GOBIERNO DE MÉXICO

SALUD
SECRETARÍA DE SALUD

COFEPRIS
COMISIÓN FEDERAL PARA LA PROTECCIÓN CONTRA RIESGOS SANITARIOS

Regulatory Certainty Strategy for the Pharmaceutical Sector

The Federal Commission for the Protection against Sanitary Risks (COFEPRIS) has a fundamental role to play in guaranteeing access to new treatments and promote the development of medical innovation in the country.

The Regulatory Certainty Strategy for the Pharmaceutical Sector 2022-2030 seeks toremedy various regulatory and operational impediments that negatively affect access to medical treatments, to the detriment of health of patients in our national territory.

Cofepris, as a regional and international reference for the protection against health risks, proposes integration and orientation in solidarity with other regulatory authorities because it accepts that providing regulatory certainty goes beyond a legal term.

Regulatory certainty means working to ensure maximum clarity between regulator and regulated in order to avoid spaces conducive to corruption.

It is the acomplishment of goals and commitments that will allow the reconstruction of a health system under the protection of the State and not under the protection of private interests.

Regulatory certainty means simplification without deregulation, to avoid unnecessary bureaucracy and corruption-prone situations. It seeks to guarantee the supply of medicines in the country.

We are convinced that after the implementation of the seven commitments developed in this document, Cofepris will attend the needs and requirements of a complex country, to develop a competitive, honest and responsible pharmaceutical sector in order to guarantee that all Mexicans have access to safe, effective and quality medicines

Jorge Carlos Alcocer Varela

Secretario de Salud Federal

I. Objective

- To provide regulatory certainty to companies in the pharmaceutical sector in order to offer medical innovations and productive development to the Mexican market.

II. Strategy

- Design a 2022-2030 work agenda within the scope of the Federal Commission for the Protection against Health Risks (COFEPRIS) to promote competitiveness, industrial and commercial growth and development, as well as to guarantee access to safe and quality health inputs.

III. Context

- Due to its strategic location, skilled labor force, and access to regional and domestic markets, Mexico has the potential to become an enabling environment for scientific innovation in health.
- However, the Mexican regulatory framework for drugs and medicines does not create the ideal conditions to allow the effective entry (from the clinical phase to obtaining marketing authorizations) of new innovative treatments, biosimilars or interchangeable generics. This has three immediate consequences:

  (i) It inhibits clinical research, investment and innovation.

  (ii) It increases the price of drugs due to the lack of competition in the market, with a direct impact on the public budget allocated to the acquisition of treatments.

  (iii) It conditions access to more effective treatments that are already marketed in other countries.
- Likewise, the Economic Commission for Latin America and the Caribbean (ECLAC) states that investment in pharmaceutical production and innovation must consider a long-term horizon.

  - For this, there must be regulatory certainty based on stable and predictable regulatory ecosystems in order to plan the development of productive capacities.

    - Any change in the regulatory ecosystem must be accompanied by governance mechanisms that allow the implementation of robust work agendas and interaction channels between regulator and regulated, with the purpose of coordinating joint actions to achieve it.

- Therefore, COFEPRIS proposes to develop and implement regulatory modifications based on sanitary evidence, which reduce entry barriers to the Mexican market and eliminate technical obstructions to trade that have been generated by our country's regulations.

IV. Definition of regulatory certainty

Cofepris defines regulatory certainty as:

- The full compliance with the regulatory framework for the protection against health risks.
    - To provide clarity to the user in: i) the authorization requirements and their definition, ii) the internal evaluation process, and iii) the time associated with each of the stages of the evaluation process.
    - Ensure a standardized evaluation based on technical-scientific criteria.
    - Effective recognition of the decisions of regulatory authorities in other jurisdictions.
    - To guarantee regulatory harmonization with internationally valid standards in order to favor industrial development, access to new medical treatments and competitiveness.
- The guarantee of instances of regulator-regulated interaction free of corruption and conflicts of interest, favoring good governance.
- The commitment that the regulatory changes to be implemented have a vision of improvement, harmonization and regulatory innovation that guarantees a stable regulatory ecosystem, with governance mechanisms, adequate implementation times and a long-term vision.

