U.S. FOOD & DRUG ADMINISTRATION

Applications and Lessons Learned for Conducting Adaptive Designs in Generic Drug Development

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval

Day 1, Session 1: COVID-19 Impact

Kairui (Kevin) Feng, PhD

Staff Fellow

Office of Research and Standards

CDER | U.S. FDA

September 21, 2021

Learning Objectives

- List some applications and lessons learned for conducting adaptive designs in generic drug development
- Clarify the acceptability of adaptive design for submission in abbreviated new drug applications (ANDAs) during the COVID-19 Pandemic

Disclaimer: This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

History and Definition of Adaptive Designs

History:

1970s

- Group sequential

1990s

- Blinded sample size re-estimation

More Recently

- Unblinded sample size re-estimation
- Adaptation to patient population
- Adaptation to treatment-arm selection
- Patient allocation
- Other aspects of study design

FDA guidance*: A clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial.

* Guidance for industry: *Adaptive Designs for Clinical Trials of Drugs and Biologics* (November 2019)

Applications of Adaptive Designs

- Possibilities of stopping a clinical study earlier based on interim study results or
- Adjusting the sample size during the study

ANDA Submissions of Adaptive Design

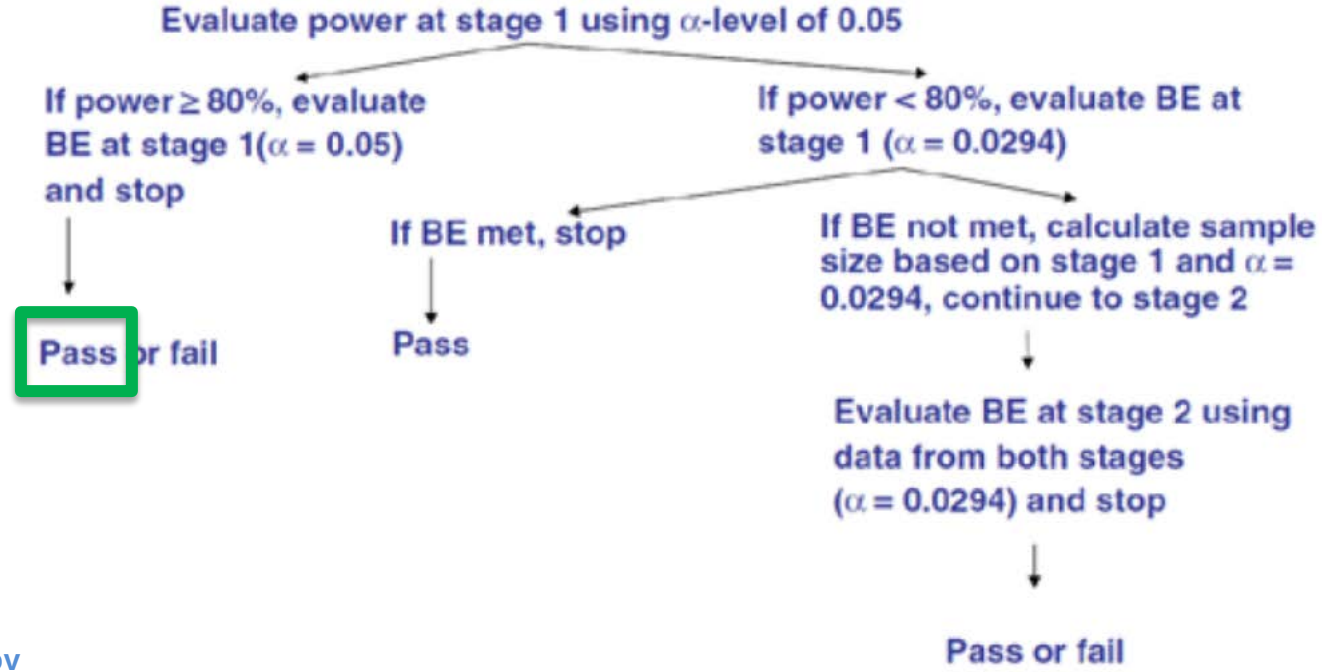
Existing ANDAs submissions from 2006 to 2019

	Two-Stage design	Group Sequential Design	Futility interim analysis
No. ANDA submissions	9	3	43
Products	Oral, injection, topical	Oral and topical	Topical products (emulsion, scream and patch)
Features	Re-estimate sample size based on stage 1 non-BE* (e.g., Potvin methods)	Predetermine sample size and type I error at each stage	Stopped only if deemed not BE

* BE – bioequivalence

Case Study 1

- A randomized, two-stage (Potvin Method C), single-dose, crossover PK study with AUC_{0-t} and C_{max} PK endpoints.



Case Study 2

- A pivotal BE study for a topical product on PD endpoint $AUEC_{0.5\text{-}24h}$
- Interim analysis at 60% of subjects (N=49 out of total 80), shows that BE is not deemed to fail
- Study continues until reaching the protocol-specified 80 subjects
- The 90% CI of the T/R ratio for $AUEC_{0.5–24h}$ falls within 80.00–125.00%, demonstrating a successful BE study

Lessens Learned

- Did not prespecify a study as an adaptive design for stopping or continuing a study
- Did not follow the procedures and statistical analysis plan specified in the protocol, e.g., study power analysis was not included before the BE evaluation at stage 1
- Did not define additional subjects as a *post hoc* add-on studies in sequential or group sequential design but was included in the data analysis

Additional Information about Type I Error

- With a two-stage adaptive sequential design using Potvin's Methods:
  - The Agency will accept appropriately designed bioequivalence studies if the applicant provides evidence that your proposed approach is validated
  - And does not inflate type 1 error supported by either peer-reviewed journal papers with same study designs or by simulation method (e.g., type 1 error controlled at the nominal level with 0.05 for a bioequivalence test).

