A global look at expedited programmes for drug and device development – EU perspective

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About Wardyński & Partners

Wardyński & Partners has been firmly rooted in the legal profession in Poland since 1988. The firm currently has over 150 lawyers serving clients in 10 languages.

We are an independent law firm with strong international foot print and member of Lex Mundi, WSG and IBA. We cooperate with industry associations such as EuropaBIO and the European Food Law Association.

Life Sciences and Healthcare Practice focuses on providing simple and practical advice to clients from pharmaceutical, biotech, medtech as well as food and healthcare sectors. Knowledge of the market, complex regulatory frameworks and internal day-to-day synergies with the M&A Practice enables our Firm to pursue major transactions in Life Sciences and Healthcare sectors. We also specialize in advising on GDPR (medical data) as well as complex IP matters.

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- Banking & Project Finance
- Business Crime
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- Data Protection (including GDPR)
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- Outsourcing
- Private Client
- Protection of Personal Interests
- Public Procurement & PPP
- Real Estate
- Regulatory
- Restructuring & Bankruptcy
- Tax

EU Pharmaceutical Package – Time for a global reform

Background

- Lessons learnt from Covid-19 pandemic
- Increasing gap between US and EU with respect to competitiveness of pharma sector
- Lack of single health market in the EU – fragmentation
- Scientifical progress → Existing legislation is no longer fit for the purpose
- "One size fits all" approach no longer applies → modulation of incentives

EU Pharmaceutical Package – Legislation pipeline

- 26 April 2023 – official release of the EU Pharmaceutical Package which revise and replace the existing general pharmaceutical legislation, e.g.:

- EU Directive 2001/83/EC on the Community code relating to medicinal products for human use and

- Regulation (EC) no. 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency

Make sure all patients across the EU have timely and equitable access to safe, effective, and affordable medicines

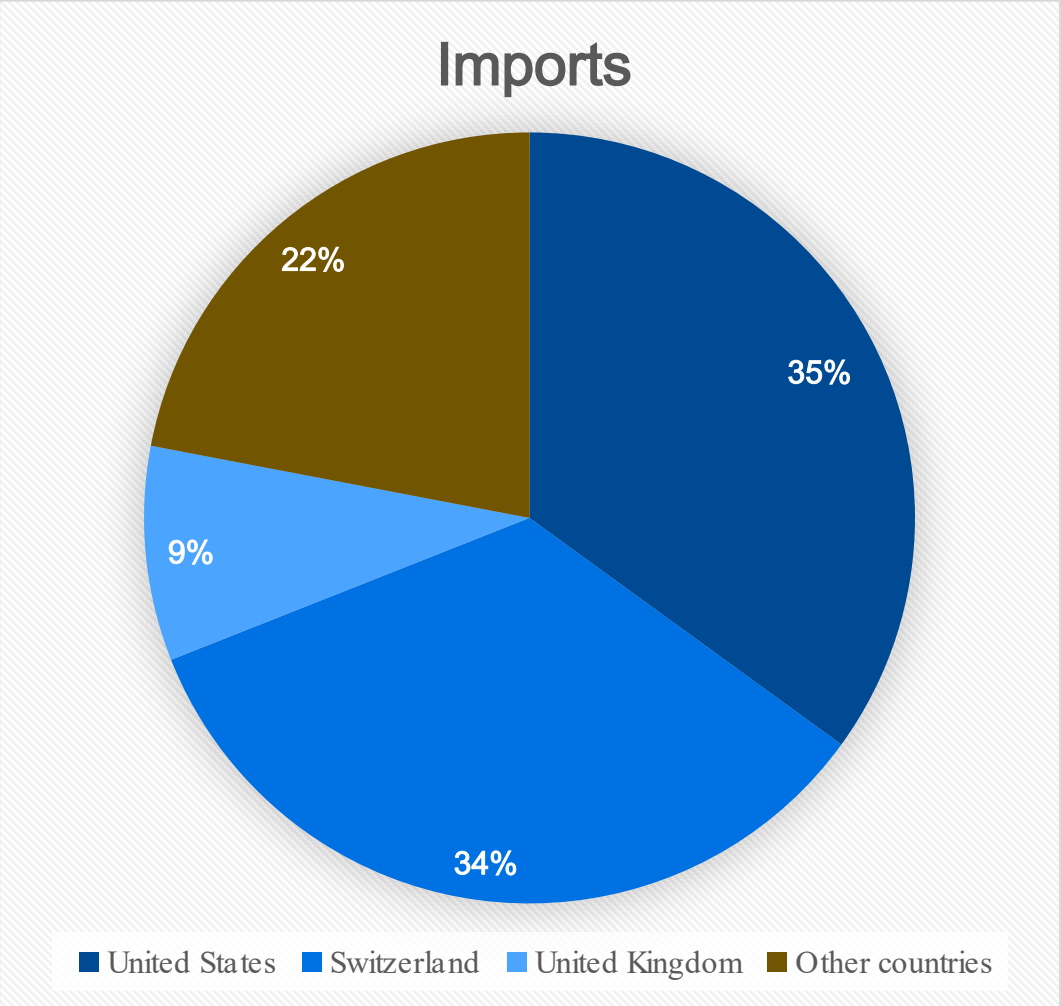
Enhance the security of supply and ensure medicines are available to patients, regardless of where they live in the EU

