Approaches to Analyzing Comparative Use Human Factors Studies

Advancing Generic Drug Development 2024:
Translating Science to Approval

Day 1, Session IV: Outlook for Drug-Device Combination Products

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Disclaimer

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

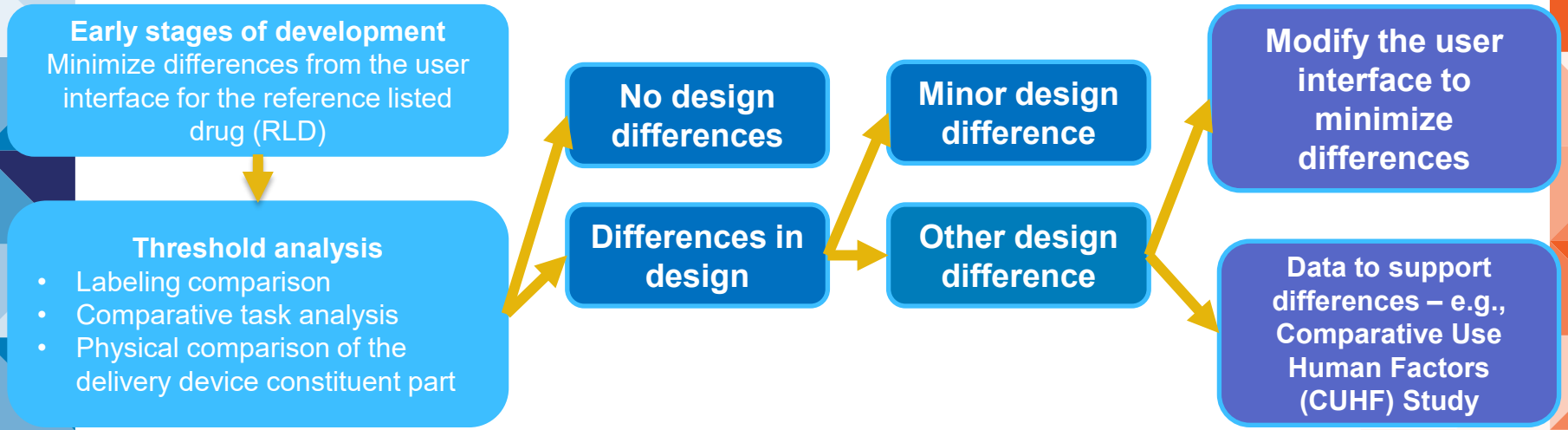
Learning Objectives

- Provide overview of the current use of Comparative Use Human Factors (CUHF) studies to support other design differences
- Discuss the analysis approach for the noninferiority test in CUHF Studies

Current Use of CUHF Studies to Support Other Design Differences

CUHF Studies

- FDA draft guidance, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017)[1]
- **CUHF studies are NOT recommended for every application of drug-device combination products**



1. When final, this guidance will represent the current thinking of FDA. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

CUHF studies

- CUHF studies: designed to confirm that the use error rate, for the critical task(s) for the proposed generic combination product, is not worse than the corresponding use error rate for the RLD.
- Procedure of comparing error rate of Test product ($\mathbf{ER_T}$) and the error rate of RLD product ($\mathbf{ER_R}$) through the **noninferiority (NI) test** in CUHF studies as discussed in the draft guidance:

Step 1 - Determine the allowable margin (*d*) by which $\mathbf{ER_T}$ could exceed $\mathbf{ER_R}$.

Step 2 - Estimate the study sample size considering assumed error rates and ***d***.

Step 3 - Observe error rates for the critical task(s) during the CUHF experiments.

Step 4 - Perform the NI hypothesis test.

$$\mathbf{H_0: ER_T - ER_R > d}$$
$$\mathbf{H_A: ER_T - ER_R \leq d}$$

NI test for CUHF studies

Step 1

Determine the allowable margin (*d*) by which $\mathbf{ER_T}$ could exceed $\mathbf{ER_R}$

- The value of *d* will differ between products, depending on the indication(s) and the clinical consequences associated with failing to perform the critical tasks appropriately.
- The acceptable *d* should be decided in consultation with the FDA before the study is conducted.

