Review of Clinical Endpoint Bioequivalence Studies in ANDAs

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Outline

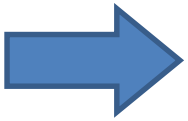
- Overview of clinical endpoint bioequivalence (BE) studies
- Challenges in the design and review of clinical BE studies
- Helpful tips and practical examples

ANDA Review Process Simplified: Significance of Hatch-Waxman Amendments (1984)

Brand name/ Innovator's Products

NDA Requirements
1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Animal Studies
7. Clinical Studies
8. Bioavailability

- Demonstrate safety and effectiveness



Generic Drug

ANDA Requirements
1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Bioequivalence

- Demonstrate BE
- Relies on FDA findings of safety and efficacy data from NDA
- No pre-clinical and clinical testing required

Bioequivalence

- 21 CFR 320.33 (a)(3)(b)

- Drug products pharmaceutical equivalents or pharmaceutical alternatives
- Administered at same molar dose
- Under similar experimental conditions
- Absence of a significant difference in the rate and extent of absorption

21 CFR 320.24

Types of evidence to measure bioavailability or establish bioequivalence

1. In vitro test
2. In vivo test in humans:
    - BE Study with pharmacokinetic (PK) endpoints
    - BE study with pharmacodynamic (PD) endpoints
    - BE study with clinical endpoints
        - Least sensitive, least reproducible of general approaches for determining BE
3. Any other method deemed adequate by FDA

Drugs with local action

- Not intended to be absorbed into the bloodstream
- Delivered directly to sites of action
  - Skin (topical acne creams, lotions, gels)
  - Nose (nasal spray for allergic rhinitis)
  - Locally acting gastrointestinal tract (oral capsule for chronic constipation)

Why is PK study not feasible for locally acting drug products?

- Not intended to be absorbed into the bloodstream
- PK correlation to site of action in question
- No obtainable PK concentration

Thus, a Clinical Endpoint BE study is requested.

Definition of a Clinical Endpoint BE Study

- A comparative clinical trial in humans that is used to determine the bioequivalence of locally acting drug products with dosage forms intended to deliver the same active moiety at an equivalent rate and extent to the site(s) of activity.
- Applies to dosage forms intended to deliver the active moiety locally and are not intended to be systemically absorbed.

BE: Approved Drug products with Therapeutic Equivalence Evaluations ("the Orange Book")

- Lists FDA approved drugs
- Reference Listed Drug (RLD): the existing drug that is the basis for an ANDA
- **Pharmaceutical equivalents**:
  - Same active ingredient(s)
  - Same dosage form and route of administration
  - Identical in strength or concentration
- **Therapeutic equivalents**:
  - Only pharmaceutical equivalents expected to have the same clinical effect and safety profile

21 CFR 320.33 (a)(3)(b): Applicable to Clinical Endpoint BE Study

- Chemically Equivalent
- Pharmaceutically Equivalent
- Therapeutically Equivalent

