CDDF & EORTC Joint Workshop

Navigating the Evolving Regulatory Landscape of Orphan Drugs in Europe

Pedro Franco
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Merck Serono Limited

EU Regulatory Fast Track Schemes
Table of content

What is a Rare disease?

Overview

- There is not a universal definition of rare disease
- A rare disease affects a small number of patients in a country or region
- Rare diseases are serious, chronic and progressive

Numbers

- There are more than **8,000 rare diseases worldwide**
- **80% of rare diseases** are **genetic** origin (e.g. Tay Sachs, Cystic Fibrosis, a number of severe metabolic disorders)
- 50% of rare diseases appear during adulthood

What is a rare disease?

Lack of treatment

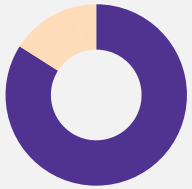
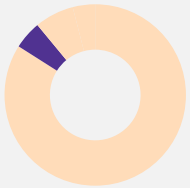
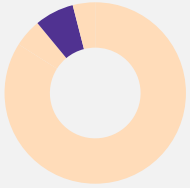
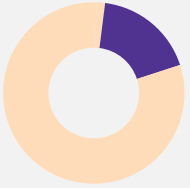
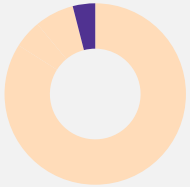
- Majority of the rare diseases have no **adequate treatment**
- Early diagnostic is key

Lack of research

- More research is needed
- Grants for research
- Investment

Navigating the Evolving Regulatory Landscape of Orphan Drugs in Europe

Distribution of rare diseases and patients according to prevalence

Prevalence	% of rare diseases	% of patients
< 1 in 1,000,000 Single cases or families	 84%	0.5%
1-9 in 1,000,000	 5%	1.5%
1-9 in 100,000	 7%	 18%
1-5 in 10,000	 4%	 80%

Source: Nguengang Wakap, S., Lambert, D.M., Olry, A. et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet 28, 165–173 (2020).[1]

Navigating the Evolving Regulatory Landscape of Orphan Drugs in Europe

What are the challenges of developing an orphan drug?

Medicines to treat rare diseases are complex development programs with high risk of failure

Payers / HTA / Insurances requirements – National budgets – delays in access after approval

Lack of scientific knowledge / Unprecedented endpoints – Patients insights are key

Different Global regulatory & National Policies requirements

Lack of scientific expertise and health care professionals

Small markets with low number of patients

Limited number of patients for clinical trials / Heterogenous population

Difficulties in return on investment – Incentives (e.g. ME)

Limited data on epidemiology

Different clinical trials design (single arm trial; Phase 2) & used of RWEs (…)

Navigating the Evolving Regulatory Landscape of Orphan Drugs in Europe
Why do we need an orphan drug legislation / policy?

Why?

1. Many patients do not have treatment(s) for their rare disease
2. To promote research and new treatments in areas of unmet need
3. To increase the number of new treatments in areas of unmet medical need – Orphan drugs
4. To create an ecosystem in which pharmaceutical industry & investors feel comfortable to invest in risky projects

