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Supplementary information

The failure to fail smartly

In the format provided by the authors

Background on analysis

In 2017, the National Academies Forum on Drug Discovery, Development, and Translation launched the Improving the Drug Development Process through Examining Late-Stage Failures Action Collaborative (the collaborative). In 2018, collaborative participants conducted interviews with 14 stakeholders directly involved in late-stage therapeutic development, including representatives from government agencies, large biopharmaceutical companies, small biotech companies, trade organizations, and non-profit organizations. The goals of the interviews were to: 1) collect definitions of late-stage failures, 2) understand trends and lessons learned based on illustrative examples of late-stage failures, and 3) identify contributing factors to late-stage failures.

Interview questions

1. What trends have you observed for late-stage failure? For example, are there specific disease categories, stages of a disease, or treatment modalities that have a higher rate of success? Do most late-stage failures arise from a lack of efficacy or the presence of toxicity, or a combination of efficacy and safety issues?

2. How do you define a late-stage failure for drugs or biologics? Is late-stage limited to phase 3 or does it include both phase 2 and 3? Is failure the inability to achieve the primary trial endpoint?

3. What are the critical gaps in understanding or lack of data sharing/tools/methodologies/resources that contribute towards late-stage failures? On a related note, are there challenges in applying the available tools?

4. Are therapeutic development experts necessary within an organization? Within a product team? How would you define a development expert?

5. Are there particular examples of a late-stage failure that you think would be illustrative of lessons learned? If so, is there relevant information from that example that you would be willing to share?

6. Were the signs of a late-stage failure present in the earlier stages of development? What do you consider the critical factors that contribute most towards the success or failure of late-stage development? What is the best way to manage risk?

Responses were anonymized, analyzed, synthesized, and supplemented by information compiled from a literature survey. The collaborative held a meeting of stakeholders on 3 October 2018, to discuss and provide input on key themes and considerations for addressing late-stage failures in drug development.

Meeting attendees

Stakeholders attending the meeting on 3 October 2018 included the following affiliations listed for attendees are those that existed at the time of the meeting): Dr. Christopher Austin (NIH/NCATS), Dr. Linda Brady (NIH/NIMH), Dr. Robert Califf (Duke University and Verily Life Sciences), Dr. Joseph DiMasi (Tufts Center for the Study of Drug Development), Dr. Steven Galson (Amgen Inc.), Dr. Carlos Garner (Eli Lilly and Company), Dr. James Hendrix (Alzheimer's Association), Dr. Lynn Hudson (Critical Path Institute), Dr. Donald Lo (NIH/NCATS), Dr. Ross McKinney (Association of American Medical Colleges), Dr. Joseph Menetski (Foundation for the National Institutes of Health), Kenneth Moch (Cognition Therapeutics, Inc.), Bernard Munos (InnoThink Center for Research in Biomedical Innovation), Dr. Colleen Rye (FasterCures), Dr. Amarnath Sharma (Janssen R&D), Dr. Rachel Sherman (FDA/Officer of the Commissioner), Dr. Ellen Sigal (Friends of Cancer Research), Dr. Peter Stein (FDA/OND), Dr. Amir Tamiz (NIH/NINDS), Dr. Pamela Tenaerts (Clinical Trials Transformation Initiative), Dr. John Wagner (Takeda), Dr. Carrie Wolinetz (NIH/OSP), Dr. Hui-Hsing Wong (HHS/ASPE), and Dr. Dennis Zaller (Celgene).

CMR data

The Center for Medical Research (CMR) International Pharmaceutical R&D Factbook utilizes a variety of sources to provide an overview of R&D trends. Sources include proprietary data from CMR International's parent company, *Clarivate Analytics*, such as *Clarivate Cortelis*' suite of solutions, and *Clarivate Derwent World Patent's Index*. Additional sources data are drawn from the Center for Innovation in Regulatory Science and the Current Patents Gazette. Figures 1 and 2 were developed by CMR International's Global R&D Performance Metrics Program, a benchmarking solution develop by *Clarivate Cortellis*. *Clarivate Cortellis*' data repository includes:

- Over 71,000 drug records
- 318,000 clinical trial records
- 159 disease briefings
- Over 203,000 regulatory reports and analytics on drugs, biologics, medical devices, and IVDs for over 80 countries
- Over 91,000 deals records
- Over 153,000 trial records with biomarkers

Late-stage failures for Alzheimer disease

Phase III trials for Alzheimer disease that failed to reach their primary endpoint have received much press, but less attention has focused on the insights gained from these negative results (*Clin. Transl Sci.* **11**, 147–152; 2018). Knowledge gaps and new directions for research and treatment indicated by these failures include:

- Although human genetic data (mutations in the genes coding for amyloid precursor protein (APP) and presenilin (PSEN)) pointed to amyloid as the driver for Alzheimer disease, the causation of the more common sporadic forms of the disease are not well established

- Inhibition of the APP processing enzymes γ-secretase and β-secretase produced unanticipated toxicities due to incomplete understanding of their pleiotropic functions

- Anti-amyloid antibodies may effectively clear amyloid plaques without improving memory

- Treatments targeting amyloid need to start at the earliest stage of disease, before memory loss is detectable, not at the stage where tau and inflammation are the predominant drivers

- To carry out prevention trials, prognostic biomarkers are needed to identify those persons most likely to develop Alzheimer disease during the trial

- The long-term treatments needed for prevention of Alzheimer disease will require careful monitoring of adverse events in light of the oedema observed in some anti-amyloid antibody trials. Of promise in recent trials are dose-dependent effects and identification of 'responder' populations. Further deep phenotyping and genotyping of these subsets could serve to stratify patients for future trials.