Rare Diseases: Regulatory Framework and Market Access

CAPRA Education Day, 2025
Oxana Iliach, PhD

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Acknowledgement

Rare Disease Organizations:

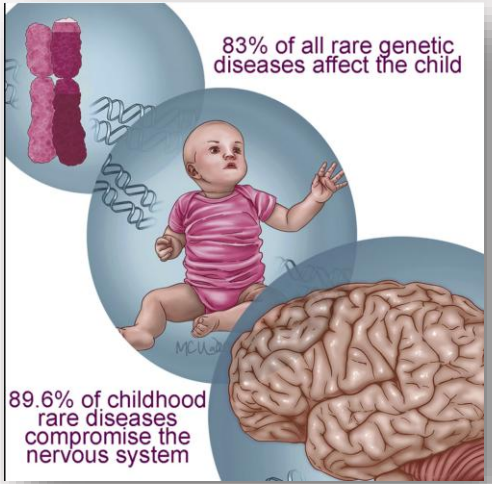
- Canadian Organization for Rare Disorders (CORD)
- International Rare Diseases Research Consortium (IRDiRC)
  - IRDiRC Regulatory Scientific Committee (RSC)

Research and Authoring Contributors:

- Fran Brown, Senior Vice President, Certara
- Maximilian Vargas, Vice President, Certara
- Sanja Stanisic, Director, Certara
- Geoff Fatzinger, Vice President, Certara

Why Rare Diseases Matter?

Devastation



Dedication

Innovation

Regulation

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Rare Genetic Diseases: Nature's Experiments on Human Development, 2020

Why therapeutic development for Rare Diseases is growing?

- Cancers, including rare cancers, and other rare diseases are among the top 10 causes of death for children in Canada, EU and United States.
- Majority of advanced therapeutical medicinal products (cell and gene therapies) are developed for rare diseases treatments

ORIGINAL ARTICLE | BRIEF REPORT

Patient-Specific In Vivo Gene Editing to Treat a Rare Genetic Disease

Authors: Kiran Musunuru, M.D., Ph.D. , Sarah A. Grandinette, B.S., Xiao Wang, Ph.D., Taylor R. Hudson, M.S., Kevin Briseno, B.S., Anne Marie Berry, M.S., Julia L. Hacker, M.S., +37 , and Rebecca C. Ahrens-Nicklas, M.D., Ph.D. Author Info & Affiliations

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- Infant with rare, incurable disease is first to successfully receive personalized gene therapy treatment:
- Neonate had received a diagnosis of severe carbamoyl-phosphate synthetase 1 deficiency, a disease with an estimated 50% mortality in early infancy, we
- Customized lipid nanoparticle–delivered base-editing therapy was developed within a months.
- Regulatory approval had been obtained for the therapy
- Patient received two infusions at approximately 7 and 8 months of age.
- 7 weeks after the initial infusion, the patient was able to receive an increased amount of dietary protein and a reduced dose of a nitrogen-scavenger medication to half the starting dose, without unacceptable adverse events and despite viral illnesses. No serious adverse events occurred.
- Longer follow-up is warranted to assess safety and efficacy. (Funded by the National Institutes of Health and others.)

Reference: Government of Canada: Leading Causes of death, total population, by age group: https://open.canada.ca/data/en/dataset/99993095-becb-454b-9568-e36ae631824e
EU: Eurostat, Causes of death statistics: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Causes_of_death_statistics
USA: CDC National Center for Health Statistics: Mortality in the United States, 2020: https://www.cdc.gov/nchs/products/databriefs/db427.htm
CDC Monthly Provisional Counts of Deaths by Select Causes, 2020-2023: https://data.cdc.gov/National-Center-for-Health-Statistics/Monthly-Provisional-Counts-of-Deaths-by-Select-Cau/9dzk-mvmi/about_data

