NATIONAL ACADEMIES Sciences Engineering Medicine

Regulatory Processes for Rare Disease Drugs in the United States and European Union

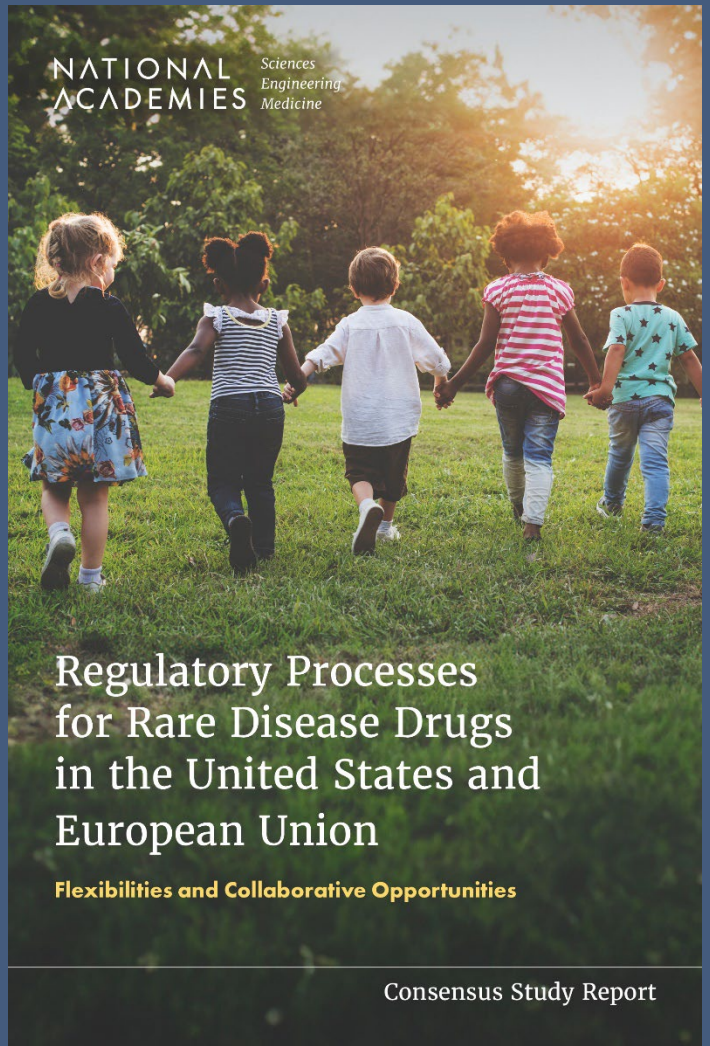
Flexibilities and Collaborative Opportunities

Public Release Webinar
September 27, 2024

Agenda

1. Report Background: Statement of Task and Committee
2. Report Overview and Methodology
3. Key Findings and Conclusions
4. Recommendations
5. Q&A with Committee Members

Report Background: Statement of Task and Committee



Committee Membership

- **JEFFREY P. KAHN** (*Chair*), Andreas C. Dracopoulos Director and Levi Professor of Bioethics and Public Policy, Johns Hopkins Berman Institute of Bioethics
- **RONALD J. BARTEK,** President, Director, and Co-Founder, Friedreich's Ataxia Research Alliance
- **TERRY JO BICHELL,** Founder and Director, COMBINEDBrain
- **EDWARD A. BOTCHWEY,** Professor, Georgia Tech and Emory University
- **SHEIN-CHUNG CHOW,** Professor of Biostatistics and Bioinformatics, Duke University School of Medicine
- **HANS-GEORG EICHLER,** Consulting Physician, Austrian Association of Social Insurance Bodies
- **PAT FURLONG,** Founding President and Chief Executive Officer, Parent Project Muscular Dystrophy
- **STEVEN K. GALSON,** Senior Advisor, Boston Consulting Group
- **GAVIN HUNTLEY-FENNER,** Principal Consultant, Huntley-Fenner Advisors
- **ANAEZE C. OFFODILE II,** Chief Strategy Officer, Memorial Sloan Kettering Cancer Center
- **ANNE R. PARISER,** Physician, Indian Health Service, Crow/Northern Cheyenne Hospital
- **JONATHAN H. WATANABE,** Professor of Clinical Pharmacy, Associate Dean of Assessment and Quality, University of California, Irvine, School of Pharmacy and Pharmaceutical Sciences