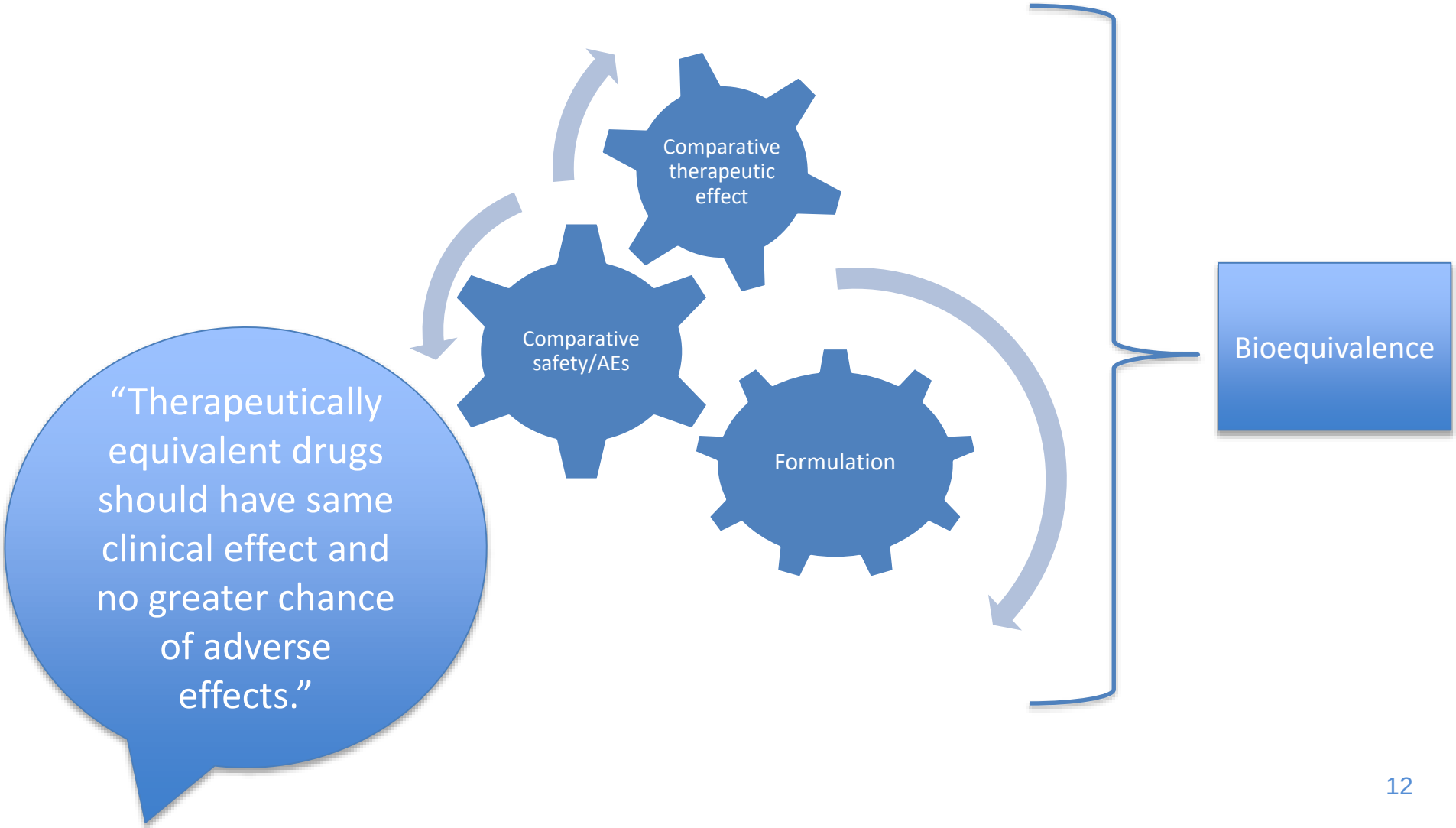
- <u>If two products are BE, can infer they are therapeutically equivalent</u>
- Therapeutic equivalence is determined on the basis of
  - Chemically equivalent and Pharmaceutically equivalent in the context of clinical use
  - True only if the product is chemically and pharmaceutically equivalent
  - Evaluation of therapeutic effect, not efficacy

PK vs. Clinical Endpoint BE Studies

PK Study	Clinical Endpoint Bioequivalence Study
▪ Cross-over study ▪ Blood concentrations ▪ Healthy subjects ▪ Single Dose ▪ Test vs. Reference ▪ AUC, CMAX, TMAX ▪ 90% CI test (T)/reference (R) ▪ 80-125% ▪ Per Protocol (PP) population	▪ Parallel study ▪ Bio-markers* ▪ Patients ▪ Multiple Doses ▪ Test vs. Reference vs. Placebo ▪ Primary Endpoints (varies) ▪ 90% CI T/R or T-R ▪ 80%-125% if T/R, +/-20% if T-R ▪ Equivalence (PP) and sensitivity (Intent-to-treat, comparison to placebo) populations

*blood cholesterol is a biomarker for risk for coronary heart disease. Serves as a surrogate for the therapeutic effect.