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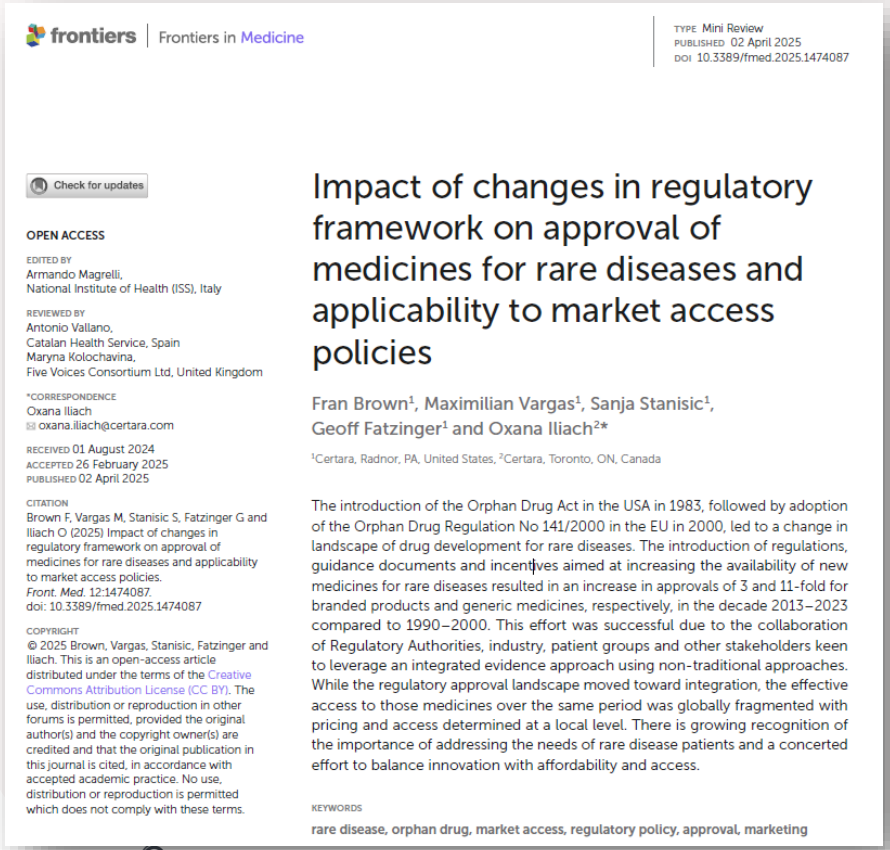
How changes in regulatory framework impact approval/access?



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EDITED BY
Armando Magrelli,
National Institute of Health (ISS), Italy

REVIEWED BY
Antonio Vallano,
Catalan Health Service, Spain
Maryna Kolochavina,
Five Voices Consortium Ltd, United Kingdom

*CORRESPONDENCE
Oxana Iliach
oxana.iliach@certara.com

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Impact of changes in regulatory framework on approval of medicines for rare diseases and applicability to market access policies

Fran Brown[1], Maximilian Vargas[1], Sanja Stanisic[1], Geoff Fatzinger[1] and Oxana Iliach[2]*

[1]Certara, Radnor, PA, United States, [2]Certara, Toronto, ON, Canada

The introduction of the Orphan Drug Act in the USA in 1983, followed by adoption of the Orphan Drug Regulation No 141/2000 in the EU in 2000, led to a change in landscape of drug development for rare diseases. The introduction of regulations, guidance documents and incentives aimed at increasing the availability of new medicines for rare diseases resulted in an increase in approvals of 3 and 11-fold for branded products and generic medicines, respectively, in the decade 2013–2023 compared to 1990–2000. This effort was successful due to the collaboration of Regulatory Authorities, industry, patient groups and other stakeholders keen to leverage an integrated evidence approach using non-traditional approaches. While the regulatory approval landscape moved toward integration, the effective access to those medicines over the same period was globally fragmented with pricing and access determined at a local level. There is growing recognition of the importance of addressing the needs of rare disease patients and a concerted effort to balance innovation with affordability and access.

KEYWORDS

rare disease, orphan drug, market access, regulatory policy, approval, marketing

- What changes took place in the rare disease regulatory landscape in major jurisdictions since 1983?
- What kind of incentive exists for rare disease development?
- Is there a correlation between changes in regulatory framework and approval?
- Is there a correlation between changes in regulatory framework and access?
- Is there a difference in impact on new product development versus generic drugs?