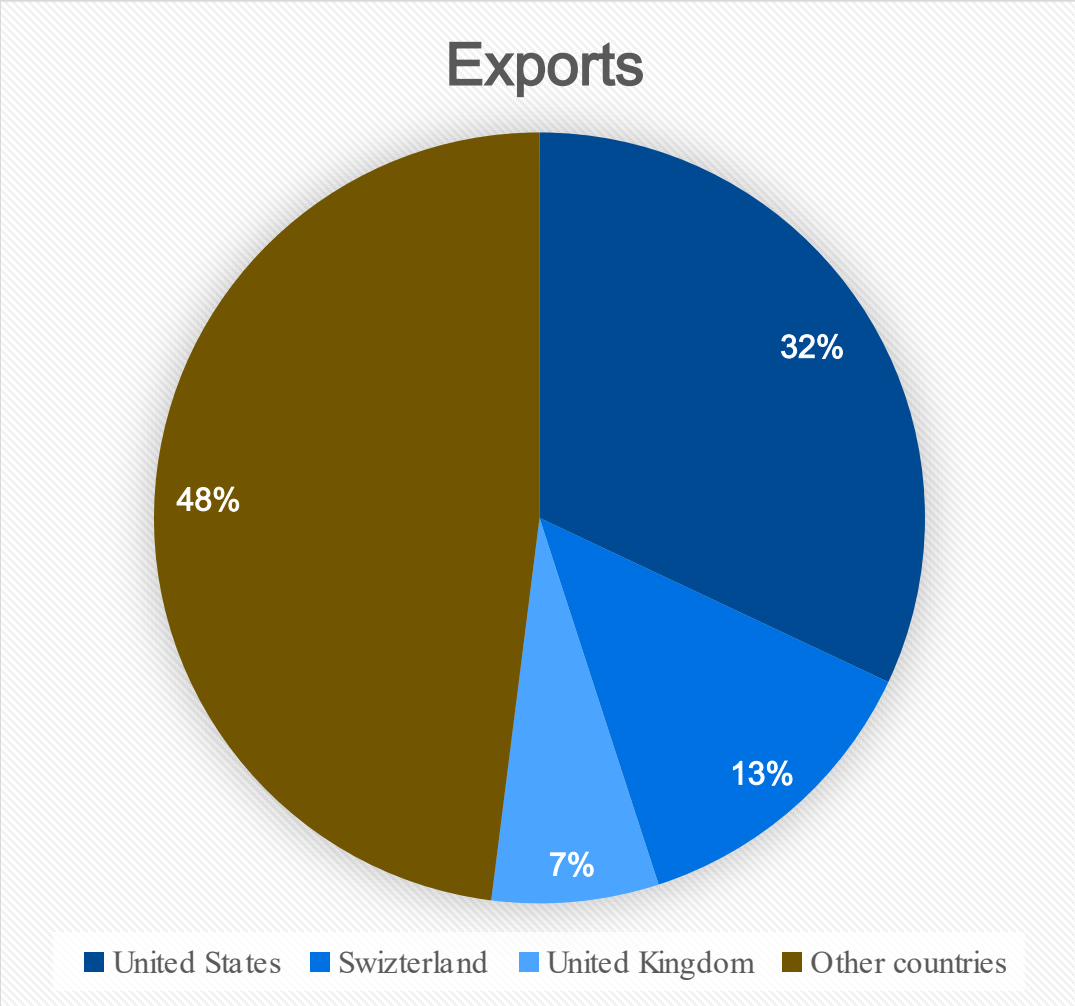
Continue to offer an attractive and innovation -friendly environment for research development, and production of medicines in Europe