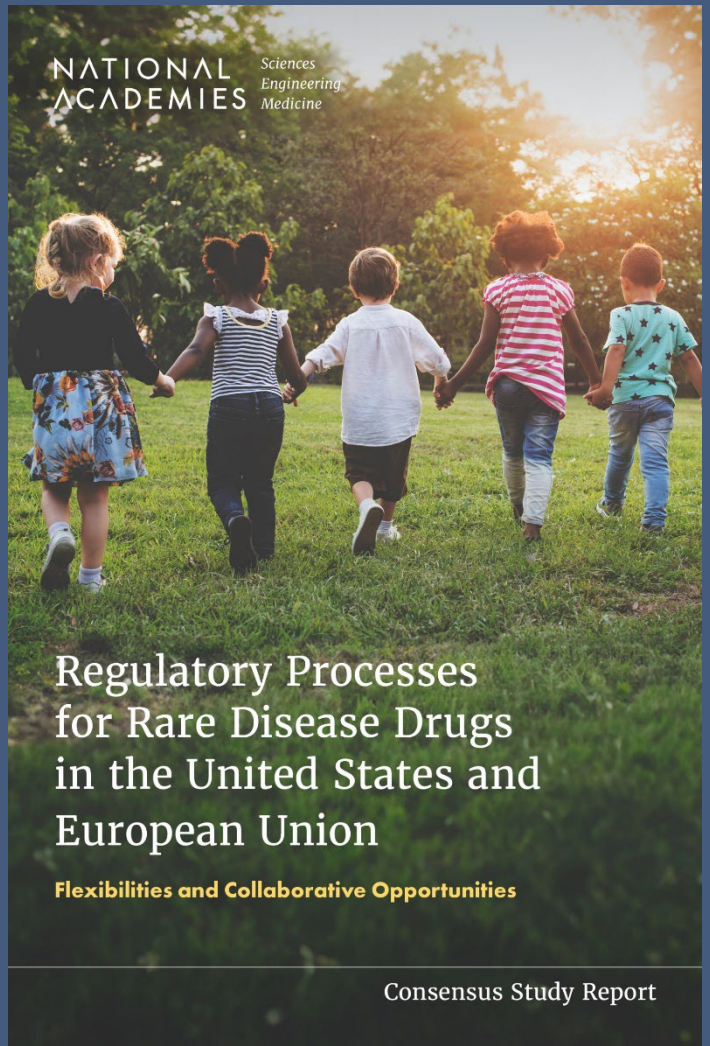
Statement of Task

In response to a Congressional request, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine will conduct a study on processes for evaluating the safety and efficacy of drugs for rare diseases or conditions in the United States and the European Union, including:

- flexibilities, authorities, or mechanisms available to regulators in the United States and the European Union applicable to rare diseases or conditions;
- the consideration and use of supplemental data submitted during review processes in the United States and the European Union, including data associated with open label extension studies and expanded access programs specific to rare diseases or conditions;
- an assessment of collaborative efforts between United States and European Union regulators related to:
  - product development programs under review;
  - policies under development and those recently issued; and
  - scientific information related to product development or regulation.

Based on its information gathering and internal deliberations, the committee will develop a report with its findings, conclusions, and recommendations for actions that Congress, federal agencies, the pharmaceutical industry, and nongovernmental organizations can take to support collaborative efforts.