Reference: Front Med (Lausanne). 2025 Apr 2;12:1474087. doi: 10.3389/fmed.2025.1474087
https://pmc.ncbi.nlm.nih.gov/articles/PMC12016575/

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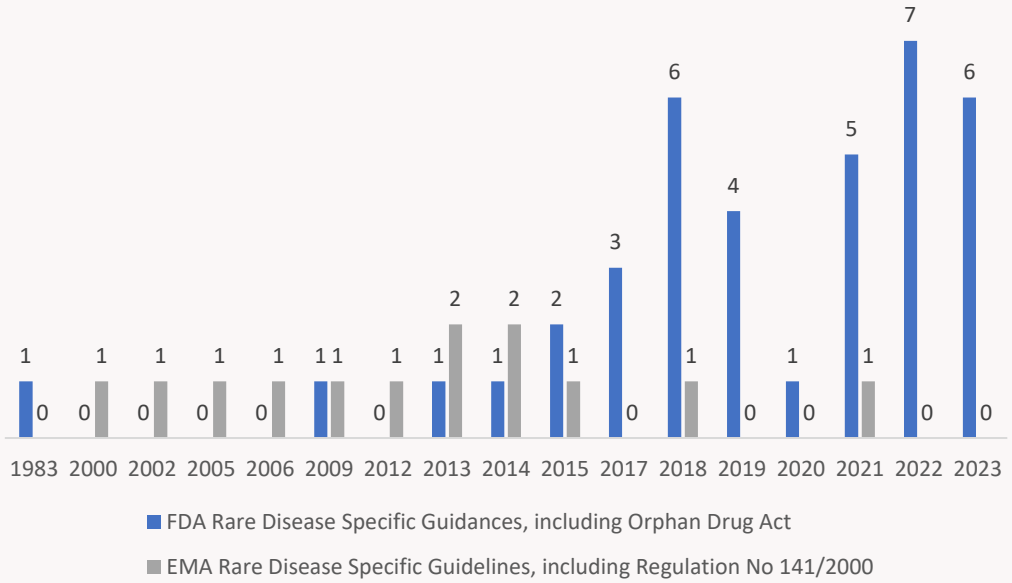
FDA and EMA rare disease specific guidances

Orphan Drug Act in the USA in 1983, followed by adoption of the Orphan Drug Regulation No 141/2000 in the EU in 2000



1983 – 2020:

- 12 EMA Rare Diseases specific guidances
- 35 FDA Rare Diseases specific guidances
- General and ICH guidances were not included in the review

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Reference: EMA and FDA websites

Summary of EMA incentives to facilitate product development for rare

Description	Incentives	Year of Implementation
Orphan Drug Designation	• Protocol Assistance • Access to the centralised authorisation procedure • Ten years of market exclusivity • Additional incentives for small and medium-sized enterprises (SMEs) • Fee reduction • Grants • Incentives in member states	1999 under Orphan Drug Regulation
PRIME	• Enhanced support from EMA, tailored to the relevant stages of development • Confirmation of potential accelerated assessment	2016 as European Commission initiative
Advanced therapy medicinal products (ATMP)	• Enhance scientific support (PRIME) for ATPs • Facilitate approval of clinical trials • Specific action plan for SMEs • Foster increased interaction between EMA and EUnetHTA on ATMPs • 65% fee reduction for a request for scientific advice for ATMPs (90% for SMEs); • 90% fee reduction for the certification procedure.	2008 under EC Regulation No 1394/2007
Support for micro, small and medium-sized enterprises (SMEs)/ SME office	• Direct contact the SME office for questions about regulations, administrative requirements or procedures • Request a briefing meeting • Receive translation assistance for the product information into all official EU languages • Receive guidance on clinical data publication; • Stay up to date with SME newsletters; • Participate in training events; • Receive support with looking for academic partners in the paediatric-medicine field	2005, Commission Regulation (EC) No 2049/2005
Conditional Marketing Authorisation (CMA)	• Fast-track approval of a medicine that fulfils an unmet medical need • Must fulfil specific obligations within defined timelines	2004, Regulation (EC) No 726/2004, further elaborated in Regulation (EC) No 507/2006.
Exceptional Circumstances	• Marketing authorisation granted to medicines where the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the condition to be treated is rare or because collection of full information is not possible or is unethical	2004, Article 14 (8) of the Regulation (EC) No 726/2004
Accelerated Assessment (AA)	• Reduce the timeframe to 150 days if the applicant provides sufficient justification for an accelerated assessment	2004, Recital 33 and Article 14(9) of Regulation (EC) No 726/2004
Parallel EMA/FDA scientific advice (PSA)	• Receiving feedback from both agencies and ability to align product development with both EMA and FDA expectations	2021, collaborative initiative between EMA and FDA
Parallel consultations EMA/HTA (EUnetHTA)	• Streamlined procedure for applicants; • Increased mutual understanding and problem-solving ability between EMA and HTA bodies through a more structured interaction; • Improved coordination with, and greater participation of HTA bodies in parallel consultations through EUnetHTA 21's Committee for Scientific Quality & Consistency in its configuration for Joint Scientific Consultations (CSCQ JSC)	2022, collaborative initiative between EMA, HTAs and EUnetHTA