Make medicines more environmentally sustainable

Address antimicrobial resistance (AMR) and the presence of pharmaceuticals in the environment through a One Health approach

EU Pharmaceutical Package – global impact



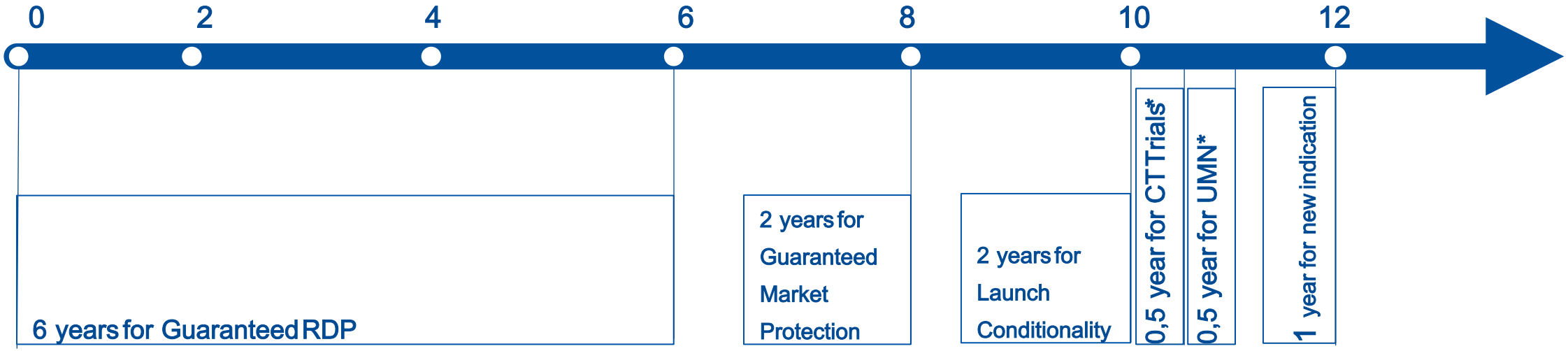


Source: Eurostat (online aata code: DS.-018995)

EU Pharmaceutical Package – Challenges

How to balance Innovation & Accessibility?

- Standard regulatory data protection (RDP) period is reduced from 8 to 6 years
- Market exclusivity remains at 2 years
- Modulation of incentives – 4 options to extend standard RDP period



* UMN - Unmet Medical Meets

* CT Trials - Comparatif Clinical Trials

Drug registration in the EU – acceleration of central registration procedures

STEP 1

Scientifical assessment by the Committee for Medicinal Products for Human Use (CHMP) of EMA

Standard	Accelerated
210 days under Regulation 726/2004 vs **180** days under the Pharma Package	**150** days Accelerated assessment procedure is used upon applicant's request when medicinal products are of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation.

STEP 2

MA grant by the EU Commission

Standard
67 days under Regulation 726/2004 vs **46** days under the Pharma Package

Drug registration in the EU – Conditional Marketing Authorization

- Conditional MA - under Art. 14a of Regulation 726/2004

> *"In duly justified cases to meet unmet medical needs of patients a marketing authorisation may, for medicinal products intended for the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases, be granted prior to the submission of comprehensive clinical data provided that the benefit of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. In emergency situations, a marketing authorisation for such medicinal products may be granted also where comprehensive clinical or pharmaceutical data have not been supplied"*

New! Temporary emergency MA - may be granted only after the recognition of a public health emergency at Union level

Drug registration in the EU – improvements under the Pharma Package

- Shorter period for scientifical assessment by EMA
- Shorter period for MA grant by the EU Commission
- New mechanism - Temporary emergency marketing authorisation

EU Pharma Package – what will happen next?