V. Guiding Principles

- Cofepris' regulatory decisions must contribute to the fulfillment of the The Mexican National Development Plan 2019-2024 and the Health Sector Program 2020-2024 to provide programmatic consistency and continuity to the changes undertaken since the arrival of the President Mr. Andrés Manuel López Obrador, such as:

  (i) Administrative simplification and regulatory improvement without deregulation to avoid unnecessary bureaucracy and situations prone to corruption;

  (ii) Guaranteeing the supply of medicines in the country; and

  (iii) The market is not a substitute for the State.

- Its construction will consider: (i) the commitments acquired through International Treaties to which Mexico is a party; (ii) the memberships aimed at harmonizing the regulation of products for human use; (iii) the Good Regulatory Practices (GRPs) of the World Health Organization (WHO), and (iv) the WHO criteria determined in the Global Benchmarking Tool for Evaluation of National Regulatory Systems of Medicines And Vaccines (GBT).

- It constitutes Mexico's contribution to the fulfillment of the Health Self-Sufficiency Plan, developed by the Economic Commission for Latin America and the Caribbean (ECLAC), developed from the explicit request of our country in exercise of the pro-tempore presidency of the Community of Latin American and Caribbean States (CELAC) and presented during the VI Summit of Heads of State, held in 2021.

VI. Measures in the process of implementation

a) Installation of the Committee on Good Regulatory Practices (GRP Committee)

- In order to ensure that all changes in the regulatory framework are coherent and feasible, with a focus on regulatory improvement and in compliance with the WHO GRPs, COFEPRIS will set up a Good Regulatory Practices Committee, which will have among its attributions:

  (i) Develop executive work plans for the correct implementation of regulatory modifications, harmonized, improved and administratively simplified.

  (ii) Supervise and accompany the implementation of regulations with change management and training actions, both within technical teams and in regulated sectors, to ensure an effective process of adoption of the new regulatory framework.

  (iii) Generate impact evaluation mechanisms before and after changes to the regulatory framework.

- The Committee will have the participation of the public, private and social sectors, and will report to the Scientific Committee of COFEPRIS.

- During the first quarter of 2023, this body will present its work agenda and will periodically make technical reports on the progress in the implementation of its objectives and actions.

b) Authorization of medicines by recognition of the decisions of regulatory authorities of other jurisdictions.

- In the context of the COVID-19 sanitary emergency, the Ministry of Health established the "administrative measures to expedite the process of sanitary registration of medicines and other health inputs coming from abroad", through an agreement published on November 18, 2020
  - This legal instrument mandates Cofepris to evaluate the approval of drugs authorized by other health authorities within a maximum period of 5 working days; otherwise, the authority will assume that the request is accepted.
    - This model was effective in guaranteeing the supply of drugs and vaccines during a critical period of the

pandemic. It is not very sustainable in terms of health and administration in the medium and long term.

- In order to achieve the recognition of the decisions of regulatory authorities from other jurisdictions, COFEPRIS developed the "Institutional Policy for the use and recognition of information, reports and decisions from other national regulatory authorities, initiatives, forums and international organizations.
    - This allowed us to outline a working path to improve the regulatory framework -from Equivalence Agreements to regulations and Mexican Official Standards (NOMs)- with the purpose of clarifying the product evaluation procedure through the unilateral recognition of technical requirements of sanitary registrations in compliance with the WHO's Good Reliance Practices (GRelP).
        - For example, memberships of health authorities to international forums, the prequalification of drugs by the World Health Organization (WHO), or the results of the evaluations through the WHO GBT will be an element of confidence in the decision of another regulatory authority.
        - In addition, the measure will have a direct impact on the agility of international public procurement of medicines, as well as on access to products from the Pan American Health Organization's (PAHO) Revolving Fund and Strategic Fund.

- In a first stage, within the first quarter of 2023, COFEPRIS will provide technical and administrative clarity for the recognition of:

    (i) Bioequivalence and biosimilarity studies to demonstrate interchangeability between reference drugs with generics and biocomparables (description of activity in subsection "e)" of this plan).

    (ii) Certificates of Good Manufacturing Practices (GMPs) of low-risk drugs or equivalent documents to guarantee their safe use in the manufacturing of drugs both in Mexico and abroad (description of activity in item "f)" of this plan).

    (iii) Release of foreign manufactured biotechnology drugs (description of activity in item "g)" of this plan).

