment of critically important new medicines.

El acceso a medicamentos innovadores es clave para mejorar la salud de toda la población, para reducir los tiempos de hospitalización, la morbilidad y la mortalidad de un país. Un proceso regulatorio eficiente tiene un impacto positivo medible en la salud, y por el contrario, acciones que retrasan o impiden la eficiencia regulatoria y su predictibilidad pueden ser perjudiciales. La parálisis reciente del Sistema regulatorio mexicano respecto a la evaluación de nuevos medicamentos innovadores conlleva un impacto negativo en la salud de la población mexicana.

Este informe analiza el impacto de la suspensión de las actividades del Comité de Moléculas Nuevas (NMC, por sus siglas en inglés) sobre el horizonte terapéutico de México. En primer lugar, comparamos la definición de nuevos medicamentos según el contexto regulatorio mexicano con las definiciones adoptadas por otras agencias reguladoras u organizaciones de salud del mundo. Asimismo, investigamos en qué medida los nuevos medicamentos que han sido autorizados por la agencia de los Estados Unidos (FDA) han obtenido también registro sanitario en otras jurisdicciones importantes; en particular, comparamos el caso de México con los de Brasil, Europa y Canadá. De esta forma esperamos lograr una mejor comprensión del impacto que ha tenido la falta de reuniones de evaluación del NMC en la disponibilidad de nuevos medicamentos para los pacientes de México.

La regulación del NMC exige que todos los medicamentos innovadores (incluyendo biotecnológicos y biosimilares) que pretendan entrar al mercado mexicano deben obtener una autorización del NMC antes de someter una solicitud de registro sanitario. La última vez que este Comité sesionó fue en mayo de 2019. A partir de entonces, COFEPRIS no ha recibido ninguna solicitud de registro sanitario de productos innovadores.

Nuestros hallazgos reflejan que la operación del sistema de autorización regulatoria previo a la suspensión de actividades del NMC, aun considerando los largos tiempos de evaluación e ineficiencias en el proceso, sí ofrecía una oportunidad para que productos innovadores obtuvieran un registro sanitario. La situación actual ha reducido drásticamente la disponibilidad de medicamentos innovadores. Esta tendencia puede mejorar si se restablecen las reuniones del NMC, y se adoptan procesos acelerados de autorización sanitaria y/o se le asigna alta prioridad a la evaluación de medicamentos innovadores que sean de importancia crítica.

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Background

Enhanced access to innovative medicines is key to improving overall population health, reducing hospitalisation time and decreasing morbidity and mortality. The effective use of innovative medicines can result in increasingly affordable access by stimulating innovative competition and the eventual introduction of generics. As part of their mission to promote innovation, maturing regulatory agencies advise pharmaceutical companies on how to overcome challenges that they may encounter in the marketing authorisation process for new drugs.

Regulatory agencies have as their primary responsibility ensuring the quality, safety and efficacy of the medicines commercialized in their jurisdiction. Consequently, agencies must balance allocating enough time to analyse new applications with ensuring timely access and authorisation of innovative new medicines. In 2014, the World Health Assembly (WHA) noted that "… effective regulatory systems are an essential component of health system strengthening…and that inefficient regulatory systems themselves can be a barrier to access to safe, effective and quality medical products." [1]

Effective and efficient regulatory systems apply a risk-based approach to balance timely results and value to society. Due to the relative paucity of experience, new medicines may entail a higher risk to society compared to therapies that have been used and characterised for many years. Therefore, the novelty of the therapeutic product, its combination with other ingredients, and the nature of the indication can contribute to the benefit-risk balance of the product.

In order to be as well-informed as possible about this balance, many agencies have implemented regulatory assessment procedures for new medicines that include being informed by external, independent advisory committees. Major jurisdictions have processes that provide predictable regulatory reviews and timelines while being informed by external advisors. For example, the US FDA does not routinely seek the opinion of its external Advisory Committees. However, when it does so, the Advisory Committee is held during the defined PDUFA time period and its time is not additive to the legislated assessment period.