- Long legislation pipeline – starts with positions of member states and consultation process
- Though negotiations between stakeholders and member states
- Works on alternative versions of most controversial mechanisms
- Discussions on values protected – balance between Innovation & Accessibility
- BUT … common understanding that the EU needs to move forward a single health market to the benefit of the patients and in order to compete on the global health market

Medical devices in the EU– placing on the market

- Medical devices - products or equipment intended for a medical purpose
- Subject to a conformity assessment to demonstrate they meet legal requirements to ensure they are safe and perform as intended
- Self certification system. Conformity assessment involves an audit of the manufacturer's quality system and, depending on the type of device, a review of technical documentation from the manufacturer on the safety and performance of the device in cooperation with “notified bodies”
- Manufacturers place a CE (Conformité Européenne) mark on a medical device – proof that products passed a conformity assessment
- The MDR went into effect in 26th May 2021 but provides for transitional provisions. Products with pre-MDR certificates can be sold until the end of 2027/2028 (depending on product classification), and products sold at least once before 26th May 2021 can continue to be sold without time limitations

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Joanna Krakowiak advises firms from the consumer products sector as well as industries governed by special regulatory regimes, including pharmaceutical law, food law and regulations governing cosmetics and medical devices, concerning market entry procedures, labelling and sales models. She reviews advertising campaigns for consumer products and advises on how to reduce the risk of advertising being challenged by competitors, consumers or regulators. She has experience in negotiating and drafting contracts for conduct of clinical trials as well as issues related to data protection and cybersecurity. She represents clients in administrative and civil litigation, including patent disputes, as well as cases involving exclusivity of products. She also deals with commercial contracts and evaluation of product liability risks with respect to manufacturers and distributors. In M&A, she participates in corporate due diligence.

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Accelerated Approval in the United States

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Plenary Session 5: A Global Look at Expedited Programs for Drug and Device Development

International Bar Association

June 2, 2023

Accelerated Approval in the U.S.

- Section 506(c) of the FD&C Act, as amended; 21 CFR part 314, subpart H; 21 CFR part 601, subpart E.

  Accelerated approval may be permitted for a drug or biologic that treats a **serious condition**

  AND

  generally provides a **meaningful advantage over available therapies**

  AND

  demonstrates an effect on a **surrogate endpoint** that is **reasonably likely to predict clinical benefit** or on a **clinical endpoint** that can be measured **earlier than irreversible morbidity or mortality** (IMM) that is **reasonably likely to predict an effect on IMM or other clinical benefit** (i.e., an intermediate clinical endpoint)

- Confirmatory trials to verify and describe the anticipated effect on IMM or other clinical benefit
- Withdrawal of drug or indication if no confirmation.

Pressures on Accelerated Approval Framework

FDA's Pazdur Proposes Changes to Accelerated Approval Program

Published: Jan 21, 2022 | By Alex Keown

Dr. Rick Pazdur, M.D./Courtesy MDedge/Neil Osterweil

Rick Pazdur, director of the U.S. **Food and Drug Administration (FDA)**'s Oncology Center of Excellence (OCE) and longtime defender of the agency's accelerated approval program, is now acknowledging that some changes are likely needed to the process to ensure timely receipt of confirmatory trial data.

CMS and Centers for Medicare and Medicaid Innovation

- CMS National Coverage Determination on Monoclonal Antibodies Against Amyloid for the Treatment of Alzheimer's Disease
  - Creates a bifurcated pathway for coverage in Medicare for the first time
- CMMI Proposal to develop payment models for drugs receiving accelerated approval
  - Model inclusion would be mandatory for Part B providers
  - Intended to incentivize expedient completion of confirmatory trials

Medicaid Waivers – States Attacking Accelerated Approval

MassHealth

- 1115 waiver submitted to CMS in September 2017
- Contained a proposal to deny formulary coverage for drugs that do not have enough clinical data to determine if they are effective, especially drugs approved through FDA's fast-track authority

Oregon Health Authority

- Contained a proposal to deny formulary coverage for drugs approved under the Accelerated Approval pathway

TennCare

- Contained a proposed "closed formulary" and granted power to exclude products that lacked "substantial" scientific evidence.

National Governors Association

- *NGA Principles for Federal Action to Address Health Care Costs*
- Includes over 25 recommendations including restricting access to select "fast-tracked" therapies

"Congress and the Administration should support state flexibility and invest in strengthening state purchasing power to address pharmaceutical costs across programs by:

- Allowing state Medicaid programs to exclude from their formularies or receive enhanced federal matching funds for select fast-tracked, first-in-class drugs that lack sufficient data on safety and efficacy, until such evidence is produced"

Reports & White Papers

Medicaid and CHIP Payment and Access Commission

- Two recommendations included in June 2021 report to Congress
  1. Require a manufacturer to pay an increased minimum Medicaid prescription drug rebate on AA therapies until the manufacturer completes post-market confirmatory trials
  2. Require a manufacturer to pay a higher inflationary rebate on AA therapies until the manufacturer completes post-market confirmatory trials

