Biotechnology Innovation Organization

Rare Disease & Orphan Drug Committee (RDOD)

NASEM Meeting

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About BIO

- BIO is the world's largest advocacy association representing biotechnology companies, state biotechnology groups, academic and research institutions, and related organizations across the United States and in 30+ countries.

- BIO members are involved in the research and development of innovative healthcare, agricultural, and environmental biotechnology products.

- BIO also produces the BIO International Convention, the world's largest gathering of the biotechnology industry, along with a portfolio of industry-leading investor and partnering meetings around the world.

BIO Mission, Purpose, & Vision

MISSION - What we do

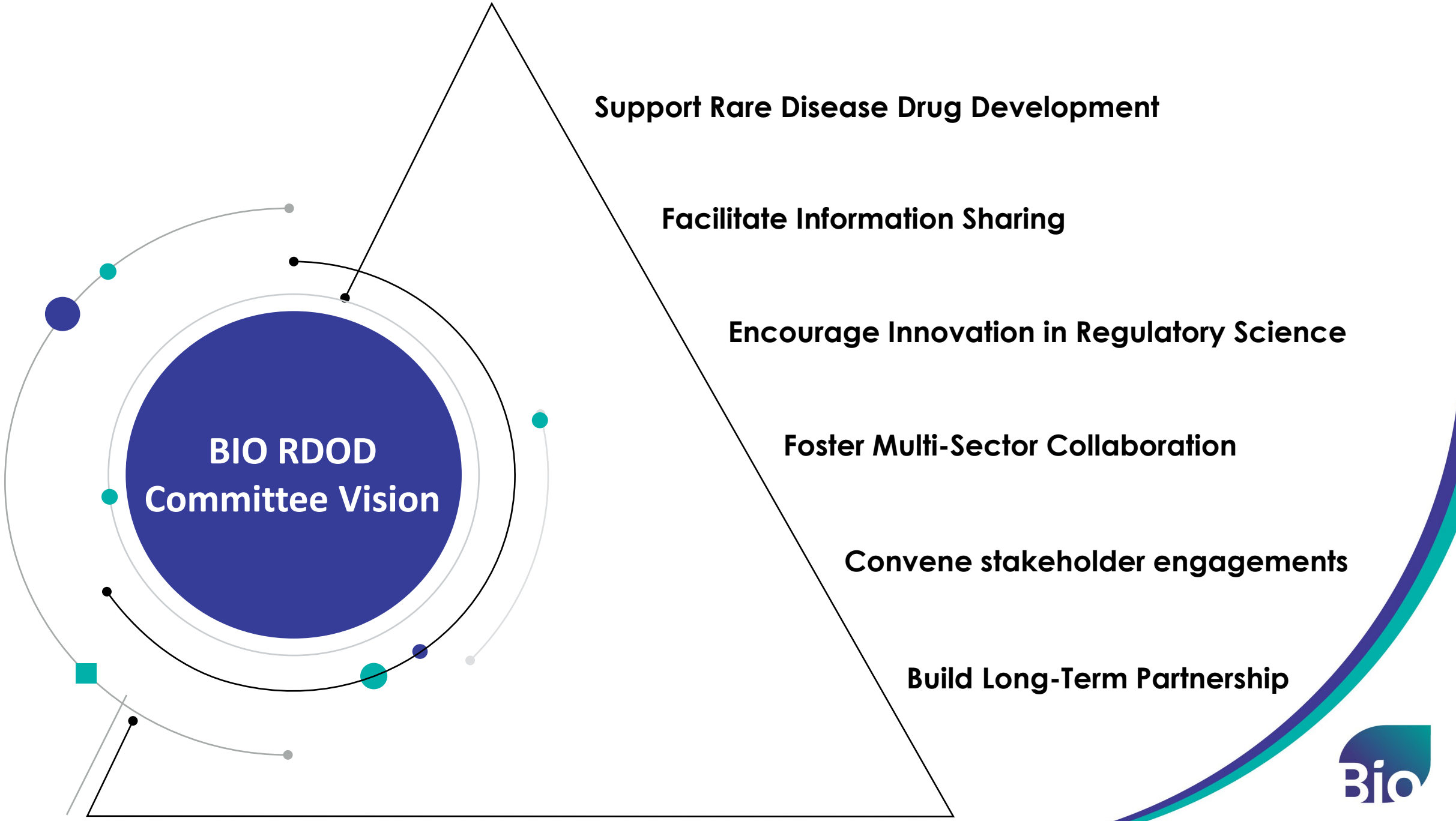
Drive a bio-revolution through Education, Collaboration, and Advocacy

PURPOSE - Why we do it

Cure patients, protect our climate, and nourish humanity

VISION - What we will achieve

Rapid biotech innovation equitably harnessed for health, sustainability and justice


BIO RDOD Committee Vision
Support Rare Disease Drug Development
Facilitate Information Sharing
Encourage Innovation in Regulatory Science
Foster Multi-Sector Collaboration
Convene stakeholder engagements
Build Long-Term Partnership

RDOD Committee Areas of Focus

- Natural History Studies & Synthetic Control Arms
- The use of external controls in regulatory decision making
- Substantial Evidence of Effectiveness
- Rare Disease Endpoints Advancement (RDEA)
- Accelerated Approval
- Application of regulatory flexibilities for rare disease indications across FDA

Case Studies – Future Item

- RDOD Committee will solicit case studies from our members to share their specific experiences across both the FDA and EMA approval process, including:
  - Application of regulatory flexibilities for rare disease indications within FDA review divisions;
  - Experiences with FDA and EMA regulatory decisions on rare disease products

Experience with Regulatory Flexibilities

While we acknowledge that rare diseases are unique from each other, we seek better understanding and consistency across the Agency regarding regulatory flexibility for rare diseases.

