Promoting Effective Drug Development Programs: Opportunities and Priorities for the Food and Drug Administration's Office of New Drugs, an Industry Perspective

Cartier Esham, PhD
Executive Vice President, Emerging Companies Section
Senior Vice President, Science and Regulatory Affairs
Biotechnology Innovation Organization

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Question 1: Where can OND provide additional guidance or prioritize additional scientific discussion in the near-term to improve clarity and encourage effective drug development?

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General Principles on Guidance Document Development

- FDA should work to finalize draft guidance, withdraw old/outdated guidance, and reissue draft guidance eliminating portions no longer applicable for overall clarity in a timely manner

- FDA should consider opportunities for greater engagement in developing priorities for guidance document development and guidance revision
  - Similar to CDRH's annual approach for seeking stakeholder input on guidance document development

Guidance to be Newly Developed

- Clarity and coordination across FDA Review Divisions and Centers on Digital Technologies
  - Coordination of FDA Centers is needed to develop guidance addressing digital technologies, including use for siteless trials, digital endpoints, combination products that contain a digital component, and digital technologies used to support patient adherence and pharmacovigilance
- Clarity regarding use of alternative preclinical tools/non-animal methods
  - The Agency encourages sponsors to use and approach the FDA with alternatives to animal testing, but specific criteria and evidence requirements for regulatory acceptance of new approach methodologies is needed
- Comprehensive, current, final guidance(s) on complying with Pediatric Research Equity Act (PREA) as modified by new pediatric oncology requirements
  - Draft guidance was to be made public in August 2019 (pediatric oncology requirements, FDARA Section 504) as outlined in statute but currently no guidance has been released
- Clarity for Sponsors developing analgesics
  - FDA recently withdrew the 2014 Draft Guidance Analgesic Indications: Developing Drugs and Biological Products and new guidance is needed

Existing Guidance to be Updated

- Pediatric-related Guidance:
  - Finalization of guidance on complying with the Best Pharmaceutical for Children Act (BPCA; 1999) to replace FDA's FAQ website
  - General Considerations for the Clinical Evaluation of Drugs in Infants and Children (1977)
    - Consider updates to content including terminology (e.g., "school-aged children", "special problems") and the addition of references to other pediatric guidance released since 1977
- Current Guidance on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (1998)
  - Consider updates to guidance reflecting use of external controls, optimize retrospective natural history, real-world evidence, patient focused drug development, totality of evidence

Areas for Additional Scientific Discussion

- Consider developing additional public opportunities for Agency -Stakeholder discussion on areas of evolving science, where it is too early for guidance development
  - Evolving methods used by statisticians to make benefit-risk decisions (e.g., Bayesian methods, use of external controls, use of retrospective natural history data to support the control arm especially in rare diseases where natural history data is limited)
  - Use of artificial intelligence in regulatory decision-making
- BIO appreciates FDA's participation in private public partnerships, where industry, academia and government, can collaborate in pre-competitive pre-clinical space and encourages continuation of such activities
- Consider collaboration between NIH, FDA and Industry on mechanisms to better translate basic science discoveries (e.g., for new medicines and/or understanding of science behind disease)

Question 2: Are there specific suggestions for guidance or policy development that OND could undertake to facilitate drug development for diseases not currently amenable to targeted therapies?

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Addressing Regulatory Challenges for Highly Prevalent Chronic Diseases

- Development of products to treat Highly Prevalent Chronic Diseases (HPCD) has unique challenges due to the length and size of clinical trials
- While the elements below are not unique to HPCD, additional guidance could address the challenges associated with HPCD drug development:
  - Improvements to the PMC/PMR process
  - Improvements to the use and acceptance of innovative clinical trial design for HPCD
  - Acceptance of RWE across the Agency
    - BIO previously submitted a comment letter and developed a position paper on the use of RWE for use of label expansion
  - Acceptance of novel endpoints
  - Use of digital technologies for data collection in clinical trials

PMC/PMR Process Reform

- To address inefficiencies associated with the PMC/PMR process, BIO suggests that the FDA consider:
  - Continuous evaluation that begins pre-approval and extends throughout a product's lifecycle including post-approval, to ensure PMC/PMRs are feasible, efficient, and effective in supporting benefit/risk assessments, and leverage modern tools

- Consider revising guidance or polices to address the following challenges:
  - PMC/PMRs are often communicated to sponsors late in the review process with little room for dialogue
  - Pre-approval development of PMRs and PMCs is not always supported through robust scientific dialogue
  - Post-approval review of existing PMRs/PMCs should consistently consider new or emerging science and allow revision accordingly

Question 3: Are there advantages and disadvantages of extending novel trial designs, such as the use of master protocols, to study multiple therapies and/or multiple diseases under a common infrastructure beyond those for serious and life-threatening diseases?