Medicaid Medical Directors Network (MMDN)

- Policy Principles
  - Special labels for rare disease therapies with AA approval based on small clinical trials with proxy inputs
  - Confirmatory trials held to defined timelines
  - Allow state Medicaid programs to waive Sec. 1927 to enact evidence-based drug formularies as opposed to relying solely on FDA approval decisions
  - Direct Federal purchasing for AA therapies accessed through Medicaid
  - Enhanced FMAP to state to cover AA therapies

Reports & White Papers

- ICER White Paper Issued in April 2021- *Strengthening The Accelerated Approval Pathway: An Analysis of Potential Policy Reforms and Their Impact on Uncertainty, Access, Innovation, and Cost*
- 10 policy reforms (FDA regulatory reforms & payment and access reform)
    1. Strengthen selection of surrogate endpoints
    2. Standardize AA review templates
    3. Great use of randomized controlled trials
    4. Create new label for AA therapies
    5. Increase enforcement of confirmatory trials
    6. Sunset approvals for therapies lacking confirmatory evidence
    7. Create separate “Safety-Only” approval pathway waiving public/private insurance coverage
    8. Increase Medicaid statutory rebate (MACPAC concept)
    9. Use pricing at marginal cost to incent completion of confirmatory trials
    10. Payment based on outcomes-based contracts

ICER

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FDA Omnibus Reform Act

- After negotiations stalled last summer, Congress passed a “clean” UFA reauthorization on September 30, under the FDA User Fee Reauthorization Act of 2022.
  - Although the Act reauthorized the UFAs for five years, it extended other FDA programs and initiatives through December 16, 2022 (under subsequent legislation, extended to December 23, 2022).
  - The expiration of these FDA programs created a critical opportunity for Congress to reconsider the riders as part of the end-of-year omnibus package.
- On December 29, 2022, President Biden signed into law the Consolidated Appropriations Act, 2023.
- The legislation included a package of US Food and Drug Administration (FDA) “riders”—deemed the Food and Drug Omnibus Reform Act, or “FDORA”—most of which were originally floated for inclusion in legislation that reauthorized the FDA User Fee Acts (UFA) for prescription drugs, medical devices, generic drugs, and biosimilars.
- Many of the proposed riders were included in FDORA – including accelerated approval reforms.

FDORA Sec. 3210 Modernizing Accelerated Approval

- Directs FDA to determine the conditions for required post-approval studies for products approved under accelerated approval.
- Permits FDA to ***require post-approval studies to be underway prior to approval or within a specified time period after approval***.
- Directs FDA to publish an explanation when it does not require a post-approval study.
- Lays out *the* ***new procedures FDA must follow to withdraw a product's accelerated approval on an expedited basis***, which include:

  (1) providing the sponsor with due notice, an explanation for the proposed withdrawal, and an opportunity to meet with the Commissioner or the Commissioner's designee;

  (2) providing an opportunity for public comment;

  (3) responding to such comments; and

  (4) convening an advisory committee relating to the proposed withdrawal if the sponsor requests one and no such advisory committee has previously advised FDA on the proposed withdrawal.

FDORA Sec. 3210 Modernizing Accelerated Approval (cont'd.)

- Requires **reports on post-approval study progress** to be made no later than 180 days after approval and every 180 days thereafter until any required post-approval studies are completed.
- Makes failure to conduct required post-approval studies with due diligence and failure to submit the required reports **prohibited acts**, which can result in a criminal prosecution.
- Requires FDA to issue **guidance** on:
  - (1) "how sponsor questions related to the identification of novel surrogate or intermediate clinical endpoints may be addressed in early-stage development meetings with [FDA];"
  - (2) the use of novel clinical trial designs to conduct post-approval studies;
  - (3) the expedited withdrawal procedures; and
  - (4) "considerations related to the use of surrogate or intermediate endpoints that may support the accelerated approval of an application . . . , including considerations in evaluating evidence related to any such endpoints."

