Common Clinical Deficiencies in ANDAs Containing Comparative Clinical Endpoint Studies

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Objective

- Understand the goal and study design of a Comparative Clinical Endpoint Bioequivalence (CCEP BE) study and Irritation, Sensitization, and Adhesion (I/S/A) studies
- Get familiar with the common deficiencies in the CCEP BE study and I/S/A studies
- Be aware of the relevant guidances for the CCEP BE study and I/S/A studies

Overview of Comparative Clinical Endpoint Bioequivalence (CCEP BE) Study

What is a Generic?

https://www.fda.gov/media/83670/download

- Same active ingredient, strength, dosage form, and route of administration, deliver identical amounts of the active ingredient over the identical dosing period and meet the identical compendial or other applicable standard of identity, strength, quality and purity = Pharmaceutical Equivalents (PE)
- Absence of a significant difference in the rate and extent to which the active ingredient becomes available at the site of drug action = Bioequivalence (BE)
- Same safety and efficacy when used in the indicated population according to the labeling recommendations = Therapeutic Equivalence (TE)
- Same Quality Standards

Drug Price Competition and Patent Restoration Act (Hatch-Waxman Amendments)

Hatch-Waxman Amendments: added section 505(j) to the Federal Food, Drug, and Cosmetic Act and established the modern system of generic drug regulation in United States (1984)

There were three basic principles to generic drug approval provided by this act:

- generic approvals must be based on scientific considerations and **minimize duplicative testing**
- all generic and brand name drugs must meet the **same quality criteria** for manufacturing
- generic versions of drugs **must be equivalent** to a degree, calculated statistically, which ensures that therapeutically equivalent drugs have the same clinical effect and no greater chance of adverse effect

What is ANDA vs. NDA?

- ANDA:
  - Abbreviated New Drug Application
  - Application for approval of a generic drug
  - Reviewed by the Office of Generic Drugs (OGD)
  - Demonstrate BE and PE
  - Relies on FDA findings of safety and efficacy data from NDA
- NDA:
  - New Drug Application
  - Application for approval of a brand name drug
  - Reviewed by the Office of New Drugs (OND)
  - Demonstrate safety and effectiveness

NDA vs. ANDA Review Process

Brand Name Drug NDA Requirements	Generic Drug ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Testing	3. Testing
4. Labeling	4. Labeling
5. Inspections	5. Inspections
6. Animal Studies	
7. Clinical Studies	6. **Bioequivalence**
8. Bioavailability	

What is Bioequivalence (BE)?

- 21 CFR 320.23(b)(1):
  - "Two drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose."
- 21 CFR 320.23(b)(2):
  - "For drug products that are not intended to be absorbed into the bloodstream, bioequivalence may be demonstrated by scientifically valid methods that are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect."

How to Establish Bioequivalence?

There are multiple study types to establish bioequivalence

- **In vitro tests predictive of human in vivo bioavailability**—in vitro-in vivo correlation
- **Waiver of In Vivo BE (In Vitro Studies only)**—for drugs that are qualitatively (Q1) and quantitatively (Q2) equivalent.
  - Q1: qualitative sameness (same components);
  - Q2: quantitative sameness (same amounts of the same components)
- **Pharmacokinetic (PK) study** —for drugs having a measurable parent and/or active metabolite concentration curve in plasma, serum, urine, etc.
- **Pharmacodynamic study** —for drugs where a PK evaluation is impossible or not relative to the therapeutic effect.
- **Comparative Clinical Endpoint BE —**for locally acting drugs. This is a comparative effects study NOT an efficacy study. Least sensitive, least reproducible of general approaches for determining BE.
- **Weight of Evidence Approach—**for complex drug products like inhaled medications; requires in vitro, PK, and Comparative Clinical Endpoint BE studies.

What is a Comparative Clinical Endpoint Bioequivalence (CCEP BE) Study?

- A comparative clinical study in humans that can determine the bioequivalence of dosage forms intended to deliver the same active moiety at an equivalent rate and extent to the site(s) of activity.

- May be applied to dosage forms intended to deliver the active moiety locally, forms that are not intended to be absorbed, or drug products for which traditional pharmacokinetic studies are not feasible.

OGD Manual of Policies and Procedures (MAPP 5210.4) revised on June 26, 2017

When to Do a Comparative Clinical Endpoint BE (CCEP BE) Study?