Report Overview and Methodology



Information Gathering

- Open presentations from topic experts
- Public comments from interested parties
- Literature review
- Commissioned data analysis
- Semi-structured interviews

Report Structure

The report contains five chapters:

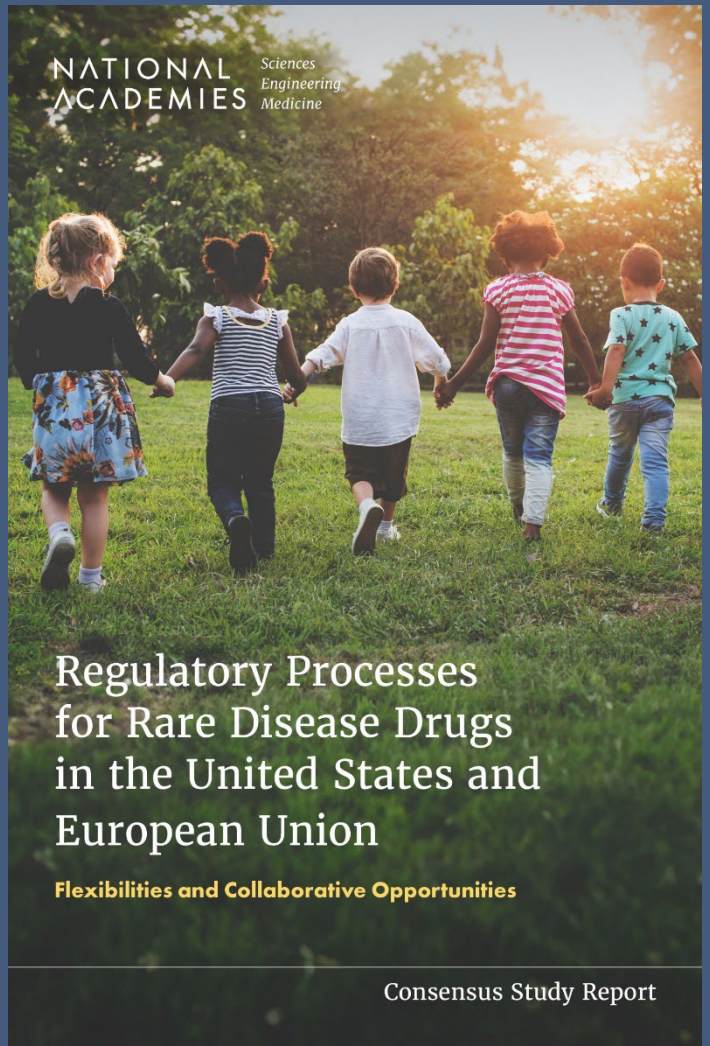
1) Introduction
2) FDA Flexibilities, Authorities, and Mechanisms
3) EMA Flexibilities, Authorities, and Mechanisms
4) Alternative and Confirmatory Data
5) FDA and EMA Collaboration

Important Considerations

- This report addresses one piece of the puzzle in rare disease drug development.

- There are several activities underway that could affect the landscape for the approval of treatments for rare diseases, including:
  - Consolidated Appropriations Act of 2023 (PL 117-328)
  - the Food and Drug Omnibus Reform Act of 2022

Key Findings and Conclusions



FDA and EMA Alignment

- The two agencies often reach the same regulatory decisions when it comes to submitted applications for marketing approval for drugs to treat rare diseases and conditions

Inclusion of Pediatric Populations

- The inclusion of pediatric populations in clinical trials should be a core component for rare disease drug development
- Orphan designated drug products are generally exempted from PREA requirements

Enhancing Stakeholder Input

Conclusion 2-2: FDA is using available mechanisms to gather patient input. However, there are opportunities to better ensure that patient input informs the development of treatments for rare diseases as well as the design and conduct of clinical trials for rare diseases. More clarity is needed on the part of patient groups and people with lived experience on how the agency is using patient input to inform regulatory decision making and what types of patient input are most relevant.

Conclusion 2-4: FDA engagement with rare disease drug development sponsors is of particular importance because compared to common diseases, rare diseases are less well understood, more often do not have regulatory precedent, more commonly lack validated endpoints and outcome measures, and involve small patient populations which limit the size and number of clinical trials that can be conducted.