Europe

Overview of the orphan regulatory Framework

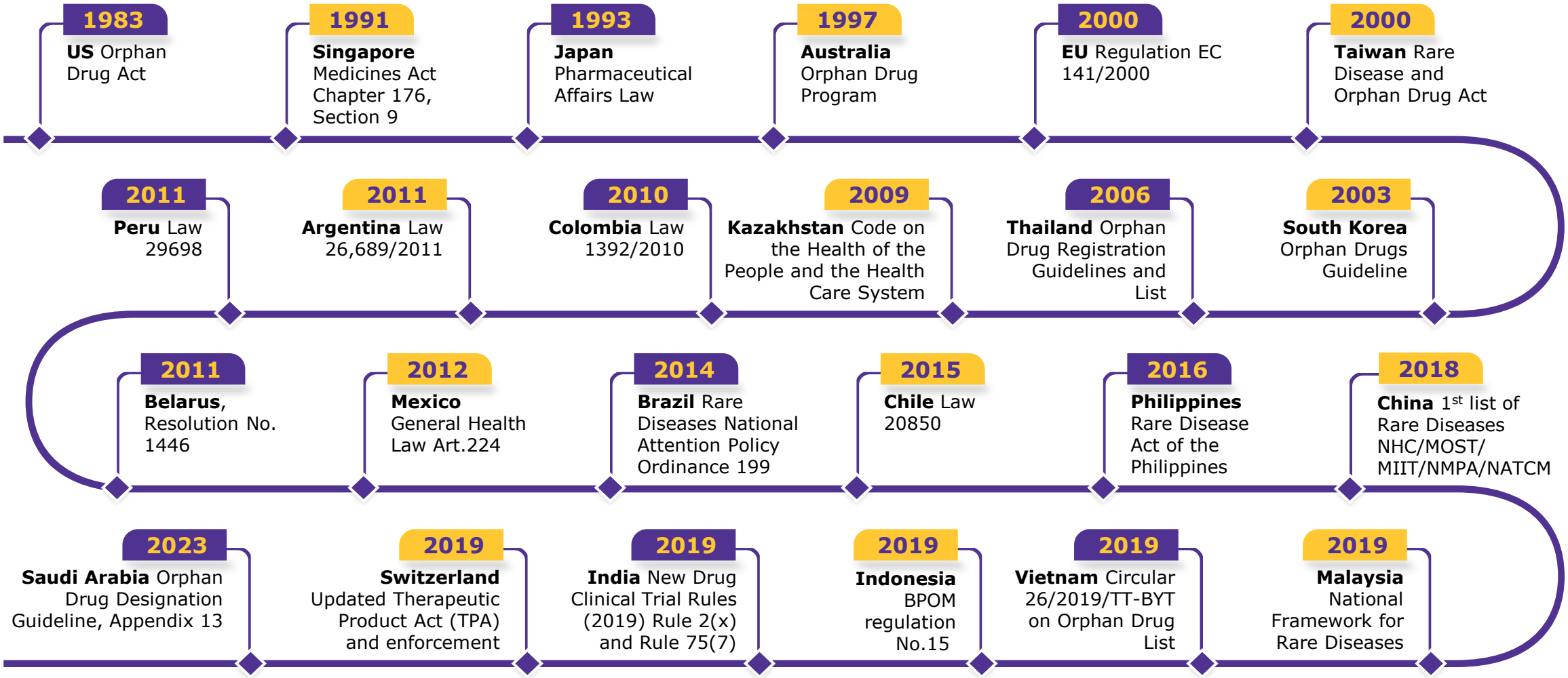
Historical Context

- **Orphan drug regulatory framework in the EU began in 2000**, 17 years after the US
- The European Orphan Drug Regulation (EC) No 141/2000 was adopted in 1999