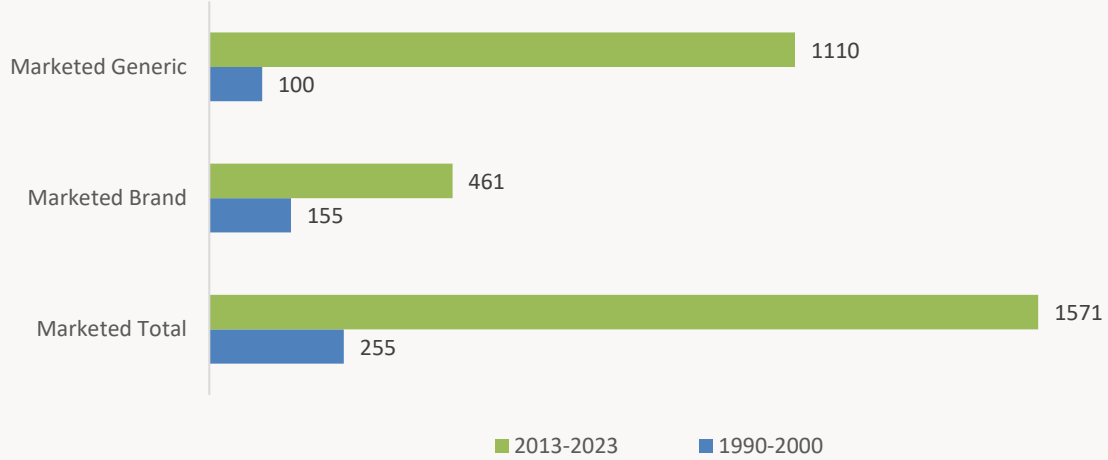
Summary of FDA incentives to facilitate product development for rare diseases

Description	Incentives	Year of Implementation
Orphan Drug Designation	• More frequent communication with FDA • Tax credits for qualified clinical testing • Waiver of NDA/BLA user fees • Eligibility for 7-year marketing exclusivity ("orphan exclusivity") upon marketing approval	1983 under Orphan Drug Act[1]
Fast Track Designation	• More frequent interactions with FDA • Eligibility for accelerated approval and priority review • Rolling review	1997 under Food and Drug Administration Modernization Act of 1997 (FDAMA) [100]
Breakthrough Therapy Designation	• Eligible for all Fast Track designation features • Intensive guidance on an efficient drug development program, beginning as early as Phase 1 • Organizational commitment involving senior FDA managers	2012 under Food and Drug Administration Safety and Innovation Act (FDASIA)[101]
Regenerative Medicine Advanced Therapy Designation (RMAT)	• Eligible for all the benefits of the fast track and breakthrough therapy designation programs	2016 under 21st Century Cures Act[104]
Priority Review	• Shorter clock for review of marketing application • 6 months compared to 10 months	1992, under the Prescription Drug User Act (PDUFA) [99]
Accelerated Approval	• Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit	2012 under Food and Drug Administration Safety and Innovation Act (FDASIA) [102]
Real-Time Oncology Review (RTOR)	• Expedite drug approval review: FDA reviews clinical data throughout the development process, and before a company formally applies for approval	2018 under collaboration of FDA Oncology Center of Excellence (OCE), with the Office of Oncologic Diseases (OOD) [103]

Reference: EMA and FDA websites

USA: 6-fold increase in access to products for rare diseases

Comparison of rare disease products in USA between 1990–2000 and 2013–2023 by type of product: brand or generic.