Critical Basics in Clinical Review



Challenges

- When drug-specific guidance is not available
- Guidance is only a framework
- Multiple treatment indications

Challenges (continued)

- Time of measurement may not be sensitive enough to detect the difference between products
- Effect size is too small that power is not adequate to demonstrate BE
- Rating scales are subjective and variable
- Very expensive

Study Design

- Use product specific recommendations (guidance)
- Other approaches acceptable but require justification
- Provide justification in original ANDA submission

Justification Needed

- Different from product specific recommendation
  - Study population, Inclusion/exclusion criteria
  - Treatment use different than in RLD label
  - Endpoints, Statistical Analysis

Justification Example

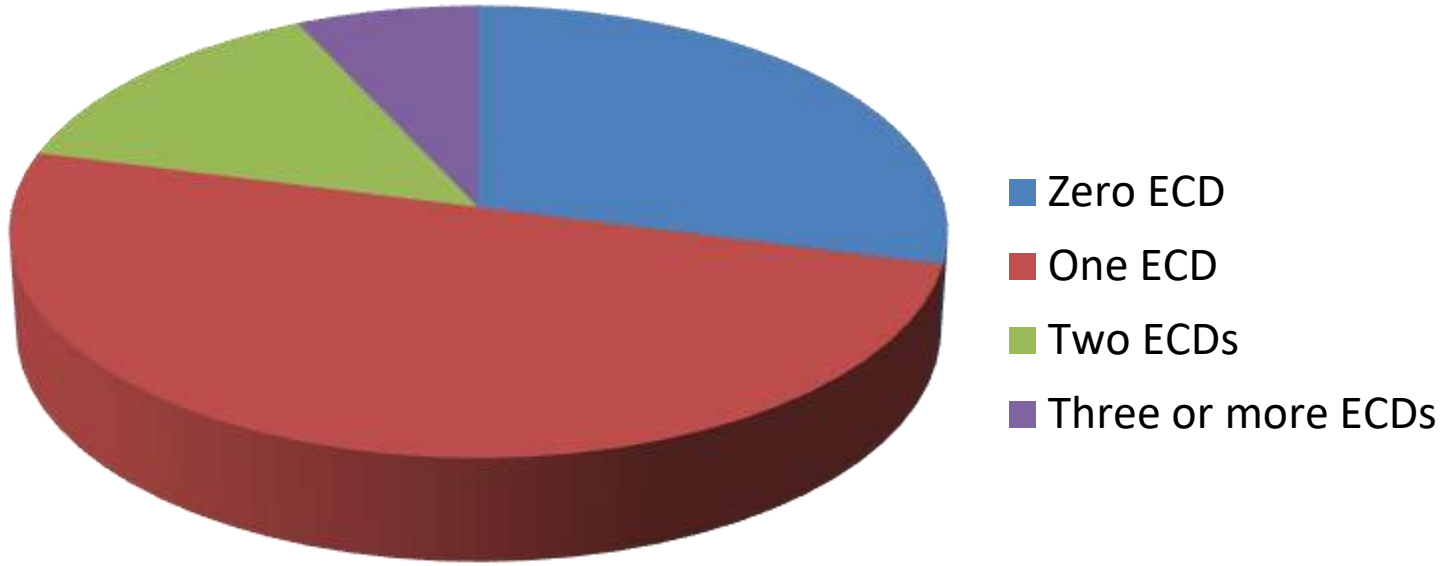
9.2 Discussion of Study Design, including the choice of control groups