NI test for CUHF studies

Step 2

Calculate the study sample size considering assumed error rates and *d*

- The draft guidance provides an example using the **Tango** method to calculate some power simulations given selected sample sizes with α= 0.05 and an allowable margin (*d*) = 0.10

Power of Paired Design to Compare Use Error Rates under Various Assumptions.

Power (%)	Within-subject Correlation	Use Error (%)	Probability	Sample Size
85	0.90	10		45
83	0.90	20		50
80	0.90	30		55
80	0.90	40		60
80	0.70	10		55
81	0.70	20		75
81	0.70	30		90
81	0.70	40		100
80	0.50	10		70
80	0.50	20		110
80	0.50	30		135
81	0.50	40		155

*Simulated power given selected sample sizes, assuming equal success probabilities, **a**= 0:05 and d = 0:10 and using the method of Tango [Statist. Med. 17, pp. 891-908 (1998)]. 2500 simulated clinical trials were used for each table line.*

NI test for CUHF studies

Tango method

- Tango method is a widely used method to calculate confidence intervals (CI) for the difference of two proportions in a paired design of clinical trials[2]

- Required information for Tango CI calculation:
  - Number of subjects who completed R tasks successfully but had errors in T tasks
  - Number of subjects who completed T tasks successfully but had errors in R tasks
  - Total number of subjects
  - Confidence level

- Of note, the Tango method is just one of the options for the analysis of CUHF studies.

2. Tango, Toshiro. "Equivalence test and confidence interval for the difference in proportions for the paired-sample design." Statistics in medicine 17, no. 8 (1998): 891-908.

NI test for CUHF studies

Step 3

Observe error rates for the critical task(s) during the experiment.

- Definition of critical tasks
- Observe error/success results of subjects for each critical task

	REF_results	TEST_results
1	1	1
2	1	1
3	1	0
4	1	1
5	0	0
6	1	1
7	0	0
8	1	0
9	1	1
10	1	1
11	1	1
12	0	0
13	1	1
14	0	0
15	1	1

NI test for CUHF studies

Step 4

Perform the NI hypothesis test.

$$H_0: ER_T - ER_R > d$$
$$H_A: ER_T - ER_R \leq d$$

- Compare the upper bound of the CI for the difference of error rates between T and R to *d*.
- If $\alpha = 0.05$ and the upper bound of 95% CI is less than *d*, H_0 is rejected and NI is demonstrated.

Data analysis for CUHF studies

- In addition to the current recommendations in the draft guidance, FDA continues to conduct research to facilitate drug development and mitigate regulatory burdens for CUHF studies
- Applicants are encouraged to propose alternative data analysis methods and/or study designs for CUHF studies

Alternative data analysis methods to consider

- Non-parametric methods
  - Bootstrap-based methods
- Bayesian methods
  - Bayesian methods to estimate the distribution of the target population's performance with the Test and RLD products

Zhang, Qunshu, et al. "Applying the noninferiority paradigm to assess exposure-response similarity and dose between pediatric and adult patients." *The Journal of Clinical Pharmacology* 61 (2021): S165-S174.

Discussions between FDA and generic drug applicants

- Applicants are advised to discuss proposed alternative data analysis methods and/or study designs with FDA before initiating CUHF studies
- Programs available for the discussions
  - **Model-Integrated Evidence (MIE) Industry Meeting Pilot**

    https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/model-integrated-evidence-mie-industry-meeting-pilot-between-fda-and-generic-drug-applicants

    A new pilot program to offer meeting opportunities to applicants who intend to use model-integrated evidence (MIE) or novel data analytics approaches for bioequivalence (BE) establishment in their ANDAs

  - **Pre-ANDA Program for Complex Generic Products**

    FDA guidance for industry, *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022), https://www.fda.gov/media/107626/download

    ANDA applicants for complex generic drug products can request product development Pre-ANDA meetings to help clarify regulatory expectations early in product development

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Challenge Question #1

In the FDA draft guidance, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017), the comparative use human factors study is recommended for every application of drug-device combination products. This statement is

A. TRUE

B. FALSE

Challenge Question #2

In the FDA draft guidance, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017), which of the following analysis methods is recommended for the noninferiority (NI) test in comparative use of human factors studies?

A. Tango method

B. Bootstrap method

C. Bayesian method

D. The guidance doesn't recommend an analysis method for NI test

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Questions?

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