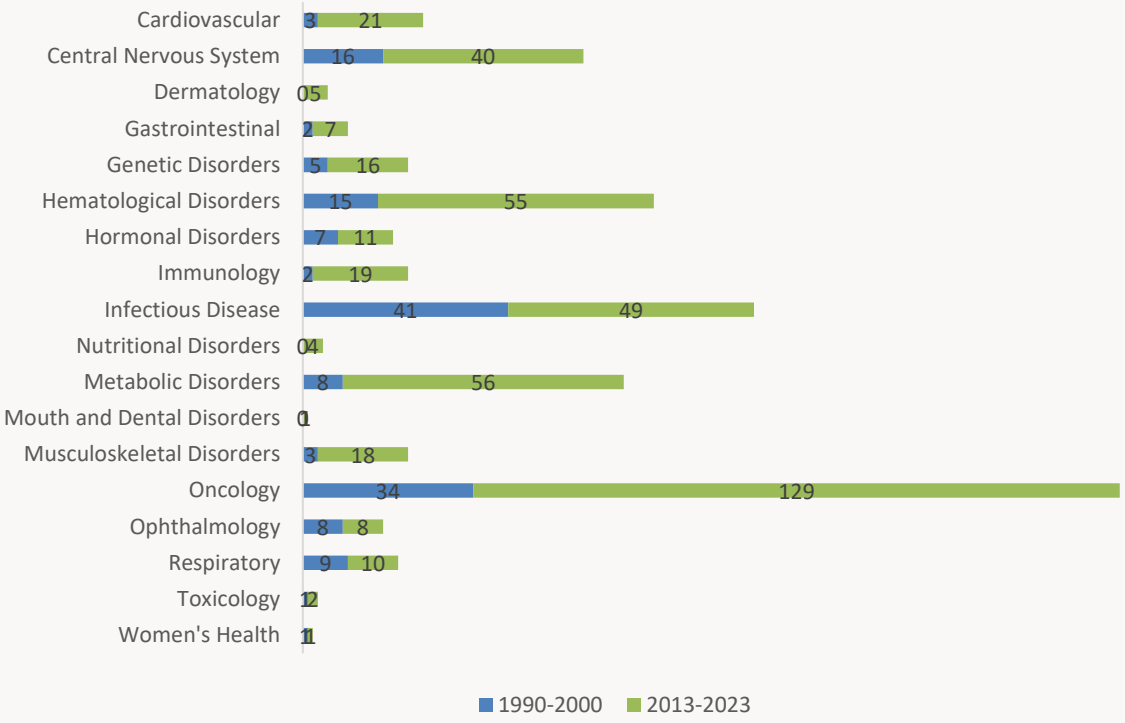


The introduction of regulations, guidance documents and incentives aimed at increasing the availability of new medicines for rare diseases resulted in an increase in market availability of 3 and 11-fold for branded products and generic medicines, respectively, in the decade 2013–2023 compared to 1990–2000

Reference: GlobalData System

Not all rare diseases are faired equally

Comparison of marketed brand products for rare disease products by therapeutic area in USA.



Therapeutic areas showing a higher increase in new products for Rare Diseases included:

- Oncology
- Metabolic disorders
- Hematological disorders
- Central nervous system disorders
- Cardiovascular disorders

Reference: GlobalData System

Collaboration in rare diseases and beyond

- 2008: EMA and FDA orphan medicinal products cluster
- 2016: EMA and FDA rare diseases cluster
- 2022: European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Organization for rare Diseases (EURORDIS) issued a joint statement bringing forward proposals to bolster HTA process and pricing and reimbursement framework for orphan drugs
- Potential role of IAMRA in harmonization of review and approval products for rare diseases….
- EMA and HTA parallel scientific advice
- Health Canada, Canada's Drug Agency (CDA) and Canadian Institute for Health Information (CIHI) collaboration

Government involvement and stakeholders' collaboration is critical to support access to Treatments for Rare Diseases

Rare Diseases lessons learned for regulatory professionals

Correlate regulatory pathway with likelihood of marketing success: new product development, generic development, biosimilar development, drug repurposing

Evaluate potential indications early in the product development and align them with patients' needs and access potential (revenue opportunities, coverage)

Applicable to any development

Leverage all incentives applicable to the development from regulatory and access perspective

Engage internally and externally: subject matter experts, key opinion leaders, patients organization, regulatory authorities, health technology assessment organizations

Questions?