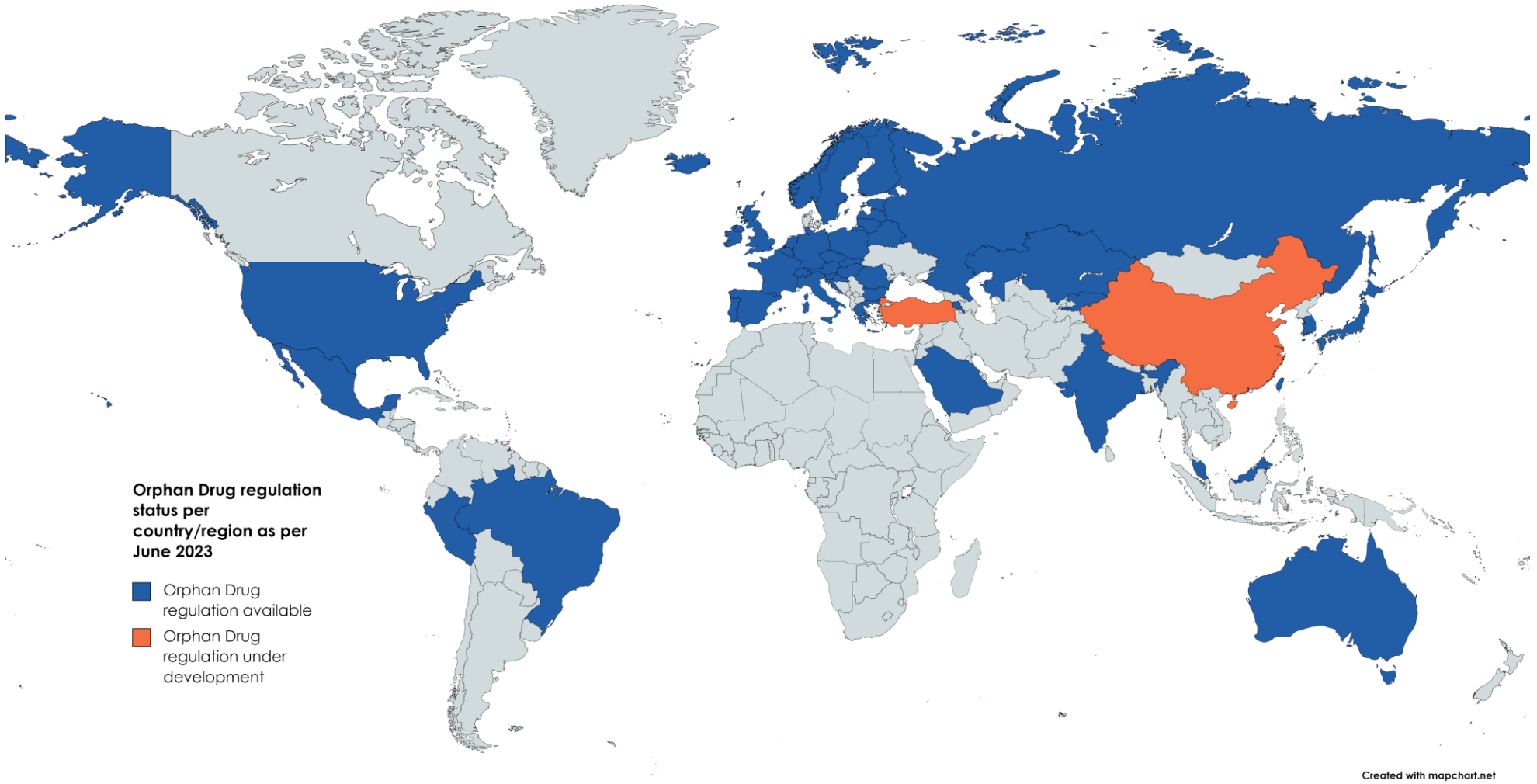
Criteria Defined in the Orphan Regulation

- **Seriousness of condition:** life-threatening and/or chronically debilitating.
- **Rarity (prevalence <5/10,000)** or non-return of investment – very rare disease.
- **No satisfactory methods or if exist will have significant benefit** (='clinically relevant adv. or major contrib. to patient care').

Historical overview
Orphan drug legislations worldwide



Orphan drug legislations available worldwide
EFPIA overview – June 2023



Europe

Impact of the orphan drug legislation in EU

EC

Only **8** medicines to treat rare diseases approved in EU before the orphan drug Regulation

In Europe, the number of orphan drugs and orphan designations approved between 2000 and 2023:

244
new orphan drugs authorised

2,871
orphan designations approved

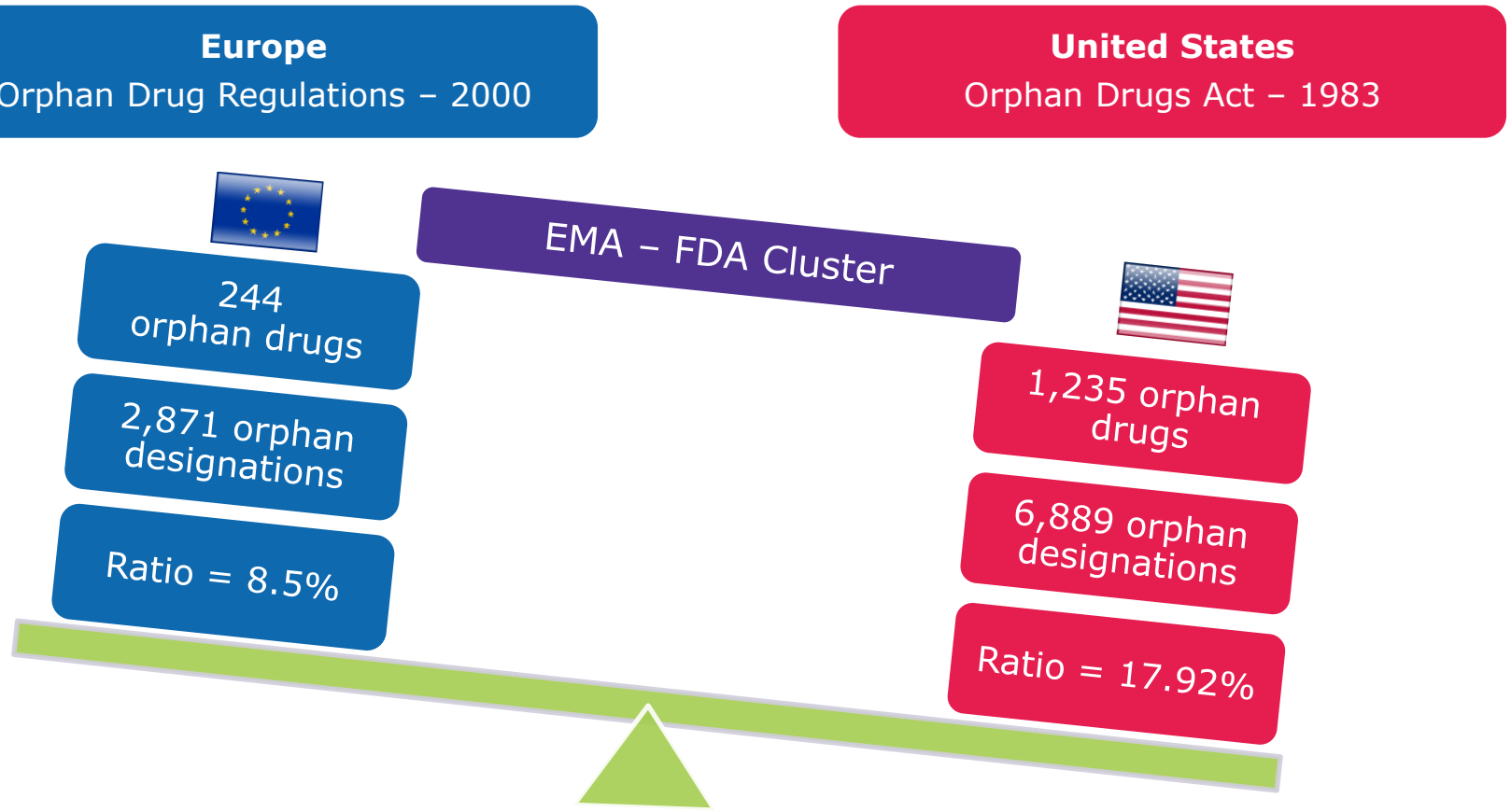
40%
of orphan drugs approved are in the area of **oncology**

8.5%
ratio of the **number of orphan drugs** authorised compared to the number of **orphan designations** approved

- **Revision of the current EU OD Regulation is ongoing**
- **The EU Regulation has worked well for rare diseases that need a stable regulatory environment**

Europe
Impact of the orphan drug legislation in EU

US
versus
Europe



European Orphan drug framework
Revision of the European Pharmaceutical Legislation

Intro-duction

What problems is this legislation trying to solve?