FDA NEWS RELEASE

FDA Commissioner and Chief Scientist Announce Decision to Withdraw Approval of Makena

For Immediate Release: April 06, 2023

Español

Today, the U.S. Food and Drug Administration announced the final decision to withdraw approval of Makena—a drug that had been approved under the accelerated approval pathway. This drug was approved to reduce the risk of preterm birth in women pregnant with one baby who have a history of spontaneous preterm birth. The decision was issued jointly by the FDA Commissioner and Chief Scientist. Effective today, Makena and its generics are no longer approved and cannot lawfully be distributed in interstate commerce.

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Accelerated Approval in the Mexico

International Bar Association

June 2, 2023

Accelerated Approval in Mexico

- AGREEMENT by which the requirements established in articles 161 Bis, 167, 169, 170 and 177 of the Health Law Regulations and the technical evaluation procedures carried out by the Federal Commission for the Protection against Sanitary Risks for the granting of the marketing authorization of the health supplies referred to in articles 2, sections XIV, XV, subsections b and c and 166, sections I, II and III of the Health Law Regulations; in relation to articles 222 and 229 of the General Health Law, the necessary requirements and evaluation procedures carried out; as well as the importation of medicines with or without marketing authorization in Mexico, aimed at any disease or condition, which are authorized by the following regulatory authorities: Swiss Agency for Therapeutic Products-Swissmed, European Commission, Food and Drug Administration of the United States of America, Health Canada, Australian Therapeutic Goods Administration, PAHO/WHO Reference Regulatory Agencies; prequalified by the Prequalification Program for Medicines and Vaccines of the World Health Organization or Regulatory Agencies members of the Pharmaceutical Inspection Cooperation Scheme. Published on **January 28, 2020** in the Mexican Official Gazette. and its modification (June 2021)

Accelerated Approval in Mexico

- Decree that was published on **January 28, 2020**, in the Federal Official Gazette by the Ministry of Health which states the sanitary requirements equivalence and allows the importation of drugs without marketing authorization in México.
- Decree that was published on **June 22, 2021**, which amends Decree that was published on January 28, 2020 in the Federal Official Gazette by the Ministry of Health which states the sanitary requirements equivalence and allows the importation of drugs without marketing authorization in México.

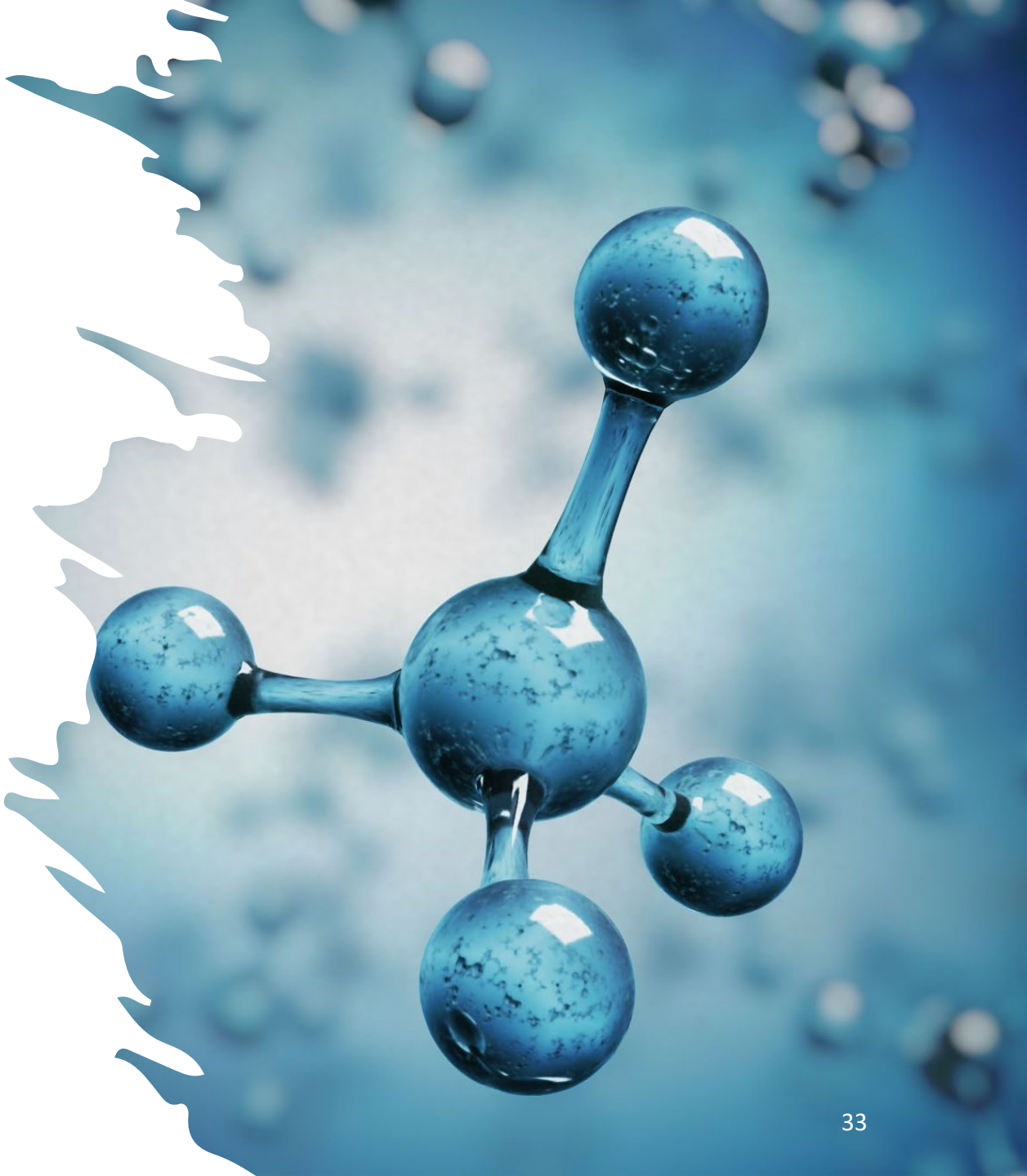
- Timelines
- Biologics
- Medical devices.