This study was designed to be a prospectively randomized, double-blind, parallel-group, multicenter, placebo (vehicle) and active drug comparison (using both Test Drug and RLD) three-arm study as per Draft FDA Guidance on (May 2011 Recommendation). In the initial study design to demonstrate clinical equivalence between Test and RLD and to achieve study sensitivity, several key modifications to the Draft FDA Guidance on (May 2011 Recommendation) were considered when developing the Study Protocol and subsequently submitted to the FDA Office of Generic Drugs (OGD) for review:

1. Owing to an industry-wide perception of high levels of the so-called "Placebo effect" in multiple clinical trials where pain medications had been compared to Placebo vehicles, we

2. Several earlier clinical studies (e.g. Barthel et al.) had suggested a possibility that a longer

Number of Easily Correctable Deficiencies (ECD) sent for Clinical Endpoint ANDA Submissions in 2016



Easily Correctable Deficiency Breakdown

	Reason for Easily Correctable Deficiency (ECDs)	Percentage of ECDs
1.	Clarification/Justification	67%
2.	Pregnancy Information	30%
3.	Formulation Related	7%
4.	Missing Case Report Forms (CRFs)	7%

1. Clarification and Justification

- Treatment failures
- Non-US population
- Clinical judgment
- Study days
- Rescue medication

1. Clarification & Justification: Treatment Failures

- **Who they are**
  - *Example: Subjects discontinued from the study because of lack of treatment effect, lack of efficacy or whose condition worsened requiring alternative or supplemental therapy provided they completed at least X consecutive days/weeks of treatment and were compliant with the dosing requirements during their time of study participation.*

1. Clarification & Justification: Treatment Failures

- **Which population included in**
  - *Example: Subjects were included in the modified intent to treat (mITT) population if the subject met all other conditions for the mITT population and included in the per protocol (PP) population if the subject used the study medication for at least X consecutive days/weeks as planned and met all other conditions for the PP population.*

1. Clarification & Justification: Treatment Failures

- **Last observation carried forward (LOCF)**
  - *Example: For the mITT and PP subjects who were discontinued due to treatment failures, the results observed from the last visit prior to becoming a treatment failure were carried forward to all subsequent missing visits and used in the statistical analysis.*

1. Non-US Population

- Clinically relevant
- Address all clinical issues
- Submit in original ANDA
- Provide references to support conclusion

1. Non-US Population Example

- No evidence of differences in therapeutically relevant COX-1 or COX-2 polymorphisms in populations that might be over-represented in some parts of the US compared to the population of the current clinical study
- About 35% of Caucasians have a slow acting form of CYP2C9. The frequency of allelic variants of the CYP2C9 gene that render the enzyme less active is highest amongst the Caucasians compared to other racial groups.
- As explained above, the population used in the current study adequately represents the therapeutic efficacy and frequency of potential side effects that may emerge in any population, including that of the USA.
- Below is a list of literature references to support this conclusion.

1. Clinical Judgment

- Doxycycline (antibiotic): not a prohibited medication in acne vulgaris study
- Subjects do not have bacterial infection in study to treat secondary bacterial infection

1. Study Days

- Provide study day (day during study) in addition to calendar date

Concomitant Medication data set

USUBJID	CMTRT	CMDECOD	CMINDC	CMDOSTXT	CMDOSFRQ	CMROUTE	CMSTDTC	CMENDTC	CMSTDY	CMENDY	CMENRF
03-0001	LORATADINE	LORATADINE	SEASONAL ALLERGIES	10 MG	PRN	ORAL	2013		•	•	ONGOING
03-0147	ADVIL	IBUPROFEN	COLD COUGH (UPPER ...	200 MG	TID	ORAL	2015-07-27	2015-08-01	61	66	
03-0251	MUCINEX	GUAIFENESIN	FLU	600 MG	PRN	ORAL	2015-06-25	2015-06-27	22	24	