In Mexico, the regulatory assessment of "New Molecules" has required a preliminary evaluation of the dossier by the New Molecules Committee (NMC). This expert committee was created as a result of the Decree Amending the Regulation of Health Sector Products (Jan 2, 2008). Subsequently, several official guidances provided details regarding the internal rules governing the NMC and amended the categories of products subject to the evaluation and opinion of this committee.

The NMC is responsible for providing Mexico's Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS) with an independent opinion on all new drugs. The NMC's regulations broadly require that all new small molecules, new combinations, new therapeutic indications, and any biologics being considered for the Mexican market must be assessed by this committee. Biologics, however, require an additional review prior to submitting a request to the NMC; their first step is the evaluation by the Subcommittee on Evaluation of Biotechnologicals (SEPB); a positive technical opinion by this committee

[1] WHA (2014) Resolution 67.20 – Regulatory system strengthening for medical products. Available at: https://apps.who.int/gb/ebwha/pdf_files/WHA67-REC1/A67_2014_REC1-en.pdf

is required before a new drug can be officially submitted for registration to the NMC and COFEPRIS. Therefore, COFEPRIS' assessment time is independent of and additive to the time required by the NMC and if applicable, that of the SEPB. In the past, the time required for the full NMC process (scheduling the meeting and conducting the assessment) was estimated to range from 10 to 18 months. The President of the NMC is responsible for, among other activities, convening and inviting experts to NMC sessions.

Unfortunately, as of this report, this key step is not actively in place. The last time this committee had a session to evaluate an innovative product was in May of 2019, at which time the NMC was disbanded by COFEPRIS. As a result, since that time COFEPRIS has not received any new submissions for registration of innovative products requiring a technical opinion from the NMC (orphans do not require this opinion).

Because the NMC has not been convened for almost a year, this has had a significant impact on regulatory activity predictability and expectations regarding access to new medicines in Mexico.

This Briefing addresses the impact of suspending the activities of the NMC on the Mexican therapeutic landscape. First, we compare the way that 'new medicines' are defined within the context of the Mexican regulatory system with definitions used by comparable regulators and health organisations. We have also investigated the extent to which new drugs approved by the US FDA have been approved by other important jurisdictions specifically Mexico, Brazil, EMA, and Canada. In this manner, we expect to gain a better understanding of the impact that changes in the Mexican regulatory environment are having on the availability of new medicines for Mexican patients.

Definition of a New Medicine

Regulators focus much of their attention on ensuring that innovative new medicines are being assessed in a comprehensive yet timely manner. Consequently, it is key that pharmaceutical companies, the agency and other stakeholders can consistently identify what is a new medicine. The names and definitions can vary across jurisdictions, with some agencies being more explicit but potentially more restrictive. Table 1 compares important aspects of the definitions of a new medicine across key jurisdictions. We have also summarised key characteristics of each definition. In some instances, the definitions are subject to interpretation and to their strict applicability.

Agency	Alternate terms	Small molecule	Bio-logic	Combination product	New therapeutic indication	Radio-pharmaceutical	Not previously approved in the country
COFEPRIS (Mexico)	New Molecule	X		X	X		X
FDA (USA)	New Drug, New Active Ingredient, New Molecular Entity	X		X	X		
EMA (EU)	New Active Substance (NAS)	X	X	X	X	X	X
Health Canada/ TPD	New Drug, New Active Substance, New Chemical Entity	X	X	X	X		X
ANVISA (Brazil)	New Medicinal Product	X	X				X

Table 1 – The definition of a 'New Medicine' across different jurisdictions

Agency: COFEPRIS
Alternate names: New molecule, New Molecular Entity
Characteristics:

- Active ingredient or medicinal product that has no registration (Registro Sanitario) worldwide and that is to be registered in Mexico
- Active ingredient or medicinal product that is registered in other countries with limited clinical experience or controversial information, is not registered in Mexico and is intended to obtain a registration in Mexico
- Medicinal product to be used in combination of two or more active ingredients and that does not exist in the national market
- Active ingredient or medicinal product that is already marketed and to be registered for any other therapeutic indication
- Herbal and homeopathic medicines with Cannabis and other Therapeutic schemes and pharmaceutical forms

Sources: Decree Amending the Regulation of Health Sector Products (Art. 2 - XV) Jan 2, 2008 On Feb 23, 2012. Internal rules of operation of the New Molecules Committee and creating the subcommittee on Biologicals, 20 July 2018. Special Technical Opinion is defined and incorporated. August 1, 2018. Guidelines for the operation of the New Molecules Committee

Agency: **FDA**
Alternate names: See Characteristics
Characteristics:

- New Molecular Entity: An active ingredient that contains no active moiety that has been previously approved by the Agency or has been previously marketed as a drug in the United States
- New Drug: Any drug that is not generally recognized among experts as safe and effective for use, except that at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, and at such time its labelling contained the same representations concerning the conditions of its use; Any drug that as a result of investigations has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.
- New Active Ingredient: A drug that contains no active moiety that has been approved by the FDA in any other application submitted
- Drug product (The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo): A finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients.

Sources: 210.3 CFR title 21; 314.108 CFR title 21; New Drug Submission Classification Codes, MAPP

Agency: **EMA**
Alternate names: New Active Substance (NAS)
Characteristics:
A chemical, biological or radiopharmaceutical substance not previously authorised in a medicinal product for human use in the European Union; an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised in a medicinal product for human use in the European Union but differing significantly in properties with regard to safety and/or efficacy from that chemical substance previously authorised; a biological substance previously authorised in a medicinal product for human use in the European Union, but differing significantly in properties with regard to safety and/or efficacy which is due to differences in one or a combination of the following: in molecular structure, nature of the source material or manufacturing process; a radiopharmaceutical substance which is a radionuclide, or a ligand not previously authorised in a medicinal product for human use in the European Union, or the coupling mechanism to link the molecule and the radionuclide has not been authorised previously in the European Union
Sources: VOLUME 2A Procedures for marketing authorisation Chapter 1. Marketing

Agency: **Health Canada**
Alternate names: New Active Substance, New Chemical Entity
Characteristics:
An active or inactive ingredient, carrier, coating, excipient, menstruum or other component, that has not been sold as a drug in Canada; A drug that is a combination of two or more drugs, and that has not been sold in that combination or in the proportion in which those drugs are combined in that drug; A drug, with respect to which the manufacturer prescribes, recommends, proposes or claims a use as a drug, or a condition of use as a drug, including dosage, route of administration, or duration of action and that has not been sold for that use or condition of use in Canada, condition of use of that drug; A drug, with respect to which the manufacturer prescribes, recommends, proposes or claims a use as a drug, or a condition of use as a drug, including dosage, route of administration, or duration of action and that has not been sold for that use or condition of use in Canada, condition of use of that drug
Sources: Section C.08.001 of the Food and Drug Regulations

Agency: **ANVISA**
Alternate names: See Characteristics
Characteristics:

- New Medicinal Product: A product formulated with active pharmaceutical ingredient not yet approved for marketing in Brazil
- Innovative Medicinal Product: A medicinal product approved for marketing in Brazil, formulated with at least one active ingredient that has been patented (expired or not) by the laboratory in charge of the research and marketing in the country of origin. Generally, it is considered as the Reference Medicinal Product by ANVISA
- Active Pharmaceutical Ingredient / Drug Substance: Substance or raw material used for medicinal or sanitary purposes

Sources: Resolution RDC 200/2017; RDC 16/2007; Resolution RDC 200/2017; Law 5.991/1973 Decree No. 74.170/1974; Decree 8077/2013; Order 344/1998 RDC 17/200; RDC 204/2006

Assessment of Regulatory Activity

Methodology

The data used for the analyses in this report have been derived from the CIRS Emerging Markets Regulatory Review Times Database, which tracks new medicines and line extensions in 18 emerging markets. In addition, data have been derived from public resources and from data provided by regional trade associations.