Decrees is intended to:

- To expedite the granting of marketing authorizations for foreign health supplies in Mexico, by establishing that if the particular health supplies in question have met all the requirements and procedures of a foreign regulatory agency, i.e. if they possess a marketing authorization, this will be equivalent to having complied with all the requirements of the Mexican legislation.
- Allopathic generic drugs, biologic biocomparable drugs, those that consist of a new molecule and medical devices, specifically: those that are not registered in Mexico but are in other countries and those that are the result of the combination of two or more known active ingredients or substances (composition/formulation).

International regulatory authorities

- International regulatory authorities (Allopathic generic drugs, biologic biocomparable drugs, those that consist of a new molecule):
  - Swiss Agency for Therapeutic Products- Swissmed;
  - European Comission;
  - Food and Drug Administration of the United States of America;
  - Canadian Ministry of Health;
  - Australian Therapeutics Product Management;
  - Reference Regulatory Agencies PAHO / WHO;
  - Drugs that were Prequalified by the Prequalification Program for Medicines and Vaccines of the World Health Organization (WHO) or regulatory agencies members of the Pharmaceutical Inspection Co-operation Scheme (PIC/S).



International regulatory authorities

- International regulatory authorities (medical devices):

- Food and Drug Administration of the United States of America;
- Canadian Ministry of Health;
- Ministry of Health, Labor and Welfare of Japan to allow the marketing of medical devices in its territory;

International regulatory authorities

And the tests and inspections carried out by the:

- Japan Agency for Pharmaceuticals and Medical Devices;
- European Comission;
- UK Medicines and Healthcare Products Regulatory Agency;
- Korean Ministry of Food and Drug Safety;
- Australian Therapeutic Goods Administration;
- National Health Surveillance Agency of Brazil.