Use of Alternative and Confirmatory Data

Conclusion 4-3: Given the variable and often long time horizons for rare disease progression, gaps in the knowledge of disease etiology, ethical concerns, severity of disease, small sample sizes, and unmet medical need, rare diseases require additional methods of demonstrating substantial evidence of effectiveness. New approaches in study design and data analysis need not require lower regulatory standards, but rather they enable the consideration of alternative and confirmatory data (ACD) and nuanced interpretation of the benefit-risk assessments that take into account the limited availability of data, limited treatment availability and the risk acceptance threshold in these unique patient populations.

FDA and EMA Collaboration

Conclusion 5-1: Despite some key differences, the FDA and EMA have similar approaches to the evaluation and approval of drugs for rare diseases. Given these parallel approaches, there are existing mechanisms for close collaboration between the two agencies, as well as opportunities for enhanced collaboration in the future, that would allow each agency to retain sovereign authority and accountability in regulatory decision making.

Clusters

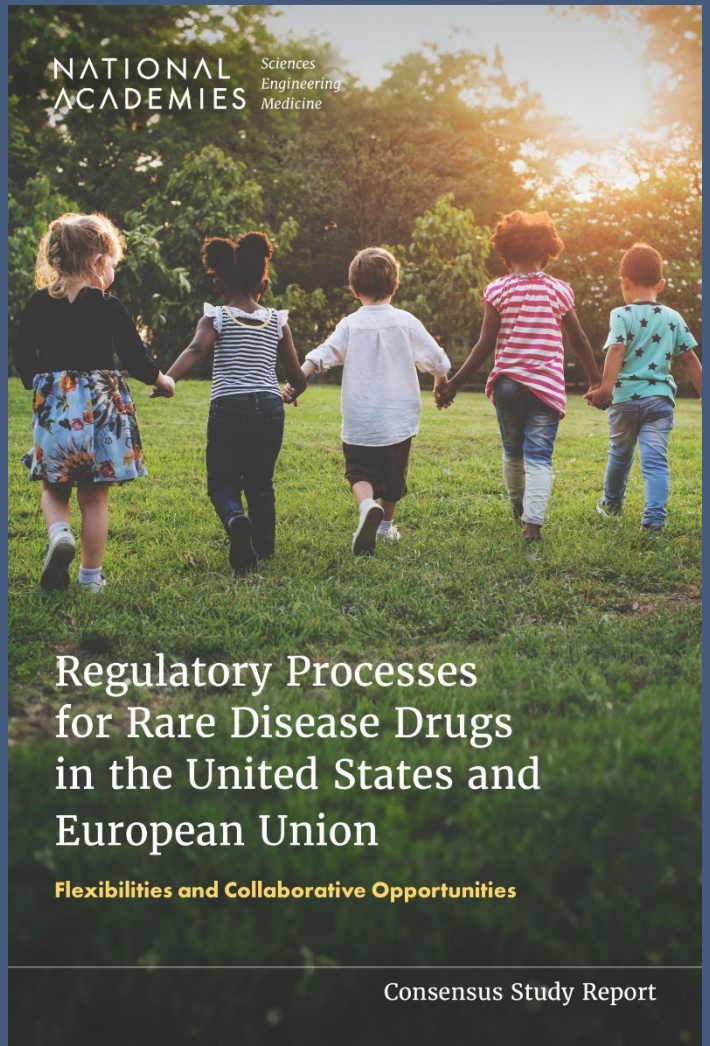
- Regular virtual meetings between EMA and FDA staff, that are focused on specific topics and therapeutic areas that would benefit from an “intensified exchange of information and collaboration”
- There is substantial unfulfilled potential in further utilizing clusters to help inform drug development and approval processes and provide a valuable forum for collaboration between the regulatory agencies
- The impact of the clusters on the drug development ecosystem may be limited by the fact that cluster discussions are largely focused on specific issues such as an existing development plan or safety concern
- An expansion and shift in focus of clusters to include prospective issues facing rare disease drug development would align with current objectives, build on existing collaborative efforts, and help inform regulatory decision making

Parallel Scientific Advice

Conclusion 5-3: Despite the underuse of the PSA program and lack of available evidence related to its impact, the committee acknowledges and expects that, in principle, concurrent scientific discourse through PSA should better enable more streamlined clinical trials, regulatory review, and approval of drugs to treat rare diseases and conditions.