Target assessment times

The extent to which new drug products are available within a country is a result of the efficiency of the agency's regulatory assessment process. When a pharmaceutical company submits its marketing authorisation dossier, it does so with an expectation of a process that is predictable in its timing and procedures. Therefore, the published agency review times become an important measure for the innovator companies, the healthcare system and importantly, the patients who await the new therapy. The target times for the review process (agency time) are compared in Table 2.

Country	Agency	Target agency times for standard review (calendar days)	Reference
USA	FDA (Food and Drug Administration)	60 days Filing Determination plus 10 months for review	2
Mexico	COFEPRIS (Comisión Federal para la Protección contra Riesgos Sanitarios) (does not include NMC time)	180 days	3
Brazil	ANVISA (Agência Nacional de Vigilância Sanitária)	365 days	4
Canada	TPD (Therapeutic Products Directorate)	300 days	5
EU	EMA (European Medicines Agency)	210 days	6

Table 2 - Target regulatory review times

[2] FDA - CDER 21st Century Review Process Desk Reference Guide. Accessed from: https://www.fda.gov/media/78941/download

[3] COFEPRIS (2008) Healthcare Regulation (RIS) and amending Decree Jan 2,

2008. Accessed from: http://dof.gob.mx/nota_detalle.php?codigo=5028081&fecha=02/01/2008

[4] ANVISA - Drugs [webpage]. Accessed on 24 April 2020 at: http://portal.anvisa.gov.br/drugs

[5] Health Canada (2020) Service Standards for Drug Submission Evaluations (Pharmaceuticals and Biological Products) under the Food and Drug Regulations – Health Canada [webpage]. Accessed on 24 April 2020 at: https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/service-standards-high-volume-regulatory-authorizations/service-standards-drug-submission-evaluations-pharmaceuticals-biologic-products-under-food-drug-regulations.html

[6] EMA - The evaluation of medicines, step-by-step [webpage]. Accessed on 24 April 2020 at: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/evaluation-medicines-step-step

Product Analyses – by country

We compared the extent to which a similar group of products was approved across the target countries through December 2019. We selected as the comparator cohort the 33 new molecular entities (NMEs) that were approved by the US FDA during the period of January 2017 through December 2018 (see Appendix). These products were submitted by 'top' multinational pharmaceutical companies defined as Pharmaceutical company with R&D spending >3 billion USD in 2017. These were selected as the companies most likely to have the infrastructure and opportunities to submit their products to multiple countries following the FDA submission.

Internationalisation

By the end of 2019, 20 of the 33 products (61%) were submitted to an additional four regulatory agencies (including EMA, TPD, Swissmedic, TGA), six (18%) were submitted to three agencies, three (9%) were submitted to one or two agencies. Four products that were approved by FDA between 2017-2018 did not become internationalised until after December 2019.

Submission and approval status of Mexico and Brazil

The status of the 33 NME products by December 2019 was as follows:

Submitted:	26
Not submitted:	5
Indeterminate:	2

Approved:	14 (54%)
In Review:	12 (46%)

Submitted:	19
Not submitted:	
Indeterminate:	14

Approved:	17 (89%)
In Review:	2 (11%)

The following assessments are derived from the details provided in the Appendix.

Overall approval times

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. COFEPRIS assessment time is independent of and does not include the NMC time. Table 3 compares the median approvals times across the target countries.

For the 33 products, the overall median approval time by FDA was 240 days. For the 13 products approved by COFEPRIS the overall median approval time was 280 days. While not the longest agency time, it is important to note that this does not include the time required to obtain a meeting with the NMC or the time required for the NMC to render its recommendation; this can extend the overall assessment time by another 10 to 18 months.

