Applications of Adaptive Designs in Generic Drug Development

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INTRODUCTION

- The possibilities of stopping a clinical study earlier based on interim study results or to adjust the sample size during the study conduct are attractive features of adaptive clinical study designs.
- Adaptive designs have been widely used in clinical trials for new drug development, as they provide potential advantages in statistical efficiency, ethical considerations, and dynamic understanding of drug effects.
- The FDA guidance “Adaptive Designs for Clinical Trials of Drugs and Biologics” provides general scientific principles on adaptive designs but it does not specifically address bioequivalence studies (BE) in support of abbreviated new drug applications (ANDAs) (1).
- Adaptive designs have been proposed and applied in BE assessments.

OBJECTIVES

- Herein, we present a survey summary of BE studies with adaptive designs in ANDAs, reflecting the current status of its utility in generic drug development.

METHODS

- An ANDA is an application that is submitted to the U.S. FDA for the review and potential approval of a generic drug product.
- ANDAs submitted from 2006 to 2019 were full-text queried with nine keywords (e.g., “adaptive design,” “group sequential design”, “2-stage design”, “Potvin,” “for futility,” or “interim analysis.”).
- The keyword search identified 2,829 regulatory reviews and correspondences from 281 ANDAs.
- Study protocols and reports were reviewed to identify if adaptive design, group sequential design, or interim analysis for futility testing was proposed and/or applied in in vivo BE studies.

RESULTS

Table 1 Summary of ANDAs containing *in vivo* BE studies with two-stage design or group sequential design

Drug product	Dosage form	Route of administration	Primary end points	Study type	Study population	Methods
Drug 1 (antineoplastic)	Liposomal injection	Injection	PK	Fasting (pivotal)	Patients	Potvin method C
Drug 2 (ophthalmic agents)	Ophthalmic suspension	Topical	PK	Fasting (sparse sampling)	Patients	Potvin method C[a]
Drug 3 (dermatological agents)	Cream	Topical	PD	*In vivo* PD BE study (pivotal)	Healthy	*Post hoc* group sequential design[b]
Drug 4	Liposomal injection	Injection	PK	Fasting (pivotal)	Patients	Potvin method C
Drug 5	Liposomal injection	Injection	PK	Fasting (pivotal)	Patients	Potvin method C
Drug 6	Liposomal injection	Injection	PK	Fasting (pivotal)	Patients	Potvin method C
Drug 7	Tablet	Oral	PK	Fasting (pivotal)	Patients	Applicant-proposed adaptive design
Drug 8	Capsule	Oral	PK	Fasting (pivotal)	Healthy	Potvin method C
Drug 9	Tablet (extended release)	Oral	PK	Fasting/fed (pivotal)	Healthy	Potvin method C[b]
Drug 10	Tablet	Oral	PK	Fasting (pivotal)	Healthy	Potvin method B
Drug 11	Tablet	Oral	PK	Fasting (pivotal)	Patients	Group sequential design (Haybittle-Pet approach)[c]
Drug 12	Tablet	Oral	PK	Fasting (pivotal)	Healthy	*Post hoc* add-on study[d]

Drug categories are based on United States Pharmacopeia Drug Classification 2020, ANDAs analyzed were submitted from 2010 to 2019. The study continued to stage 2. Drugs 1, 4, 5, and 6 were for same reference drug products.
ANDAs, abbreviated new drug applications; BE, bioequivalence; PD, pharmacodynamic; PK, pharmacokinetic.

Usage of Interim Futility Analysis

- There are 43 ANDAs with interim analyses only for futility assessment in the BE studies for topical products.
- These studies would be stopped only if the test product was deemed not to be equivalent to the reference product.
- However, no quantitative criteria for stopping for futility were used in these ANDAs, and no detailed stopping rule was prespecified in the protocol or statistical analysis plan.

Application of Adaptive Designs in BE Studies

- These ANDAs included oral drug products, injections, and topical drug products. The total number of subjects in the BE studies ranged from 12 to 230 (mean ± SD: 57 ± 54).
- Potvin’s methods (2) were used in eight ANDAs. Seven studies were conducted in patients and the other five BE studies were conducted in healthy subjects. In a group sequential design, the sample size and type I error rate, at each stage were predetermined.
- The two-stage design allowed the applicants to re-estimate sample size based on the estimated interim variance when BE was not established at the interim stage.

Deficiencies in the Implementation of Adaptive Designs

- Deficiencies identified can be categorized into:
  - (i) deficiencies in study protocols (i.e., the applicant did not prespecify a study as an adaptive design or statistically sound criteria for stopping a study or continuing study; the applied method was inadequate for the specific design)
  - (ii) deficiencies in method implementation (i.e., the applicant did not follow the procedures and statistical analysis plan specified in the protocol; study power analysis was not included before the BE evaluation at stage 1).

CONCLUSIONS

- Although there were common deficiencies in implementing adaptive designs, a few ANDAs have successfully applied adaptive designs in in vivo BE studies. Due to potential challenges, we encourage generic drug applicants to have early alignment and communication with the FDA.
- Of note, the COVID-19 pandemic has posed unprecedented challenges to conduct in vivo BE studies and may have led to study interruptions that can lead to using multiple batches in a single study due to batch expiration, partial data due to patient drop out, or truncated PK curves (3). Under these circumstances, adaptive designs and model-based analysis may be useful to support protocol revisions by generic applicants. The exact cost saving of using adaptive designs in BE assessments warrants further investigations.

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ACKNOWLEDGEMENTS & References

The authors gratefully acknowledge Dr. Stella C. Grosser (OB/OTS/CDER/FDA), Dr. Ethan Stier (OB/OGD/CDER/FDA), Dr. Devvrat Patel (OB/OGD/CDER/FDA), Dr. Lei K. Zhang (ORS/OGD/CDER/FDA), and Dr. Robert Lionberger (ORS/OGD/CDER/FDA) for insightful comments and discussion.

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