*BIO's **Case Example 1: Clinical Studies Required for Demonstration of Safety and Efficacy** from Docket No. FDA–2019-N-3453 (Appendix slide 12):*

- Not all review divisions consistently apply flexibility when considering the kind and quantity of data and information a Sponsor is required to provide to meet the statutory standards

Division X – Rare Disease Review

Requires **one** adequate and well-controlled clinical study to demonstrate safety and efficacy

Division Y – Rare Disease Review

Requires **two** adequate well-controlled clinical studies to demonstrate safety and efficacy citing statutory standards

However, given the rare nature, this may not be feasible

Innovative Approach Challenges

- Acceptance of innovative drug development approaches across all therapeutic areas such as Bayesian clinical trial design, complex adaptive clinical trial design, use of pharmacometrics modeling, alternative methods for nonclinical testing vary across review divisions.
    - Use of external controls, and use of retrospective natural history data to support the control arm especially in the context of rare diseases where natural history data is limited
    - Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory

Please reference Appendix slide 12-13 for BIO's comments in response to

- *Docket No. FDA–2019-N-3453: Promoting Effective Drug Development Programs: Opportunities and Priorities for the Food and Drug Administration's Office of New Drugs*
    - ***Case Example 2: Acceptance of Innovative Clinical Trial Designs***
- *Docket No. FDA–2015–D–2818 Draft Guidance for Industry: Rare Diseases— Common Issues in Drug Development*
- *Docket No.FDA-2019-D-0481-0002 – Draft Guidance for Industry: Rare Diseases: Natural History Studies for Drug Development; Guidance for Industry*

Additional Topics to Address

- Due to the nature of rare diseases, studies often need to be conducted globally, however, there is often uncertainty whether various global regulators will align on the proposed development, and it is often unclear how to address different perspectives in these global programs, especially due to small patient populations

- Ability of rare disease experts and patients to participate in Advisory Committees

- Integration of patient experience data into development and understanding its use in regulatory review

Thank you

We look forward to engaging again in the future

Appendix

BIO's comments in response to Docket No. FDA–2019-N-3453: Promoting Effective Drug Development Programs: Opportunities and Priorities for the Food and Drug Administration's Office of New Drugs

Link here to Document

- Case Example 1: Clinical Studies Required for Demonstration of Safety and Efficacy: Not all review divisions consistently apply flexibility when considering the kind and quantity of data and information a Sponsor is required to provide for a particular drug to meet the statutory standards (21 CFR 314.105). For example, for a rare disease, a particular review division may require Sponsors to conduct one adequate and well-controlled clinical study to demonstrate safety and efficacy whereas for a similar therapy used to treat a different rare disease another review division may require two adequate well-controlled clinical studies to demonstrate safety and efficacy citing statutory standards, even for a rare disease where two studies may not be feasible.
- Case Example 2: Acceptance of Innovative Clinical Trial Designs: Acceptance of innovative drug development approaches across all therapeutic areas such as Bayesian clinical trial design, complex adaptive clinical trial design, use of pharmacometric modeling, alternative methods for nonclinical testing vary across review divisions. For example, while guidances have been developed for use of master protocols and for use of seamless “expansion cohort” designs, these are specific to oncology. Yet these types of trial designs and other innovative designs could greatly improve the efficiency of drug development in other serious disease areas with high unmet need, particularly those characterized by low patient numbers.
- While FDA guidance is extremely important to assist Sponsors who are developing therapies for FDA review, presently there are several areas that are important and are rapidly evolving or in early stages. We understand that it may be difficult for the FDA to develop guidance in these areas given the evolving landscape. In these cases, BIO strongly believes that the opportunity for additional scientific discussions between FDA and stakeholders would help to facilitate understanding and collaboration. These discussions could take many forms based on the topic, for example public meetings, milestone meetings, collaborations with other agencies, or the development of consortia or public-private partnerships. Such areas include but are not limited to:
    - Methods used by statisticians to support benefit-risk decisions such as Bayesian methods, use of external controls, and use of retrospective natural history data to support the control arm especially in the context of rare diseases where natural history data is limited.

Additional BIO positions on utilizing innovative approaches:

- BIO's comments in response to Docket No. FDA–2015–D–2818 Draft Guidance for Industry: Rare Diseases— Common Issues in Drug Development
  - Link here for document
- BIO's comments in response to Docket No.FDA-2019-D-0481-0002 – Draft Guidance for Industry: Rare Diseases: Natural History Studies for Drug Development; Guidance for Industry
  - Link here for document

TO SUBMIT IN DECEMBER 2023:

BIO's comments in response to Docket No. FDA-2023-D-2318; Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence

DRAFT TOPICS– NOT FINAL

- Expand on the use of early clinical data as confirmatory evidence and provide more examples
- Evidence from a Relevant Animal Model
- Real-World Data/Evidence