What guidance development would be most useful?

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Benefits of Innovative Clinical Trials Designs (ICTD)

- Fit-for-purpose ICTD can increase trial efficiency and feasibility across therapeutic areas, including rare diseases and highly prevalent chronic diseases and in people with the same genetic mutation, but different diseases (outside of oncology)

- ICTD (e.g., Bayesian, adaptive, basket, and platform trials), can help address clinical development challenges, including:
  - Minimize unnecessary patient risk, for example, by using non-concurrent controls arms, or limiting the number of patients assigned to sub-optimal or ineffective therapy
  - Assure adequate efficacy and safety assessment (e.g., assessing multiple interventions in one study), thus minimizing clinical trial completion times and accelerating delivery of medicines
  - Maximize efficient use of study information and magnify the significance of individual test based on exchangeability of treatment effect

Benefits of ICTD (*cont.*)

- Advancement of science and technology introduces tremendous opportunity that fit-for-purpose CIDs can synergize, such as:
  - Efficient identification of optimal treatment doses/schedules
  - Efficient identification of optimal combination treatments (best risk/benefit profile)
  - Efficient incorporation of and stratification on new biomarkers/diagnostics
  - Ethical early termination of ineffective or intolerable treatment
  - Efficient use of external data to reduce study size and improve reliable decision making

Suggested Topics for Development of Further Guidance on ICTD

- To further advance the use and acceptance of ICTD across the FDA, the Agency could provide further clarity (e.g., in the form of guidance) on:
  - Study conduct and data integrity when using a master protocol
  - Adequate evidence for decision making (e.g., early study adaptation, final interpretation of results)
  - Adequate interventional and control arms (e.g., when there are changes over time, or changes due to adaptation)
  - Adequate safety monitoring and comparisons

Question 4: Are there circumstances when OND review divisions are implementing guidance in different ways, which are not explained by case-specific features?

Are there topics where further clarity of the Agency's current thinking may be warranted?

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Opportunities for Supporting Consistency

- OND should work to introduce greater consistency, structure, transparency, and efficiency in the basic elements of regulatory engagement between sponsors and the Agency
- To better facilitate efficiency and consistency across Divisions, FDA should explore opportunities for cross-Division discussions with Sponsors during review, as appropriate
- Regulatory flexibility for rare diseases
  - Not all review divisions apply consistent flexibility when considering the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards (21 CFR 314.105)
- Greater consistency for pediatric drug development
  - Not all review divisions are implementing the use of extrapolation from adults to pediatrics and the conduct of pediatric PK studies consistently

Opportunities for Supporting Consistency

- 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
- Use of expedited approval pathways and/or designations
  - There are differences in how review divisions grant and apply processes to use of expedited approval pathways (i.e., accelerated, priority, fast-track) and designations (i.e., breakthrough)
- FDA may consider making publicly available and implement learnings from:
  - 21st Century Cures Act/PDUFA VI mandated pilot programs across review divisions (e.g. innovative clinical trials designs, MIDD, use of real-world evidence, PFDD)
  - Innovative approaches being tested in various review divisions (e.g. RTOR, Collaborative review approaches like Project Orbis , summary level review)

Opportunities for Supporting Consistency

- The Agency may also consider:
  - Mandatory training on rare disease issues for FDA Staff
  - When novel approaches are identified or piloted, mechanisms to support consistent adoption across the Agency
  - When novel approaches/technologies are identified or piloted, mechanisms to increase knowledge both within and outside the Agency (e.g., webinars or FAQs when final guidance released)
- BIO fully supports the FDA's modernization and reorganization efforts to drive consistency across review divisions and looks forward to their implementation and evaluation of impact

Question 5: Innovative approaches can bring additional uncertainty to drug development, since the advantages and disadvantages of the approaches may not yet be fully understood by either the Agency or sponsors because of their novelty. Sometimes, a well-understood development pathway may be chosen solely because of existing precedents in the therapeutic area.

How can OND promote effective drug development programs when this tension exists?

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Mechanisms for Addressing Innovative Approaches

- To aid areas where advantages and disadvantages of novel approaches are not fully understood, the FDA should consider:
  - Mechanisms for dissemination of learning across centers and divisions
  - Mechanisms for dissemination of learning with stakeholders (even if not final FDA guidance)
  - Encouraging FDA Staff to be open to innovative approaches to support the use of new tools
  - Ensuring FDA staff has latest training on new concepts/science; building expertise within FDA, allowing additional expert input
  - Ensuring portfolio development meetings with sponsors are common practice across review divisions

- BIO is pleased to provide further input or expertise, as needed

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