	FDA	COFEPRIS	ANVISA	TPD	EMA
Number of approved products	33	14	13*	29	27
Median approval time (calendar days)	240	267**	305	343	388
Fastest approval time (calendar days)	57	32	213	201	217
Slowest approval time (calendar days)	1088	717	665	871	840

Table 3 - Comparison of approval times across jurisdictions
**Submission dates not available for four products*
***Does not include NMC time*

Products still in review

All products in this cohort that had a submission date to Health Canada and the EMA were reviewed by December 2019. 15 of the 17 products submitted to ANVISA (88%) were approved by December 2019. In contrast, of the 26 products submitted to COFEPRIS during this time period, half (13) were still in review by the end of 2019. Four products were submitted to COFEPRIS after the NMC ceased operation in May 2019 (see Appendix), suggesting that a recommendation had been made by the NMC; all four products are still pending authorisation.

Approval sequence

For the 14 products that could be compared between Brazil and Mexico, 10 (71%) were approved first in Brazil and four (29%) were approved first in Mexico. Naturally many factors affected this sequencing. For instance, for three products that were approved first in Brazil, these were not submitted to Mexico until after the Brazil approval (Imfinzi, Aimovigm Tremfya) illustrating a role for company strategy in submission sequencing.

Lag Time

For the purpose of this study, the time from the approval of a product by the FDA to the date of approval in a target country is considered the 'Lag Time'. This is the time that patients need to wait until products reach approval in their country compared to the availability in the United States. Lag Time is affected by many factors [7,8]. These include the sponsor's ability to support the regulatory filing in the specific country, the commercial opportunity in the country, product availability and local regulatory requirements that may impact submissions.

For the 15 products that were approved by ANVISA, the median Lag Time was 298 days (range, 179 to 769 days). By comparison, the median Lag Time for 12 products approved by COFEPRIS was 474 days

[7] Wang T, McAuslane N (2014) *CIRS R&D Briefing 53 - Availability of new medicines: characterising the factors influencing drug roll out to six mature markets*. April 2014.

[8] Liberti L, McAuslane N, Patel P (2012) *CIRS R&D Briefing 51 - Characterising the influencers of submission Lag Time for medicines in the Emerging Markets: Analysis of short and long Lag Time factors*. August 2012.

(range, 136-924 days). Interestingly, one product (baricitinib; Eli Lilly and Co) was approved by COFEPRIS 230 days before it received FDA approval.

Expedited pathways

Expedited pathways are used by many agencies to accelerate the quality review of submissions for important new medicines. For example, these include the EMA 'Accelerated Assessment', Swissmedic 'Fast Track' and FDA/PMDA/Health Canada/TGA 'Priority Review'. ANVISA offers a priority review pathway and Mexico has several pathways that can be used to expedite the assessment of NMEs, including a Rare Disease pathway and the Equivalence agreement.

Of the 33 products approved by FDA, 22 (67%) benefitted from the use of an expedited review pathway. Of the 13 products that were approved by COFEPRIS by the end of 2019, none used an expedited assessment pathway.

Orphan Drug status

Many of the NMEs being developed are designed for the treatment or management of diseases that occur rarely in a small number of affected individuals. In these cases, the products may qualify for Orphan status. Depending on the jurisdiction, Orphan status qualifies the sponsor of the drug for various development incentives, including tax credits for clinical testing and reduced assessment fees. The granting of the Orphan designation does not change the standards for regulatory requirements for marketing authorisation but may qualify the product for a priority review.

Of the 33 products approved by FDA, 13 (39%) were assigned the Orphan designation by the agency; all received an expedited (Priority) review. Two of these products, acalabrutinib (Astrazeneca, September 2018) and midostaurin (Novartis, July 2017) were submitted to COFEPRIS as Orphan drugs. The median time to approval was 227 days (company and agency time) for the Orphan products at FDA and 249 days at COFEPRIS.