- Drug products that have negligible systemic uptake
- There is no identified pharmacodynamic measure
- The site of action is local
  - 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)

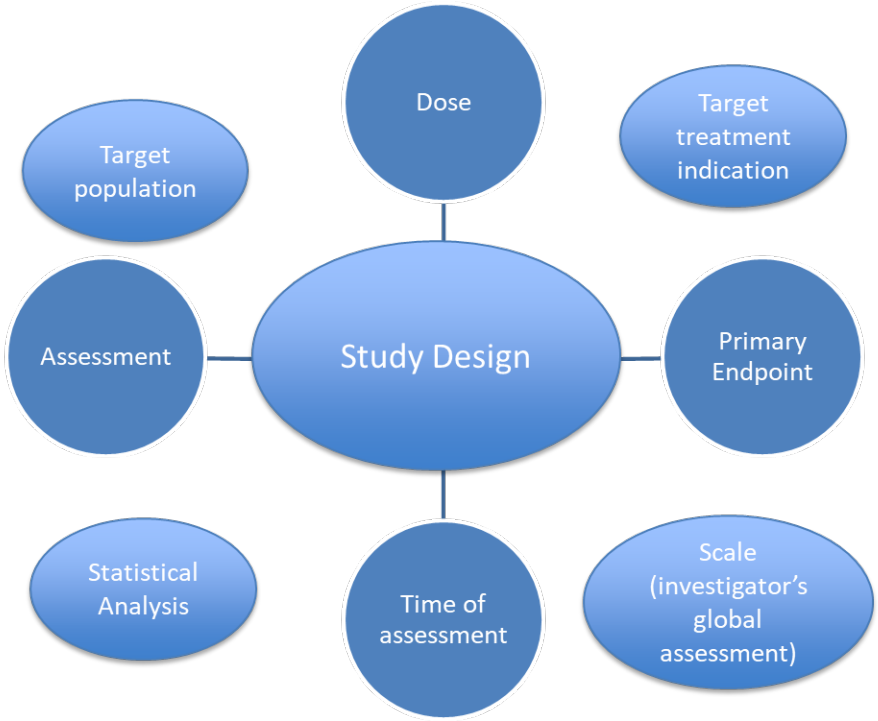
Study Design

Goal*:* To demonstrate that two products [generic (Test, T) and reference (R)] are BE, so the T can be substituted for the R

Design: a blinded, randomized, parallel study

- Use lowest dose possible to detect more sensitive response to formulation differences
- Show equivalent therapeutic effect of a T and R product
- Show both T & R products are superior to the effect of a placebo
- To ensure that two products have same clinical effect and safety profile when given to patients under the same conditions

Study Design (cont.)



Relevant Guidances

- Product-Specific Guidances for Generic Drug Development
- ANDA Submissions | Amendments to Abbreviated New Drug Applications Under GDUFA | FDA
- ANDA Submissions -- Refuse-to-Receive Standards Rev.2 | FDA

Overview of Irritation, Sensitization, and Adhesion (I/S/A) Studies

Definition

- Skin irritation: A locally arising reaction of the affected skin tissue and appears shortly after stimulation. It is caused by a local inflammatory reaction involving the innate (non-specific) immune system of the skin tissue.

- Skin sensitization reaction: Refers to an allergic skin reaction (i.e., allergic contact dermatitis) to a substance resulting from previous exposure, and is usually characterized by redness, swelling, and itching.

Reference: OECD (Organization for Economic Co-operation and Development) in their TG (test guideline) #439 Globally Harmonized System of Classification and Labelling of Chemicals (9th edition)

Goal of Irritation, Sensitization, and Adhesion (I/S/A) Studies

- To demonstrate the irritation, sensitization potential and adhesion performance of proposed generic Transdermal or Topical Drug Delivery System (TDS) (T) is not worse than the reference TDS (R) (non-inferiority test)

Regulatory History

- Draft Guidance for Industry for Adhesion
  - "Assessing Adhesion with Transdermal and Topical Delivery Systems for ANDAs" (posted June 2016, revised October 2018, April 2023)
  - https://www.fda.gov/media/98634/download
  - Study Design & Statistical Analysis Method for adhesion evaluation recommendations
- Draft Guidance for Industry for Irritation and Sensitization
  - "Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs" (posted October 2018, revised April 2023)
  - https://www.fda.gov/media/117569/download
  - Study Design & Statistical Analysis Method for irritation and sensitization evaluation recommendations
- Product-Specific Guidances (PSG) for Generic Drug Development
  - https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm
  - Updated all the TDS PSGs after the two general guidances were published in October 2018

Study Design

- Combined Irritation/Sensitization (I/S) Study
  - Evaluator-blinded, randomized study
  - 6 weeks: Induction phase (21 days), rest period (14-17 days), challenge phase (5 days), re-challenge (if needed)
  - Treatment arms:
    - To-be-marketed T and R (comparison between the T and R)
    - Vehicle TDS (without active) and positive control TDS produces mild irritation (e.g., less than or equal to 0.1% sodium lauryl sulfate)

Study design (cont.)