- In a second stage, starting in the fourth quarter of 2023 and until the last quarter of 2024, the health agency will make regulatory and operational changes for the recognition of:

    (iv) Drug GMPs or equivalent documents from health agency members of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) for drugs.

    (v) Assessment of the clinical performance of innovative

medicines by WHO-recognized National Regulatory Reference Authorities.

(vi) Post-authorization changes in the chemistry, manufacturing process and controls (CMC) of pharmaceutical products.

- In addition, in order to provide a regulatory pathway for emergency health contexts, the Mexican health authority is committed to develop a specific framework for the authorization of emergency use of pharmaceuticals for emerging or neglected diseases.
    - This regulatory pathway will be formalized in the first half of 2024
- COFEPRIS is confident that the development of mechanisms for the recognition of decisions of other health agencies will allow for the optimization of the attention times for innovative, generic and biosimilar products of foreign manufacture, as there is evidence that this mechanism is useful for optimizing attention times and thus directing institutional capacities to the evaluation of nationally manufactured drugs.
    - For example, from March 2021 to the end of 2022, of the 584 resolutions issued by the New Molecules Committee between March 2021 and December 2022, 47% were addressed through the recognition of authorizations issued in other jurisdictions.

c) Regulatory harmonization

- Since November 2021, Mexico was accepted as a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).
    - This membership is considered a priority strategy for COFEPRIS, as it will allow for the harmonization of regulation, surveillance and technical evaluation parameters.
- As part of the commitments assumed by Cofepris to be accepted in ICH is the creation of the Mexican Official Standard (NOM) on Good Clinical Practices with the purpose of implementing the ICH E6 guide
    - In accordance with the procedure established in the Quality Infrastructure Law, the new NOM is in the final phase of the study and discussion process by the working group formed for this purpose, so it is expected that the public consultation will begin in the first quarter of 2023.
    - Considering the deadline for the integration of responses and regulatory adjustment during the public consultation, it is foreseeable that the new standard for the surveillance of Good Clinical Practices will be published in the Official Gazette of the Federation in the second quarter of 2023, giving a reasonable application phase for the adaptation of the Quality Management Systems of clinical research centers.
- Additionally, COFEPRIS has a 2021-2026 work plan, which considers from regulatory adaptation to training components, for the adoption

of the following guidelines:

- ICH M4. Common Technical Document (CTD) for the registration of pharmaceutical products.
- ICH M1. MedDRA "List of terms directly related to pharmacovigilance, with descriptions of adverse events".
- As part of this second phase of adoption, ICH requires the adoption of the guidelines ICH E2A "Clinical Safety Data Management: Definitions and Standards", ICH E2B "Data Elements for the Transmission of Safety Reports on Individual Cases" and ICH E2D. "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting," however, COFEPRIS does not consider them in its work plan because they were already adopted in the national regulation.

- Cofepris will finish adopting the rest of the ICH guidelines by 2030, achieving full harmonization of health regulation to the highest international standards.

d) Digitalization as a path to optimization

- Currently, the health authority implements specific actions for the reduction of the backlog and compliance with legal timeframes in the evaluation of pharmaceutical products and other health inputs. COFEPRIS is undertaking a two-pronged digitalization project:
  - (i) Creation of automatic response procedures, also known as self-managed.
  - (ii) Virtual evaluation with direct impact on time reduction.
- In 2022, COFEPRIS released the first functionalities of the digital platform, including the electronic evaluation of the first extension of pharmaceutical products and the issuance of automatic resolutions for subsequent extensions of the same.
- This allowed: i) A reduction from 356 to 76 days in the evaluation time for the first extension of pharmaceutical products; ii) A 32% increase in productivity compared to the previous year; and iii) A sustained reduction in the number of procedures outside the legal timeframe.
  - The foregoing underscores the importance of continuing with other virtual evaluation modalities.
    - In addition, throughout 2022, COFEPRIS released 30 self-managed digital procedures (such as operating, health and advertising notices). Thanks to this modality, the agency concluded 26 thousand 745 processes electronically.

Handling of controlled substances

- On November 23, 2022, COFEPRIS presented the Integrated Substances System (SISUS), an electronic platform that will provide traceability and trust mechanisms for the entry and effective use of chemical

precursors, narcotics, psychotropic drugs and essential chemicals.