Report Recommendations

FDA Flexibilities, Authorities, and Mechanisms



Recommendation 2-1

Congressional action is needed to encourage and incentivize more studies that provide information about the use of rare disease drug products in pediatric populations. To that end, Congress should remove the Pediatric Research Equity Act Orphan exemption and require an assessment of additional incentives needed to spur the development of drugs to treat rare diseases or conditions.

Additionally, the U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH) in partnership with nongovernmental organizations, including patient groups, clinical investigators, and biopharmaceutical companies, should work to provide clarity regarding the evolving regulatory policies and practices for the inclusion of pediatric populations as early as possible in rare disease clinical trials. Actions should include, but are not limited to the following:

- FDA should convene a series of meetings with relevant stakeholders and participate in relevant meetings convened by others to clarify what data are required to support the early inclusion of pediatric populations in clinical trials for rare diseases as well as other key considerations.
- Publish or revise guidance for industry on pediatric study plans for rare disease drug development programs.

Recommendation 2-2

The U.S. Food and Drug Administration (FDA) should strengthen mechanisms to integrate input from people living with a rare disease or condition, their caregivers, and patient representatives, especially patient groups that are small and under-resourced, throughout the full continuum of the drug development process. To that end, FDA should take the steps necessary to fully implement Section 1137 of the Food and Drug Administration Safety and Innovation Act (Public Law 112-144), which directs the Secretary of Health and Human Services to develop and implement strategies to solicit the views of rare disease patients during the full range of regulatory review discussions. This should include but not be limited to:

- Implementing strategies to meaningfully engage people living with a rare disease or condition, their caregivers, and patient representatives throughout the review process, from initial review discussions to final regulatory decision.
- Ensuring equitable representation of people living with a rare disease or condition, their caregivers, and patient representatives throughout the review process by actively recruiting and supporting participation from underrepresented and under-resourced patient groups, providing necessary support and accommodations to enable their full participation.
- Developing a structured approach to directly engage people with lived experience (those living with or caring for someone living with a rare disease or condition), including in all open public hearing sessions of advisory committee meetings by establishing a mechanism to prioritize and provide speaking opportunities for people with lived experience, particularly patients and caregivers, to inform advisory committees on how primary or secondary outcome measures relate to functional status and quality of life.
- Developing in-person and hybrid education and training programs to assist rare disease patient groups in creating and maintaining tools (e.g., patient registry, natural history data, translational tools) that can contribute to research and development.

Recommendation 2-3

The U.S. Food and Drug Administration and the National Institutes of Health in collaboration with the European Medicines Agency, nongovernmental organizations, patient groups, and biopharmaceutical sponsors, should implement a sponsor, investigator, and patient group navigation service to support the development of drugs to treat rare diseases and conditions (1) by advising on the range of available regulatory pathways and flexibilities and (2) by providing clarity on how to comply with regulatory policies, apply guidances, and meet requirements in rare disease drug development. Actions should include:

- Facilitation including, but not limited to consultation, referral to other organizations, services to identify and overcome regulatory barriers, needs assessment, regular follow up, and consultation; and
- The development of educational materials and tools.