Adverse Events data set

USUBJID	AETERM	AEDECOD	AEBODSYS	AESEV	AEREL	AEOUT	AESTDTC	AEENDTC	AESTDY	AEENDY
03-0218	HEADACHE	Headache	Nervous system disorders	MODERATE	NOT RELATED	RECOVERED/RESOLVED	2015-06-11	2015-06-12	29	30
03-0332	COLD	Nasopharyngitis	Infections and infestations	MILD	NOT RELATED	RECOVERED/RESOLVED	2015-08-24	2015-08-28	39	43
03-0590	COLD SORE	Oral herpes	Infections and infestations	MILD	NOT RELATED	RECOVERED/RESOLVED	2015-10-06	2015-10-19	50	63

Note: Subject ID numbers are not real.

1. Rescue Medication

- Include a separate data set
- Each day should be separate listing (row)
- Examples: inhalers, pain medication, etc.

Rescue inhaler medication data set

USUBJID	TRT02P	RESCMED	PUFFS	EPOCH	RESSTC	RESSTDY	PPROTFL	MITTFL	SAFFL
01000236	REFERENCE	Albuterol 90ug inhaler	2 puff(s)	TREATMENT	2015-01-17	19	Y	Y	Y
01000236	REFERENCE	Albuterol 90ug inhaler	1 puff(s)	TREATMENT	2015-01-20	22	Y	Y	Y
01000540	REFERENCE	Albuterol 90ug inhaler	6 puff(s)	TREATMENT	2014-12-25	3	Y	Y	Y
01000540	REFERENCE	Albuterol 90ug inhaler	2 puff(s)	TREATMENT	2014-12-27	5	Y	Y	Y
01000540	REFERENCE	Albuterol 90ug inhaler	2 puff(s)	TREATMENT	2014-12-28	6	Y	Y	Y

Note: Subject ID numbers are not real.

1. Missing Documents

- Pregnancy
  - Outcome, attempts to obtain follow up information
- Study Protocols (all versions including dates)
  - Differences between versions
- IRB Approval Forms (protocols and consent forms)
- Financial Disclosure (FDA Form 3454)

2. Pregnancy

- **Provide dates and follow up information**
  - *Example: Subject A from site #7 was early terminated from the study on 9/14/2016 due to pregnancy confirmation. The subject stated that a sonogram was performed on 11/3/2016 at her first OB/GYN visit. Upon follow up, it was learned that the Subject had a normal delivery on 4/2/2017.*

2. Pregnancy

- **Include documentation**
  - *Example: Attached are the initial and final pregnancy notification forms.*

2. Pregnancy

- **Document attempts to obtain follow up information**
  - *Example: Subject B from site #19 was discontinued from the study on 8/28/2016 due to pregnancy confirmation. The Subject was contacted by telephone on 12/1/2016. The subject became a lost to follow-up as of 12/24/2016. The site made two attempts at calling the patient and has also sent the subject a certified letter. As of 3/1/2017, the subject never contacted the site after communication attempts were made for further follow-up communication.*

3. Formulation

- Formulation for Test and Placebo
- Justification of inactive ingredients if different than Reference Listed Drug (RLD)
- Manufacture Date / Expiration Date
- Lot / Batch Number

4. Case Report Forms

- Needed for subjects with serious adverse events (SAEs), deaths, and pregnancies
- Include narrative for same subjects
- Recommend for all subjects but minimum of 10%

Summary

- Understand challenges and goal of a clinical endpoint BE study outcome
- Use product specific recommendations (guidance)
- Provide justification in original ANDA submission

References

- Guidance for Industry Bioequivalence Recommendations for Specific Products
- Product Specific Recommendations for Generic Drug Development
- Guidance for Industry ANDA Submissions – Amendments and Easily Correctable Deficiencies
- ANDA Submissions – Refuse to Receive for Lack of Justification of Impurity Limits Guidance for Industry

Thank You!

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