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

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FDA Question 1: We are interested in input from stakeholders about where OND can provide additional guidance or prioritize additional scientific discussion in the near-term to improve clarity and encourage effective drug development. Given that OND's portfolio includes a diverse spectrum of drugs and diseases, such input should focus on specific policy needs for various clinical areas linked by a shared therapeutic context (e.g., drugs intended to treat serious, life-threatening rare diseases; non-serious, self-limited conditions; etc.), rather than focusing on any specific disease or condition.

Posting FDA Reviews for New Indication Supplements
Policy Opportunity for OND to Consider

- **Sponsors would benefit, and perhaps FDA as well, if review summaries for new indication efficacy supplements were posted to the FDA website as is currently done for original NDAs/BLAs.**

- **Potential benefits:**
  - Promotes a learning environment where sponsors gain insights from recent FDA decisions that can be applied to ongoing/planned development programs
  - Facilitates more focused FDA meetings and briefing packages, with better informed questions being posed to FDA reviewers
  - More efficient to share information broadly than for individual sponsors/stakeholders to request review summaries individually through Freedom of Information (FOI) requests

FDA Question 3: Some therapeutic areas, particularly those that include serious and life-threatening diseases, have begun to implement novel trial designs, such as the use of master protocols to study multiple therapies and/or multiple diseases under a common infrastructure. We are interested in stakeholders' views regarding the advantages and disadvantages of extending these approaches to additional therapeutic areas, and what guidance development would be most useful.

Use of Historic/External Data in Clinical Development
Need for Scientific Dialogue

– **Sponsors would benefit from scientific dialogue and enhanced clarity on the acceptable use of historic/external data in clinical development, specifically in those clinical trials which provide substantial evidence of benefit/risk which form the basis of regulatory decisions (e.g., NDA/BLA, sNDA/sBLA, and label changes).**

– **The potential impact is for more efficient drug development through utilization of all available data to inform assessment of benefit/risk of new and current medicines, with potential benefit of reducing number of patient exposures and reducing development timelines.**

Use of Historic/External Data in Clinical Development
Recent Examples

- **It is recognized that clinical studies that utilize historic/external data have a place in drug development. As a result, a number of clinical trial designs have been proposed to leverage historical/external data to boost information content and improve efficiency in a given trial and/or development program.**

- **Recent examples of development programs employing historic/external data:**
  - Increasing precision of current trial by using historical data from past studies (for both control and experimental arms) (Lim et.al. 2018)
  - Extrapolation from one population (adults) to another (pediatrics) (Gamalo-Siebers et.al. 2017)
  - Leveraging data across different but related disease subtypes within a clinical trial (e.g., a "basket trial") (Viele et.al. 2018)
  - Sharing information about patient responses to different therapeutic interventions (e.g., a "platform trial")

Use of Historic/External Data in Clinical Development
Statistical Methodologies and Areas of Uncertainty

– **A number of statistical methodologies, both frequentist and Bayesian, have been developed to ensure the robustness of the inference drawn when utilizing historic/external data:**
  – Dynamic borrowing (Schmidli et.al. 2014, Hobbs et.al. 2012),
  – Propensity score matching (Lin et.al. 2018),
  – Synthetic control arms (Berry et.al. 2017),
  – Model-based meta-analysis (Boucher and Bennetts 2016 & 2018)

– **Some areas of regulatory uncertainty:**
  – Selection of historic/external data to be utilized in the study,
  – Analysis methodologies to ensure the robustness of the study inference (e.g. minimize bias due to large drift between the current and historic/external data), and
  – Appropriate metrics to evaluate the operating characteristics, including alternatives to strict control of type 1 error

Use of Historic/External Data in Clinical Development
Policy Opportunities for OND to Consider

- **Use of historic/external data is discussed in several FDA guidance documents, however, a singular FDA guidance on the use of historic/external data in clinical development does not exist:**
  - Rare Diseases: Natural History Studies for Drug Development, Draft, March, 2019
  - Non-Inferiority Clinical Trials, Final, November 2016
  - Adaptive Design Clinical Trials for Drugs and Biologics, Draft, October 2018

- **Regulatory policy opportunities for OND to consider:**
  - Encourage an open public scientific dialogue on the appropriate use of historic/external data for regulatory decision making (e.g., public workshops)
  - Enhance regulatory clarity through guidance document development focused on use of historic/external data in clinical development

Thank You

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