- In the first phase, from the last quarter of 2022 to the end of the second half of 2023, the SISUS will enable electronic control book requests for precursor chemicals and essential chemicals used in the manufacture of medicines. In addition, companies will be able to report annual estimates to be requested to the United Nations International Narcotics Control Board (INCB).

- As a second stage, expected by the end of 2024, companies will be able to apply for import and export permits, as well as manufacturing and storage site inspections through SISUS.

Modifications to Registration Conditions

- By the end of the first quarter of 2023, COFEPRIS foresees the release of the digital modality for the attention of requests for Modifications to Registration Conditions, also known as CMC Post-Authorization Changes, a regulatory innovation process that considered:

    - The adoption of the ICH Q12 guide. Technical and Regulatory Considerations for the Life Cycle Management of Pharmaceutical Products.

    - The European Medicines Agency (EMA) model, which uses three classification categories (minor, moderate and major) based on risk assessment.

        - For the first two categories, COFEPRIS will provide automatic responses, as they are administrative procedures with an impact on the post-marketing surveillance process that do not compromise the stability of the drug or medicine.

Clinical Research

- In order to contribute to competitiveness and promote pharmaceutical research in Mexico, COFEPRIS will launch a specific platform for the initial evaluation and modification of clinical protocols. This platform will be operational as of the second quarter of 2023.

    - This process will consider a reclassification of initial applications for the development of clinical trials and a separation of technical and administrative modifications. The latter will result in automatic resolutions due to the low risk involved in their attention.

    - In addition, in a second stage, the project foresees a comprehensive restructuring of the National Clinical Trials Registry (RNEC) so that the information captured in this platform can be integrated into the WHO's International Clinical Trials Registry Platform (ICTRP), contributing to the exchange of information in real time on the development of new pharmaceutical products from their clinical phase.

    - Technical and administrative optimization actions have reduced protocol authorization from an average of 195 days

at the beginning of 2021 to an average of 85 days at the end of 2022. Therefore, COFEPRIS is confident that with the new digital platform for clinical trials, the health agency will reach an average of 60 days in 2023 and reach an average of 50 days in 2024.

Migration and integration of databases

- To install a robust digital platform in the regulatory ecosystem, throughout 2024, the digitalization team will focus part of its efforts on migrating the more than 70 databases to a single IT repository, with standardized criteria and business rules, which will allow COFEPRIS to continue expanding its digital services.
    - Our health agency will carry out a process of regulatory improvement and administrative optimization, in order to adapt complex procedures to the digital reality.
- Accompanied by an internal and external change management strategy for each stage or product, developing a digital culture that drives the transformation of COFEPRIS.
- In conclusion, COFEPRIS estimates that before the end of the second half of 2023, more than 30% of the procedures will have a digital application, evaluation and resolution process.

e) Bioequivalence and Biocomparability Studies

- On May 3, 2021, COFEPRIS published the emergency modification to NOM-177-SSA1-2013 on bioequivalence and biocomparability studies.
    - This one-year regulatory change allowed the health authority to be able to recognize bioequivalence studies conducted abroad, optimizing the sanitary registration of generic drugs in our country.
        - The COFEPRIS regulatory committee voted to integrate the emergency modifications permanently into the NOM. The modification to NOM-177-SSA1-2013 will be published in the Official Journal of the Federation at the beginning of the first quarter of 2023.
- In order to guarantee full recognition of bioequivalence and biosimilarity studies conducted in countries with the same or higher criteria than Mexico, as well as the integration of the bioexemption figure used in other jurisdictions promoted by organizations such as ICH or WHO, this health authority will include NOM-177 in the Supplement to the National Quality Infrastructure Program 2023, in order to make an exhaustive modification of the same, the results of which may be reflected in 2024.

f) Safe Use of Active Pharmaceutical Ingredients

- As a result of the global integration of supply chains and the progress in the mutual or unilateral recognition of certifications issued by health authorities in other jurisdictions, a considerable fraction of Active Pharmaceutical Ingredient (API) manufacturers have GMPs or equivalent documents issued by High Surveillance Regulatory Agencies that comply with the provisions of ICH, PIC/S and the WHO, which:

(i) Simplifies obtaining product marketing authorizations

(ii) Avoids the need for companies to request and obtain a GMP from this authority.

(iii) Encourages the entry of foreign pharmaceutical inputs.