Therapeutic area effects

The 33 products in the FDA cohort addressed a number of important therapeutic areas. The most common therapeutic area was related to ATC Code L (Anticancer and immunomodulators) (19 of 33 products, 58%). The median FDA approval time for these products was 209 days (range 127-867 days). This acceleration was driven in large part by the use of expedited pathways; all but 3 products benefitted from these pathways. For EMA, the median approval time for the 15 ATC code L products was 390 days, which was similar to the overall EMA median of 388 days. This is primarily due to the legislative time constraints imposed on the EMA, CHMP and European Commission for their reviews. The median approval time for the 8 ATC Code L products reviewed by COFEPRIS was 268 days (range 142-597 days). Importantly, 14 Code L products had been submitted to COFEPRIS for review and 6 (43%) remained pending a decision by the end of 2019.

Observations

The regulatory assessment of new medicines is a complex, multifactorial process that involves a coordinated effort across pharmaceutical companies, governmental agencies and advisors. An efficient, effective and predictable regulatory environment is among the most important factors that contribute to timely access to quality, safe and effective innovative products[9].

Improvements in the efficiency of the regulatory process can be reflected in measurable positive impacts on patient access to medicines, health care and overall population health. Conversely, activities that slow or impede regulatory efficiency and predictability can be detrimental. Therefore, it is illustrative to consider the effect of the changes that have been observed in the Mexican regulatory landscape over the past year and to reflect on the real impact of these changes. We addressed this by comparing regulatory authorisation activities across several key agencies. Overall, we observed patterns that indicate that the Mexican public is being negatively impacted by the approaches taken by the agency regarding assessments of innovative new products.

The definition of a new medicine varies across jurisdictions. Comparing definitions in various jurisdictions or identifying what types or products are considered as innovative products allows one to visualise the different regulatory approaches and risk perceptions of the agencies. While we observed differences, we also observed a trend towards simplifying the definition by focusing on 'new molecules' while limiting the inclusion of other types of products or compounds. This is key to providing transparency around assessment pathways and processes. While the definition used by COFEPRIS is generally in line with those used by other agencies, ensuring that the definition of a new medicine aligns with global approaches will provide predictability and facilitate the integration of COFEPRIS into global regulatory submissions of innovative products.

While the published target times for regulatory assessment by COFEPRIS (180 days) is the shortest among the agencies assessed, this does not include the time required to obtain a consultation with and obtain a recommendation from the NMC. These activities can add 10 to 18 months to the assessment process resulting in an overall assessment period of up to two years. The predictability of the review process could significantly improve if the NMC estimated time was considered as part of the official target review time.

In our study cohort, 79% of the products were also submitted to COFEPRIS, a high proportion indicative of the interest of pharmaceutical companies to make their products available to Mexican patients. However, products in this cohort appeared to languish in the Mexican regulatory system. All of the products submitted to Health Canada as well as 88% of those submitted to Brazil received an authorisation. By comparison, half of the products submitted to COFEPRIS remained in review by the end of 2019. Because the NMC has not convened since May 2019, all four products in this cohort submitted after that date remaining pending authorisation. When these observations are combined with the observation that 71% of the comparable products were approved first by Brazil, and that 43% of anticancer and immunomodulators products submitted to COFEPRIS remained in review as of the end of 2019, there is a measurable impact on the availability of innovative medicines in Mexico.

Our findings indicate that the regulatory approval system that had been in place prior to the NMC ceasing its activities provided an opportunity for innovative products to obtain regulatory approval, despite recognised long timelines and process inefficiencies. The current situation has severely curtailed the availability of innovative products; this landscape could be improved by the reinstitution of the NMC, the more effective use of accelerated pathways and by prioritising the assessment of critically important new medicines.

[9] Liberti L et al. (2013) Regulatory review: How do agencies ensure the quality of decision making? *Clinical Pharmacology & Therapeutics* 94(3):305308. Available at: https://doi.org/10.1038/clpt.2013.127

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About CIRS

The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independently managed UK-based subsidiary company, forming part of the Clarivate Analytics group. CIRS' mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, 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 medical products through these activities. This is CIRS' purpose. CIRS is operated solely for the promotion of its purpose. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities, special projects and grants.