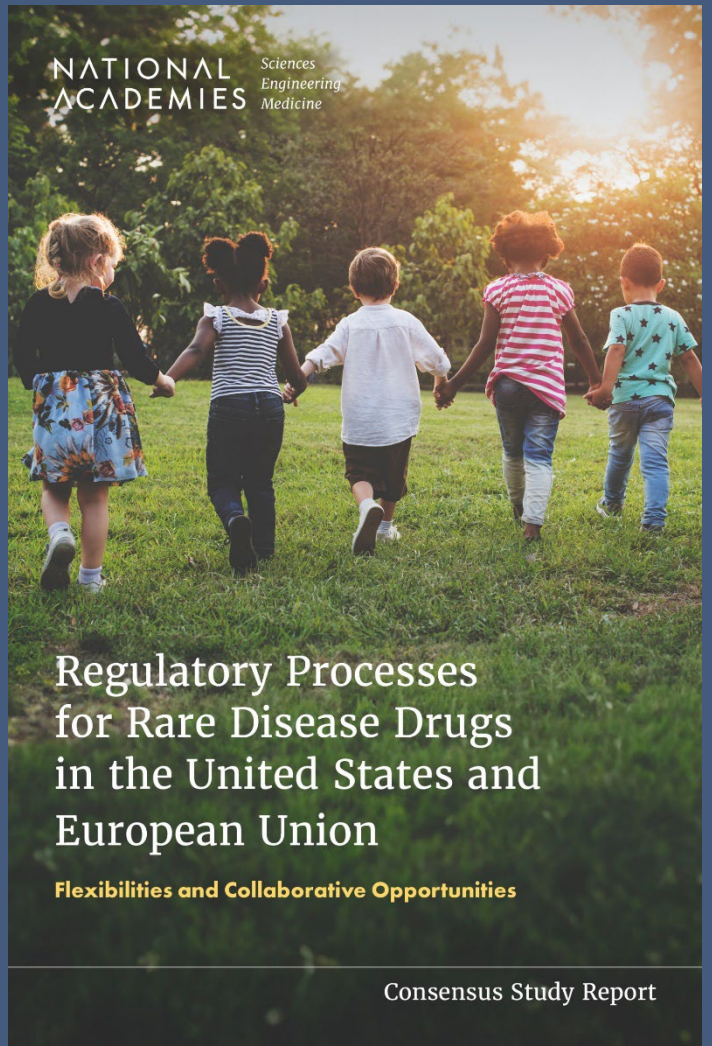
Recommendation 2-4

The U.S. Food and Drug Administration (FDA) should assess the impact of new and ongoing programs and approaches that support drug development for rare diseases and conditions to improve the regulatory decision making process; publicly share the results of these assessments in a timely manner; take steps to ensure that lessons learned across different programs are disseminated throughout FDA centers and divisions, including a summary of regulatory flexibilities and novel innovative approaches that were considered acceptable; scale-up and expand successful programs across therapeutic areas; and modify or sunset programs that are not improving the regulatory decision making process. Programs and regulatory approaches should include, but not be limited to:

- Rare Disease Endpoint Advancement pilot program; Support for clinical Trials Advancing Rare disease Therapeutics pilot program; Complex Innovative Trial Design meeting program; FDA-NIH Bespoke Gene Therapy Consortium; Programs and pilots led by the Oncology Center of Excellence (e.g., Real-Time Oncology Review; Project Orbis);
- Flexibility and leadership in the review and oversight of genetically-targeted advanced therapeutics (e.g., genetic therapies), especially for very low-prevalence patient populations;
- Adoption and support of master protocols, particularly basket trials, to support mutationally defined product approvals;
- Guidance development on cutting-edge topics to support drug research and development, such as the use of accelerated approval in tissue-agnostic drug development (i.e., drugs that target specific molecular alterations) and master protocols, among others.

Report Recommendations

Alternative and Confirmatory Data



Recommendation 4-1

FDA should enable the collection and curation of regulatory-grade natural history data to enhance the quality and accessibility of data for all rare diseases. This should include, but not be limited to:

- Continuation and expansion of support for current rare disease natural history design and data collection programs, such as the FDA's Office of Orphan Products Development awarding clinical trial and natural history study grants
- Continuation and expansion of data aggregation, standardization, and analysis programs, including, but not limited to Critical Path Institute's Rare Disease Cures Accelerator-Data and Analytics Platform
- Support, education, training, and access to resources/infrastructure for nascent rare disease advocacy groups to enable the standardization and integration of patient-level data for future regulatory use.
- Continuation and expansion of collaboration with other agencies (e.g., National Institutes of Health Rare Disease Clinical Research Network) to expand natural history design and data collection resources for all rare diseases.
- Periodic assessment regarding the impact and opportunities for improvement of ongoing programs for the collection, curation, and use of natural history data in regulatory decision making for rare disease drug development programs.