Challenge Question #1

Which of the following statements is NOT true?

A. When BE fails and the power <80% at the stage 1 of the two–stage design using Potvin C method, the applicant can continue to stage 2.

B. At futility interim analysis, the applicant can stop the study when BE was deemed to be unsuccessful using 60% of the planned subjects.

C. Additional subjects were included for data analysis when the subjects were prespecified in a group sequence design.

D. When BE passed and was evaluated using $\alpha = 0.05$ at stage 1 without power analysis, BE is concluded as a successful study.

Adaptive design during COVID-19 Pandemic

- To provide detailed information including proposed plans, rationale, and justification supporting your proposal when communicating with the Agency.

Bioequivalence Studies for Submission in ANDAs during the COVID-19 Pandemic.

- A reference for the challenges and potential opportunities for implementing adaptive designs for BE studies on generic drugs

Jieon Lee, Kairui Feng, Mingjiang Xu, Xiajing Gong, Wanjie Sun, Jessica Kim, Zhen Zhang, Meng Wang, Lanyan Fang, Liang Zhao. Applications of Adaptive Designs in Generic Drug Development, 2021 Jul;110(1):32-35. doi: 10.1002/cpt.2050

Case Study 3

- ANDA submission for a fully replicate BE study (Fasting and Fed)
- Product-Specific Guidance available and approved ANDAs
- Because of COVID-19, about 20 out of 60 recruited subjects could not be included in the final analysis due to missing data for at least one period

Challenge Question #2

Which of the following statements is NOT true due to COVID-19?

A. The applicant can do the BE data analysis based on the available subjects. If it fails, additional subjects can be added to increase the power as an adaptive design.

B. The applicant can do the BE data analysis based on the available subjects. If it passes, BE is concluded as a successful study.

C. The applicant can recruit additional subjects by prespecifying as an adaptive design in the protocol prior to data unblinding.

D. The applicant can send a controlled correspondence and ask the Agency's agreement for recruiting more subjects as an adaptive design prior to data lock.

Case Study 3 Results

- The substantial reduction in sample size due to COVID-19 affected the study power, which resulted in wider confidence intervals and failed Cmax in both studies for the reference scaled average BE (RSABE) criterion.
- Without the interruptions by COVID-19, Cmax for the RSABE criterion for both studies would have been met and therefore, BE would be concluded.

Statistical guidance for COVID-19

- The Agency published the guidance for industry on *Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency* (June 2020) which recommends that modifications to the analysis of the primary or key secondary endpoints should be reflected in an updated statistical analysis plan **before locking the database**.

BE Guidance for COVID-19

- FDA's *guidance for industry on Protecting Participants in Bioequivalence Studies for Abbreviated New Drug Applications During the COVID-19 Public Health Emergency (January 2021)*, protocol and statistical analysis plan changes should be pre-specified in your statistical analysis plan with sufficient information and justification and made **prior to data lock and unblinding**.

Post-hoc analyses

- Any additional analysis after the data lock and unblinding are post-hoc in nature.
- The Agency considers post-hoc analyses as hypothesis-generating, and generally expects a prospectively designed study to be used to establish BE within an ANDA submission.
- The study protocol should prespecify how missing data will be handled and the applicants should justify the method chosen, including modeling and simulations.

Study Power

- It is the applicant's responsibility to design an adequately powered BE study for the proposed study design and the acceptability of your proposed adaptive design will be determined during the scientific assessment of the ANDA.

Lessons Learned

- The protocol should prospectively identify how the study will handle participant illness (either from COVID-19 or some other reason) during the conduct of the study (e.g., consider whether to remove, replace, or provide another method to address missing data for that participant).
- Protocol and statistical analysis plan changes should be made prior to data lock and unblinding; for example, the protocol should prospectively state how missing data will be handled in the statistical analyses and provide appropriate justification for the method chosen.

Summary

- Applicants and Lessons learned help future adaptive designs in generic drug development.
- Communicating with the Agency is encouraged for adaptive design during COVID-19 Pandemic prior to data lock and unblinding.

Resources

- Bioequivalence Studies for Submission in ANDAs during the COVID-19 Pandemic.
- Jieon Lee, Kairui Feng, Mingjiang Xu, Xiajing Gong, Wanjie Sun, Jessica Kim, Zhen Zhang, Meng Wang, Lanyan Fang, Liang Zhao. Applications of Adaptive Designs in Generic Drug Development, 2021 Jul;110(1):32-35. doi: 10.1002/cpt.2050
- Guidance for industry, *Adaptive Designs for Clinical Trials of Drugs and Biologics* (November 2019)
- Guidance for industry, *Protecting Participants in Bioequivalence Studies for Abbreviated New Drug Applications During the COVID-19 Public Health Emergency* (January 2021)
- Guidance for industry, *Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency* (June 2020)

U.S. FOOD & DRUG ADMINISTRATION

Questions?

Kairui (Kevin) Feng, PhD
Staff Fellow
Office of Research and Standards
CDER | U.S. FDA

[Kairui.feng@fda.hhs.gov]


FDA
U.S. FOOD & DRUG
ADMINISTRATION