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Appendix - Comparison of key product characteristics and milestones

Generic Name	Brand Name	ATC	Company/Sponsor	FDA Orphan Status	FDA Approval date	EMA Approval Date	HealthCanada Approval date	ANVISA Approval date	COFEPRIS Submisson Date	COFEPRIS Approval date
ABEMACICLIB	Verzenio	L01	ELI LILLY AND CO	N	28/09/2017	26/09/2018	05/04/2019	11-Mar-19	09-Jul-18	15-Oct-19
acalabrutinib	Calquence	L01	ASTRAZENECA	Orphan	31/10/2017		23/08/2019	24-Dec-18	28-Sep-18	29-May-19
Apalutamide	Erleada	L02	JANSSEN BIOTECH	N	14/02/2018	14/01/2019	03/07/2018	15-Oct-18	06-Mar-18	Pending
axicabtagene ciloleucel	YESCARTA	L01	Kite Pharma Inc.	Orphan	18/10/2017	23/08/2018	13/02/2019	26-Nov-18	under review	pending
baricitinib	Olumiant	L04	ELI LILLY AND CO	N	31/05/2018	13/02/2017	17/08/2018	26-Nov-18	13-Mar-17	13-Oct-17
BENRALIZUMAB	Fasenra	R03	ASTRAZENECA AB	N	14/11/2017	08/01/2018	22/02/2018	4-Jun-18	28-Jul-17	15-Jul-19
COPANLISIB DIHYDROCHLORIDE	Aliqopa	L01	BAYER HEALTHCARE	Orphan	14/09/2017				under review	pending
dacomitinib	Vizimpro	L01	PFIZER INC	Orphan	27/09/2018	02/04/2019	26/02/2019		not submitted	
Damoctocog alfa pegol	Jivi	B02	Bayer Healthcare LLC	N	29/08/2018	22/11/2018	18/10/2018		13-Dec-19	pending
DORAVIRINE	Pifeltro	J05	MSD MERCK CO	N	30/08/2018	22/11/2018	12/10/2018		28-Feb-19	16-Dec-19
DURVALUMAB	Imfinzi	L01	ASTRAZENECA UK LTD	N	01/05/2017	21/09/2018	03/11/2017	26-Dec-17	24-Mar-18	11-Nov-19
ELAGOLIX	Orilissa	H01	ABBVIE INC	N	23/07/2018		05/10/2018		24-Sep-19	pending
EMICIZUMAB	Hemlibra	B02	GENENTECH INC	Orphan	16/11/2017	23/02/2018	02/08/2018	16-Jul-18		
EMTRICITABINE, BICTEGRAVIR SODI	Biktarvy	J05	GILEAD SCIENCES INC	N	07/02/2018	21/06/2018	10/07/2018	25-Nov-19	24-Apr-18	14-May-19
erenumab	Aimovig	N02	AMGEN INC	N	17/05/2018	26/07/2018	01/08/2018	25-Mar-19	25-Mar-19	01-Sep-19
ERTUGLIFLOZIN	Steglatro	A10	MERCK SHARP DOHME	N	19/12/2017	21/03/2018	09/05/2018		15-Mar-19	07-Oct-19
Galcanezumab	Emgality	N02	ELI LILLY AND CO	N	27/09/2018	13/11/2018	30/07/2019	22-Jul-19	20-Nov-18	pending
glasdegib	Daurismo	L01	PFIZER INC	Orphan	21/11/2018				not submitted	
glecaprevir / pibrentasvir	Mavyret	J05	ABBVIE INC	N	03/08/2017	26/07/2017	16/08/2017	16-Apr-18	15-Nov-17	17-Dec-17
GUSELKUMAB	Tremfya	L04	JANSSEN BIOTECH	N	13/07/2017	10/11/2017	10/11/2017	26-Mar-18	11-Jun-18	31-Oct-18
inotuzumab ozogamicin	Besponsa	L01	WYETH PHARMS INC	Orphan	17/08/2017	29/06/2017	15/03/2018	25-Sep-19	not submitted	
LETERMOVIR	Prevymis	J05	MERCK SHARP DOHME	Orphan	08/11/2017	08/01/2018	01/11/2017		17-Jul-19	pending
lorlatinib	Lorbrena	L01	PFIZER INC	Orphan	02/11/2018	06/05/2019	22/02/2019		01-Feb-19	22-Nov-19
midostaurin	Rydapt	L01	NOVARTIS PHARMS CORP	Orphan	28/04/2017	18/09/2017	21/07/2017	9-Apr-18	31-Jul-17	12-Apr-18
moxetumomab pasudotox-tdfk	Lumoxiti	L01	ASTRAZENECA AB	Orphan	13/09/2018				under review	pending
OCRELIZUMAB	Ocrevus	L04	GENENTECH INC	N	28/03/2017	08/01/2018	14/08/2017	26-Feb-18		
ribociclib succinate	Kisqali	L01	NOVARTIS PHARMS CORP	N	13/03/2017	22/08/2017	02/03/2018	30-Jul-18	23-Jan-17	30-Oct-17
SARILUMAB	Kevzara	L04	SANOFI SYNTHELABO	N	22/05/2017	23/06/2017	12/01/2017		not submitted	
sodium zirconium cyclosilicate	Lokelma	V03	ASTRAZENECA PHARMS	N	18/05/2018	22/03/2018	25/07/2019		under review	pending
tafenoquine	Krintafel	P01	GLAXOSMITHKLINE	Orphan	20/07/2018				not submitted	
talazoparib	Talzenna	L01	PFIZER INC	N	16/10/2018	20/06/2019	06/09/2019		17-Dec-18	pending
tisagenlecleucel	KYMRIAH	L01	Novartis Pharmaceuticals	Orphan	30/08/2017	22/08/2018	05/09/2018		under review	pending
VOXILAPREVIR	Vosevi	J05	GILEAD SCIENCES INC	N	18/07/2017	26/07/2017	16/08/2017		19-Dec-18	pending