Recommendation 4-2

The U.S. Food and Drug Administration (FDA) should invite the European Medicines Agency (EMA) to jointly conduct systematic reviews of submitted and approved marketing authorization applications to treat rare diseases and conditions that documents cases for which alternative and confirmatory data have contributed to regulatory decision making. The systematic reviews should include relevant information on the context for whether these data were:

- found to be adequate, and why they were found to be adequate
- found to be inadequate, and why they were found to be inadequate
- found to be useful in supporting decision making and to what extent

Findings from the systematic reviews should be made publicly available and accessible for sponsors, researchers, patients, and their caregivers through public reporting or publication of the results. EMA and FDA should establish a public database for these findings that is continuously updated to ensure that progress over time is captured, opportunities to clarify agency thinking over time are identified, and information on the use of alternative and confirmatory data to inform regulatory-decision making is publicly shared to inform the rare disease drug development community.

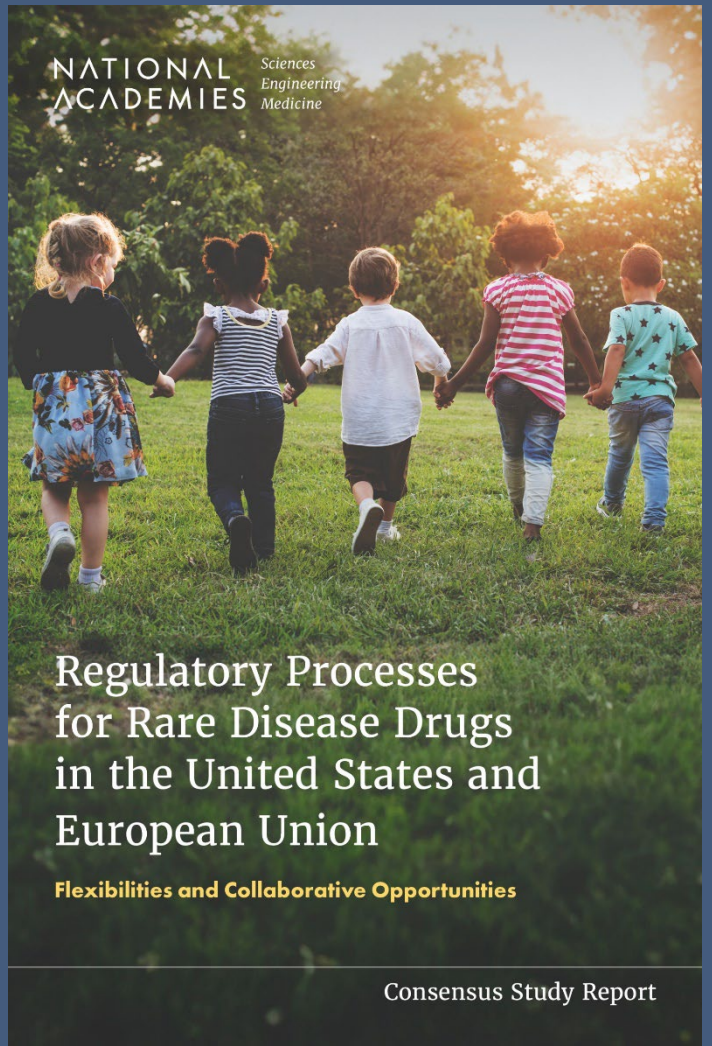
Recommendation 4-3

The U.S. Food and Drug Administration (FDA) should collect and disseminate information on how state-of-the art regulatory science; innovative study designs and methods; tools, including biomarkers and surrogate endpoints; and effective applications of alternative and confirmatory data inform regulatory decision making for rare disease drug products by:

- Annually convening the European Medicines Agency, National Institutes of Health National Center for Advancing Translational Sciences, industry, patient groups, and the broad stakeholder community to review new advances in regulatory science (pre-clinical, clinical, and platform technologies), iterate on innovative study design and methods, and consider other uses of alternative and confirmatory data for regulatory decision making. Following each meeting, FDA and NIH should publish a publicly accessible summary of key themes and issues discussed;
- Publishing innovative methods for data analysis that have been used to support regulatory approval of drugs for a rare disease or condition, including information about how the methods were used or considered by the agency;
- Collaborating on the validation of clinical and pre-clinical drug development tools for drugs to treat rare diseases and conditions.

Report Recommendations

FDA and EMA Collaboration



Recommendation 5-1

The U.S. Food and Drug Administration (FDA) should take steps to make relevant information on marketing authorization submissions, review milestones, approval and negative review decisions (refusal to file, clinical hold, and complete response letters), and the use of regulatory flexibilities for rare disease drug products publicly available and easily accessible to inform sponsors, patients, researchers, and reviewers on decision making rationales and when and how available policies are applied. While the committee acknowledges the legal challenges surrounding disclosure of information, actions should include, but not be limited to:

- Mirroring the level of information disclosed by the European Medicines Agency (EMA) presented on submissions, review milestones, and review decisions, such that there is parity between what the FDA and EMA share publicly;
- Building on the work of the 2010 FDA Transparency Task Force, to implement Phase II product application's disclosure requirements : considerations for product applications (including investigational applications);
- Organizing and structuring the information made public in such a way that the public can identify trends (e.g., increases or decreases in the use of regulatory flexibility by product type or therapeutic area over time and expedited and designation program use);
- Linking clinical trials to FDA disclosures by using national clinical trial identifiers to allow the public to better understand the connection between clinical trials and the regulatory process.

Recommendation 5-2

To facilitate the efficient global development of orphan drugs, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) should build upon the existing clusters relevant for rare diseases by undertaking the following:

- Create a forum, which includes key decision-makers within the agencies, for forward-looking discussion of issues and common challenges for rare disease drug development that EMA and FDA could use to achieve a more harmonized approach to rare disease development.
- Devote resources to discuss and resolve misalignment related to rare disease drug development.
- Publicly issue findings on key scientific or regulatory topics related to rare disease drug development.
- Conduct and publicly share an annual review of all orphan drug applications for the agencies to facilitate more immediate sharing of lessons learned and surface issues that cut across rare disease drug development programs.

Recommendation 5-3

The U.S. Food and Drug Administration (FDA), along with the European Medicines Agency (EMA) and other key stakeholders, should assess the impact of the Parallel Scientific Advice (PSA) program over the past decade on drug development for rare diseases and conditions, publicly share the results of this assessment, seek sponsor input on approaches to improve and enhance the use and utility of the program, and take action to increase access, use, and impact of the PSA program going forward. This assessment and plan for improvement should include:

- Reasons (real and perceived) for continued underuse of the PSA program and address the issues identified;
- Information-gathering on sponsor experience with PSA regarding the practical considerations (e.g., resources, location) for large and small companies to participate in PSA;
- Incentives that encourage use of the PSA program earlier in development (i.e., prior to enrolling patients in trials);
- Metrics for assessing the impact of the PSA program; and
- Criteria and goals for demonstrating improvement of the PSA program with established timeframes over a five-year period.

If the actions taken do not lead to an increased use and greater impact of the PSA program within a five-year period after the assessment and improvement plan has taken place, the FDA should implement other mechanisms for parallel advice between FDA and EMA on drug development programs for rare diseases and conditions.

Thank you

Free pdf of the report can be accessed using this link or QR Code: https://nap.nationalacademies.org/catalog/27968/regulatory-processes-for-rare-disease-drugs-in-the-united-states-and-european-union

For any questions about the report, please contact Carolyn Shore (cshore@nas.edu) and Tequam Worku (tworku@nas.edu).

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