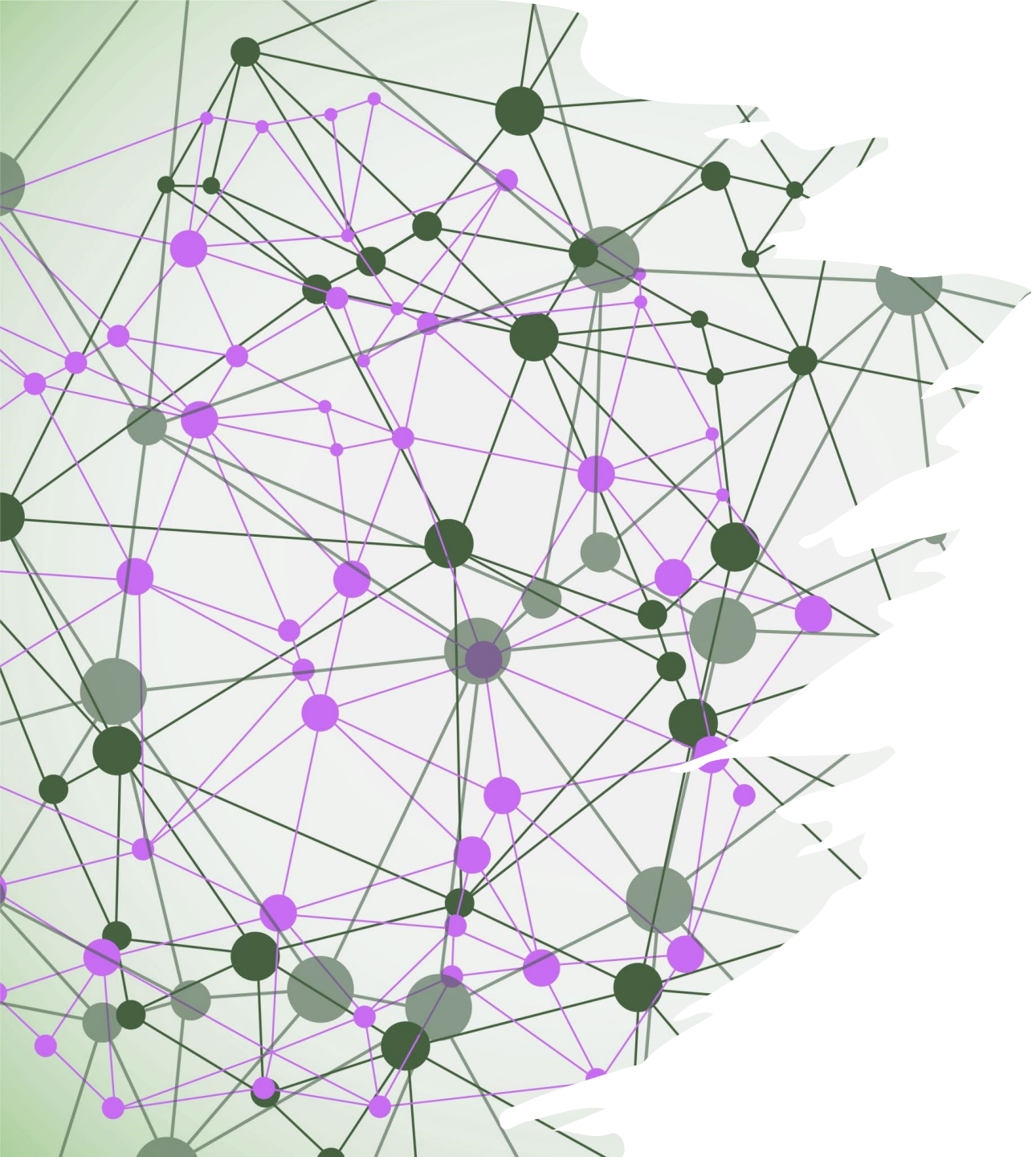
Timelines

Drugs

Standard	Accelerated
180 and 240 working days (6 to 8 months)	**10 days** between the import and the deadline for requesting a marketing authorization and; **45 days COFEPRIS has to issue a decision**.

Medical Devices

Standard	Accelerated
30, 35 and 60 working days depending on the class of medical device	**10 days** between the import and the deadline for requesting a marketing authorization and; **COFEPRIS will reduce the attention of the requests to half the established term.**



DIGIPRiS

- DIGIPRiS is the digital platform of the Federal Commission for the Protection against Sanitary Risks (COFEPRIS) that allows more agile online procedures and services.

- Through DIGIPRiS, it is sought that natural persons and companies can digitally enter their procedures, 24 hours a day, 365 days a year.

- Since last year the use of said platform was launched, however, being very recent, it is constantly updated.

- Requests for operation and advertising notices may only be submitted through the DIGIPRiS platform and will receive an automatic response. All the modalities of the procedure may be entered, i.e., health supplies such as medicines and medical devices; health services, for example, doctors' offices and clinics; cosmetics and foodstuffs.

Challenges

IP rights.

Safety and efficacy.

Venues to approach public and private health institutions.

Product liability.

In brief…

- There are grounds to have product approved through an accelerated program.
- There are still some concerns and challenges yet the system is robust and looks prepared to the proposals within the decree.
- The authorities are working to improve the tools to expedite the granting of MA's, thus the near future looks promising.
- The industry is willing to assist the authorities if necessary to continue to strengthen the current venues and build the necessary tools to contribute to a prompt and safe access t medicines