- **Unmet medical needs (UMN) not addressed Combating AMR**
- **Patients have unequal Access across EU**
- **Affordability of medicines challenging for health systems**
- **Environmental Sustainability**
- **Competitive Regulatory framework**
- **Availability of medicines/shortages**

European Orphan drug framework
Revision of the European Pharmaceutical Legislation

"General pharmaceutical legislation – GPL"

(regulates authorisation, manufacturing, distribution and monitoring of medicines + provides regulatory protection to reward innovative medicines)

Directive (2001)
on the Community code relating to medicinal products for human use

Regulation (2004)
laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency

"Orphan regulation" and "Paediatric regulation"

(complement the general pharmaceutical legislation – support the development of medicines in previously neglected areas)

Regulation (2000)
on orphan medicinal products

Regulation (2006)
on medicinal products for paediatric use

From THREE to ONE

Directive
on the Union code relating to medicinal products for human use

Regulation
laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency

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General Pharma Legislation
Timelines Forecast

European Parliament

ENVI Amendments

ENVI Debate

ENVI Draft Report

ENVI Vote

Parliament negotiation mandate

Plenary Vote

European elections

NOW

Indicative: 2025-2026

Entry into force *Indicative: 2026-2028*

Parliament endorsement

Delegated acts

European Commission

Legislative proposal (26 Apr 2023)

Sept *Oct* *Nov* *Dec* *Apr* 6-9 *June*

H1 2024

H2 2024

[...]

Trilogue negotiations

Indicative: 2025-2027

Council Working Party meetings

Presidency compromise draft

COREPER I (ambassadors)

General approach (ministers)

Council negotiation mandate

Council approval

Application/ Transposition + 18 months

Council of the European Union

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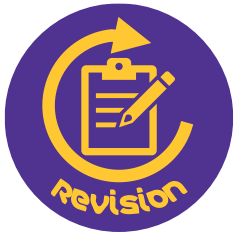
European Orphan drug framework
Revision of the European Pharmaceutical Legislation



What are the topics under discussion concerning orphan drugs:

- Definition of Unmet Medical Need & High Unmet Medical Need
- **Incentives:**

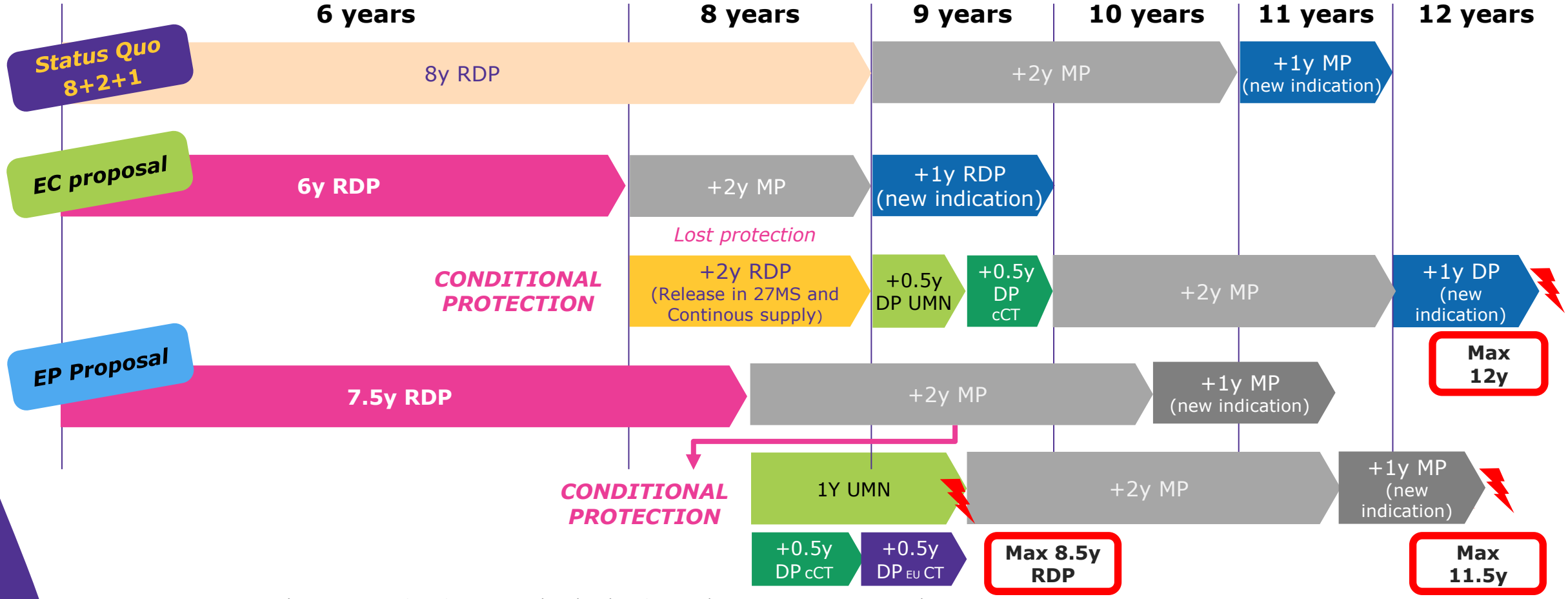
Marketing Exclusivity duration for all products including well established use