- Combined Irritation/Sensitization (I/S) Study
  - In general, a subject's body movement should not be restricted during the study. For products with a wear period of equal to or greater than 24 hours, the Agency recommends that:
    1. subjects be permitted to bathe or shower routinely during the study, in a manner consistent with the labeled use of the RLD, and
    2. the TDS should not be protected from direct exposure to water during such routine activities.

Study Design (cont.)

- Adhesion alone study or combined Adhesion/pharmacokinetics (PK) study
  - Single-dose, randomized, two-treatment, two-period crossover study
  - Treatment arms: to-be-marketed T and R
  - Duration: maximum labeled duration of wear of the R

Study Design (cont.)

- Adhesion alone study or combined Adhesion/ PK study
  - In general, subjects should be allowed to freely conduct normal activities within the study unit and/or at home (e.g., to perform real-world activities like showering) that may reasonably be expected to occur during the labeled duration of use for the product.
  - For products with a wear period of up to or greater than 24 hours, FDA recommends that subjects be permitted to bathe or shower routinely during the study, in a manner consistent with the labeled use of the RLD, and that the TDS should not be protected from direct exposure to water during such routine activities.

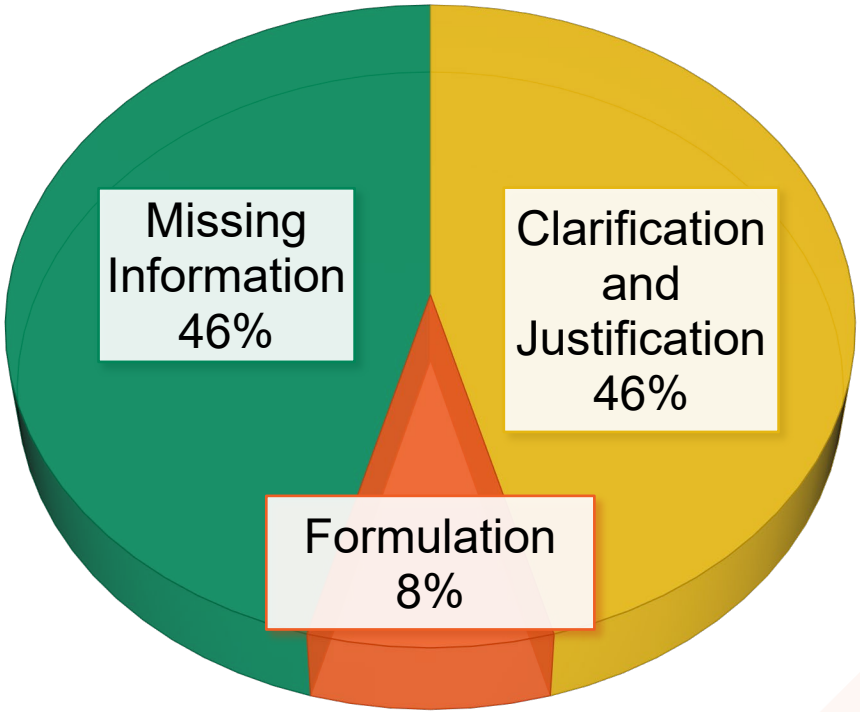
Relevant Guidances

- Product-Specific Guidances for Generic Drug Development
- ANDA Submissions | Amendments to Abbreviated New Drug Applications Under GDUFA | FDA
- ANDA Submissions -- Refuse-to-Receive Standards Rev.2 | FDA
- Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs Draft Guidance for Industry | FDA
- Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs | FDA

Common Deficiencies Identified in Review of CCEP BE and I/S/A Studies

Easily Correctable Deficiency (ECD) or Information Request (IR) in 2014-2024

- Clarification and justification
- Missing information (e.g., documents, dataset)
- Formulation related issues