- However, there are manufacturers of low-risk drugs that, due to their geographic location, are accredited by health agencies with a lower degree of maturity than COFEPRIS, which makes it difficult to recognize the documentation of origin during the process of sanitary registration or CMC post-authorization changes.

- Therefore, and in accordance with the guiding principle of guaranteeing the supply of medicines, COFEPRIS plans to issue a legal instrument that provides clarity for the accreditation of Good Manufacturing Practices (GMP) of low-risk drugs when there are no GMPs or equivalent documents issued by High Surveillance Regulatory Agencies.

    - With this regulatory solution, COFEPRIS will allow pharmaceutical companies to accredit drug GMPs through: (i) GMP of the drug or equivalent document issued in the country of origin and (ii) A program of audits to suppliers of APIs that must be attached to the standards expressed in the national regulation (NOM-164-SSA1-2015 and NOM-059-SSA1-2015, of GMP of drugs and medicines, respectively), as well as the provisions of ICH (ICH Q7, ICH Q8, ICH Q9 and ICH Q10) and PIC/S (Annexes of guidelines).

    - The aforementioned instrument is expected to be published in the Official Gazette of the Federation at the beginning of the second quarter of 2023.

g) Entry of foreign-manufactured biotechnological drugs

TNOM-059-SSA1-2015, Good Manufacturing Practices for Medicines, obliges companies that produce biotechnological products outside the country to have a GMP issued by our health authority for their internment and commercialization in the country.

- This measure is contrary to GRelP, constitutes a technical barrier to trade, and generates an internal contradiction, because while COFEPRIS recognizes the GMPs of PIC/S member countries for the sanitary registration process, the pharmaceutical sector does not have a legal framework that allows it to enforce the decision of the health authority in the process of releasing batches of biotechnological drugs.

    - Therefore, our institution is committed to carry out an emergency modification of NOM-059-SSA1-2015 in the first quarter of 2023 in order to eliminate this commercial barrier and allow the entry and release of batches of biotechnological drugs that are not considered vaccines to companies that have a GMP from a High Surveillance Regulatory Agency and other documentation that certifies the quality of pharmaceutical products, in compliance with the provisions of PIC/S, as well as other regulations issued by the WHO.

        - This measure will be accompanied by the strengthening

of the Post-Marketing Surveillance Program (PVPC) in order to simplify the process of releasing batches of biotechnological products and strengthen the capacity to detect health risks through the supervision of the activities of companies in the sector during the process of sale and distribution of pharmaceutical products.

- In addition, Cofepris is committed to integrate NOM-059 in the Supplement to the National Quality Infrastructure Program 2023 in order to achieve a permanent modification of this technical standard.

Measures to be implemented	2022	2023	2024	2025	2026	2027	2028	2029	2030
Committee of Good Regulatory Practices									
Work Schedule design									
Committee installation									
Publication of reports of technical performance reports									
Authorization of medicines by recognition of the decisions of regulatory authorities of other jurisdictions									
Institutional policy developmen									
Development of critical path of work									
Stage I Implementation									
Stage II Implementation									
Technical, operational and administrative clarity for recognition of GMPs									
Technical, operational and administrative clarity for clinical performance evaluation									
Technical, operational and administrative clarity for post-authorization CMC changes									
Development and publication of framework for emergency use authorization									
Regulatory harmonization									
Adoption of the ICH E6 guide (Clinical Practices)									
Adoption of ICH M1 guide. MedDRA									
ICH M4 guide adoption. CTD									
Adoption of the rest of the ICH guidelines									
Digitization as a way of optimization									
Release of Platform for Electronic Extensions									
Development and release of the Self-management Procedures Platform									
Development and release of CMC post-authorization changes (Modifications to the Registration Conditions)									
Development and release of the Comprehensive System of Substances									
Development and release of the Clinical Trials Platform									
Comprehensive database migration project									
Development and release of complex procedures (Sanitary Registries, GMPs)									
Bioequivalence and Biocomparability Studies									
Validity of emergency modification NOM-177									
Partial modification NOM-177									
Development of integral modification NOM-177 (with bioexemption)									
Safe Use of Active Pharmaceutical Ingredients									
Development and publication of criteria for recognition of GMPs and audit programs									
Entry of foreign-manufactured biotech drugs									
Development of emergency modification of NOM-059									
Development of integral modification of NOM-059									