Yellow= first approval Salmon=submitted after NMC ceased deliberations Green= Orphan designation at COFEPRIS

WHO ATC classifications:

- A - Alimentary and metabolism: Drugs for acid related disorders, gastrointestinal disorders, antiemetics and antinauseants, bile and liver therapy, laxatives, antidiarrheals, intestinal antiinflammatory/antiinfective agents, drugs used in diabetes.
- B – Blood and blood forming organs: Antithrombotic agents, antihemorrhagics, antianemic preparations, blood substitutes and perfusion solutions, other hematological agents.
- C - Cardiovascular: Cardiac therapy, antihypertensives, beta blocking agents, calcium channel blockers, agents acting on the renin-angiotensin system, serum lipid reducing agents.
- H – Systemic hormonal preparations: excludes insulins, anabolic steroids, catecholamines, sex hormones, sex hormones used in treatment of neoplastic diseases, metreleptin used for treatment of complications of leptin deficiency in patients with generalised lipodystrophy.
- J - Anti-infectives: Antibacterials for systemic use, antimycotics for systemic use, antimycobacterials, antivirals for systemic use, immune sera and immunoglobulins, vaccines.
- L - Anticancer and immunomodulators: Antineoplastic agents, endocrine therapy, immunostimulants, immunosuppressive agents.
- N - Nervous system: Anesthetics, analgesics, antiepileptics, anti-parkinson drugs, psycholeptics, psychoanaleptics, other nervous system.
- P – Antiparasitic products, insecticides and repellents: antiprotozoals, antihelmintics, ectoparasiticides including scabicides, insecticides and repellents
- V – Various: this group contains many different types of products including allergens, all other therapeutic agents, diagnostic agents, general nutrients, all other non-therapeutic products, contrast media, diagnostic radiopharmaceuticals, therapeutic radiopharmaceuticals, surgical dressings