Vouchers concept

Data Protection & Market Protection

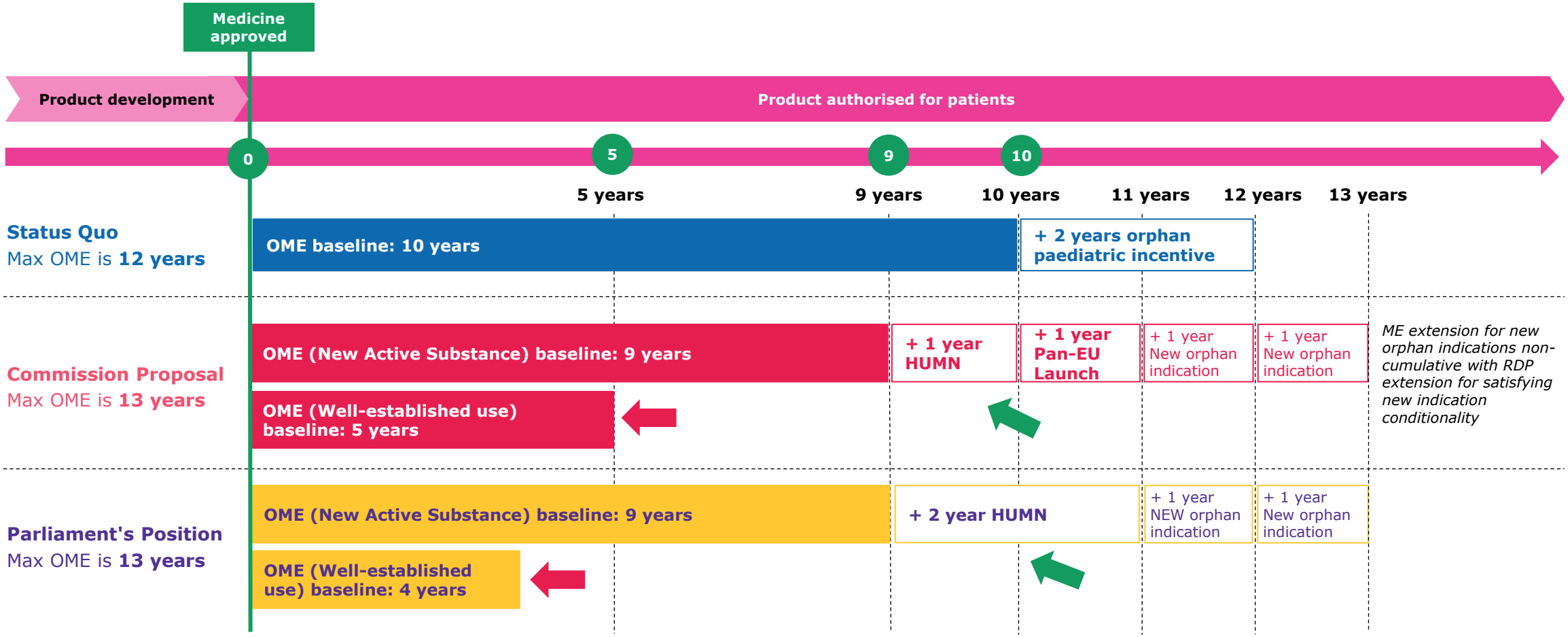
- Orphan drug Committee versus Working Party
- Orphan designation definition – keeping Prevalence = 5/10000
- Orphan designation validity 7 years – impact in innovation of small biotech and startups
- Significant benefit definition

