Recent Initiatives of PMDA: Highlights and Selected Review Cases

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ABSTRACT

The Pharmaceuticals and Medical Devices Agency (PMDA) is Japan's regulatory agency for pharmaceuticals and medical devices. It has three main responsibilities: scientific reviews of marketing authorization application of pharmaceuticals and medical devices, monitoring of their post-marketing safety, and providing relief compensation for sufferers from adverse drug reaction and infections by pharmaceuticals or biological products. The PMDA is the only public agency in the world that combines these three functions.

In this presentation, first, the recent initiatives within the PMDA's Biostatistics Group will be introduced. This presentation will outline the electronic data submission, Data Science Round Table Discussion (DSRT) and the recently issued Early Consideration “Points to consider for externally controlled trials”. The electronic data submission, which means submission of subject-level clinical study data in electronic format with new drug submission, is expected to lead to cross-product research and the associated streamlining of clinical development by PMDA. DSRT is an annual workshop for young biostatisticians from industry, academia, and PMDA to discuss practical topics. This year, the discussion topics were “estimand”, “digital biomarker”, and “innovative trial design in practice”. The “Points to consider for externally controlled trials” summarizes PMDA's current thinking about externally controlled trials using subject-level data from either RWD or clinical trials as external control of a single-arm trial.

Next, advanced designs and related review issues we have encountered during actual new drug review will be presented. The examples include Vutrisiran for transthyretin-mediated familial amyloidotic polyneuropathy and Efgartigimod Alfa (Genetical Recombination) for chronic inflammatory demyelinating polyneuropathy, approved in Japan in 2022 and 2024, respectively. For Vutrisiran, an externally controlled trial using data from previous clinical trials was conducted, and the adequacy of the comparison with external control was discussed. For Efgartigimod Alfa, a randomized discontinuation design was adopted, and its effectiveness in patients with active disease was discussed.

Keywords: External controlled trial; Randomized discontinuation design; New drug review

Statistical Methods and Regulatory Considerations in Phase I Clinical Trials

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ABSTRACT

This presentation explores the statistical methodologies and regulatory considerations pertinent to Phase I clinical trials. It begins with an introduction to the fundamental objectives of Phase I trials, which primarily aim to assess the safety, dosage, and pharmacokinetics of investigational drugs. The discussion then delves into various dose-escalation designs, including traditional, model-based and model-assisted approaches, highlighting their advantages and limitations in determining the maximum tolerated dose (MTD).

Subsequently, the presentation examines the role of simulation studies in optimizing trial designs and predicting outcomes. A hypothetical trial is presented to illustrate the application of these statistical methods in a real-world context. The session concludes with remarks on the importance of adhering to regulatory guidelines, such as those from the International Council for Harmonization (ICH), to ensure the ethical conduct and scientific validity of clinical trials.

Key words: Phase I clinical trials, Dose-escalation designs; Maximum tolerated dose (MTD)

Adaptive Designs for Clinical Trials: Principles and Recommendations from the Draft ICH E20 Guideline

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ABSTRACT

The International Council for Harmonisation (ICH) has released its draft E20 guideline on "Adaptive Designs for Clinical Trials" for public consultation. It acknowledges the high potential for adaptive designs to accelerate the process of drug development and to allocate resources more efficiently without lowering scientific and regulatory standards. Some of the approaches may affect the nature and timing of interactions between industry and regulators at confirmatory trial planning and assessment. The final guideline will indicate key adaptive design principles and approaches for which discussion of adaptive design features, and the rationale for their use, are particularly critical at the planning stage.

This presentation reviews the draft ICH E20 guideline and outlines a transparent and harmonised set of principles for the design, conduct, analysis, and interpretation of adaptive clinical trials, with the aim of supporting regulatory review of these studies in global drug development programmes. These principles are also intended to provide flexibility for evaluating and discussing innovative approaches to clinical trial design throughout the development process.

Keywords: Adaptive design; ICH

Evolving Regulatory Statistical Considerations in Drug Development and Evaluation

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ABSTRACT

Statistical methodologies in drug development and regulatory evaluation have evolved significantly, driven by advances in trial design and regulatory expectations. This presentation reviews the history of statistical methods in regulatory submissions, highlights recently adopted approaches like adaptive designs, imputations, estimands, and Bayesian statistics, and explores future trends shaped by the integration of artificial intelligence (AI) in regulatory agencies. By examining past and present practices, we project how AI-driven analytics and real-world evidence will transform statistical practices in drug development.