Regulatory Data and Market Protection
Status Quo vs Commission Proposal vs EP Position



DP = Data protection; MP = Market protection; cCT = Comparative clinical trials; MS = member states; UMN = unmet need
EU CT= pre-clinical and clinical, was conduct in the EU and at least in part in collaboration with public entities.

Orphan Market Exclusivity (OME):
Status Quo vs Commission Proposal vs EP Position

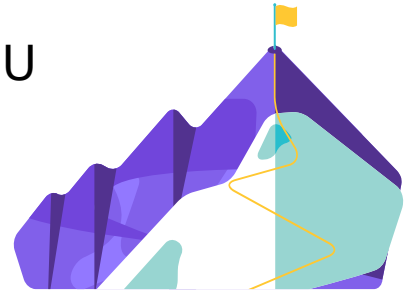


GOMA in COM Proposal & EP Position: ME starts from the date of the first orphan MA granted in the European Union

Future of EU regulatory framework
Advocacy plan

Industry Goals

1. Preserve incentives for R&D investment in Rare disease treatments
2. Facilitate patient access to Orphan medicines across Europe
3. Continue to improve the Orphan ecosystems
4. Continue improving Orphan drug legislation and research in the EU



EU regulatory framework
Why have orphan drug regulations been successful?

- **Created a positive ecosystem** in which sponsor feels comfortable to invest in risky rare diseases projects:

Incentives

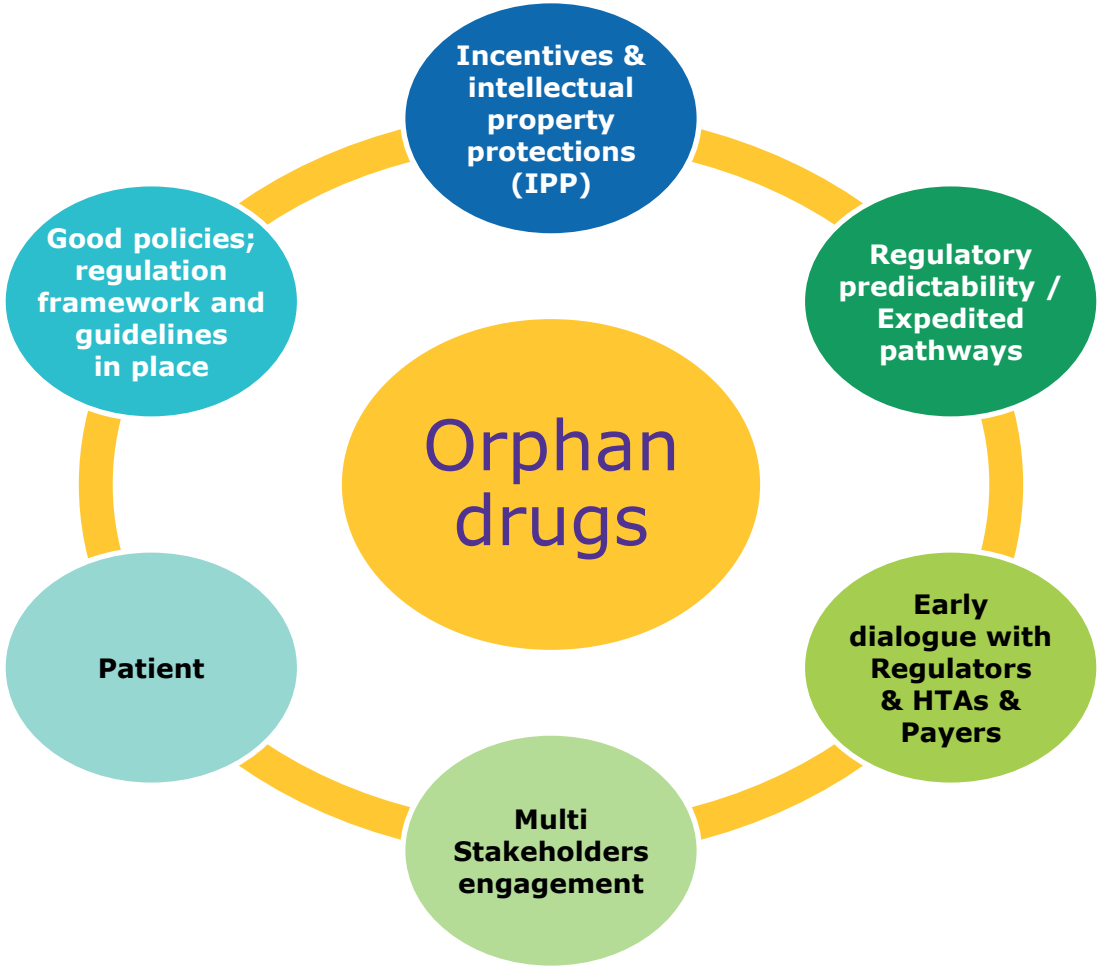
Regulatory flexibilities

Additional protection – Marketing Exclusivity & Data protection

- The current orphan drug regulations have been effective in supporting successful development and market access for rare diseases and address market failures
- Increase the number of treatments in the area of rare diseases
- Key to these successes are the stability and predictability of regulatory incentives, regulatory flexibilities and intellectual property protections (IPP)

Is the orphan drug development at Risk
Create an optimised orphan drug ecosystem

Need to improve the R&D ecosystem for basic research and company take-up of development

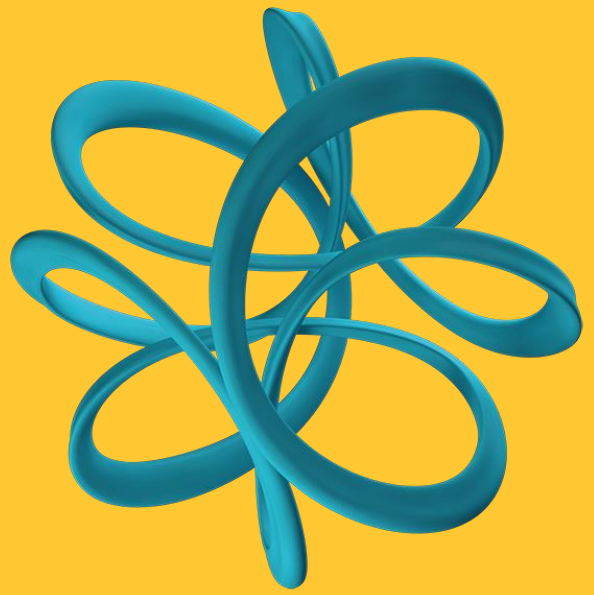


Need to improve the system of financial incentives and rewards

Key take-aways

- **Success of Mature Orphan Drug Legislations** have proven effective in driving the development of new treatments for rare diseases
- **Collaboration and working with Patient Advocacy Groups** is key. They are driving forward early access of new medicines in rare diseases
- **Global Approach to Orphan Drug Development** is crucial
- **Need for Regulatory and Economic Incentives** to promote and support the development of new treatments for rare diseases, encouraging investment and innovation in this critical area of healthcare
- Importance of **preserving the EU ecosystem of orphan drugs during the revision of the EU Pharma legislation**
- Cooperation between Health Authorities, Governments, HTA bodies, and Payers to ensure effective access to treatments for rare diseases
- **Foster local policies** to ensure improved access to treatments for rare diseases, addressing specific regional needs and challenges

Thank you for your attention!



Do you have any questions?

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