1. Clarification and Justification

- Study days (e.g., concomitant medication)
- Rescue information
- Different from guidance recommendations
- Inconsistent information (e.g., between the study report and case report form)

Study Days

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

Concomitant Medication data set

USUBJID	CMTRT	CMDECOD	CMINDC	CMDOSTXT	CMDOSU	CMDOSFRM	CMDOSFRQ	CMROUTE	CMSTDTC	CMENDTC	CMSTDY	CMENDY
A4C-01-01	AZITHROMYCIN	AZITHROMYCIN	APPLICATION SITE DRYNESS	250	mg	TABLET	BID	ORAL	2022-09-24	2022-09-28	11	15
A4C-01-02	NADIFLOXACIN + CLOBETASOL PROPIONATE	CLOBETASOL PROPIONATE,NADIFLOXACIN	APPLICATION SITE DRYNESS	Finger Tip	APPLICATION	CREAM	PRN	TOPICAL	2022-09-24	2022-09-28	11	15
A4C-01-03	DOLO	PARACETAMOL	FEVER	650	mg	TABLET	BID	ORAL	2022-11-24	2022-11-27	59	62
A4C-01-04	DOLO	PARACETAMOL	BODY PAIN	650	mg	TABLET	BID	ORAL	2022-11-24	2022-11-27	59	62

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.

Rescue Medication

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

Rescue inhaler medication data set

USUBJID	NAME	DOSE	DOSE UNIT	RESDATE	RESTIME	V1DATE	RESDAY	V1DAY	V2DAY	V3DAY
B8E-02-04	Albuterol HFA (90 mcg/inhalation)	3	PUFF(S)	10/19/2022	19:51	10/20/2022	-1	1	7	16
B8E-02-05	Albuterol HFA (90 mcg/inhalation)	2	PUFF(S)	10/23/2022	20:41	10/20/2022	4	1	7	16
B8E-02-06	Albuterol HFA (90 mcg/inhalation)	2	PUFF(S)	10/24/2022	11:43	10/20/2022	5	1	7	16
B8E-02-07	Albuterol HFA (90 mcg/inhalation)	2	PUFF(S)	11/01/2022	21:39	10/20/2022	13	1	7	16
B8E-02-08	Albuterol HFA (90 mcg/inhalation)	1	PUFF(S)	02/01/2023	15:54	02/01/2023	1	1	14	•

Note: Subject ID numbers are not real.

Different from Guidance Recommendations

- Examples:
  - Use different scales: Convert to the scales that guidance recommended and submit the study result
  - TDS moved prior to reaching the excessive irritation score (e.g., different as you predefined in the protocol): Provide explanation when it happens

2. Missing Information

- Missing documents
- Missing dataset and data definition files

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)

Missing Dataset and Data Definition Files

- Examples:
  - Datasets in SAS. xpt format
    - Adverse events
    - Concomitant medications
    - Rescue medications (if applicable)
    - Medical history
    - Reasons for subject discontinuation from the study
  - Data definition files for all variables

3. Formulation Related Issues

- Formulation for Test and Placebo
- Justification of inactive ingredients if different than Reference Listed Drug (RLD)
- Manufacture Date / Expiration Date
- Lot / Batch Number
- Clarification on whether to-be-marketed formulation was used in the studies

Summary

Summary

- Understand the goal and study design of a CCEP BE study and I/S/A studies
  - Goal: to demonstrate the generic product is BE to the RLD, so the generic product can be substituted for the RLD (CCEP BE study)
  - Goal: to demonstrate the I/S potential and adhesion performance of the proposed generic product is not worse than the RLD (I/S/A studies)
- Use product specific recommendations (guidance)
- Other approaches may be acceptable but require justification
- Provide justification/clarification or other information in original ANDA submission

References

- Product-Specific Guidances for Generic Drug Development
- ANDA Submissions | Amendments to Abbreviated New Drug Applications Under GDUFA | FDA
- ANDA Submissions -- Refuse-to-Receive Standards Rev.2 | FDA
- Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs Draft Guidance for Industry | FDA
- Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs | FDA

Challenge Question #1

To minimize delay of review process of ANDAs that may delay approval of generic drug products, Applicants are strongly encouraged to submit all relevant information in the original ANDA submission including:

A. Clinical study protocol (including all revisions)

B. Pregnancy information and follow-up information (if applicable)

C. Datasets (e.g., medical history, concomitant medication, rescue medication (if applicable))

D. Formulation (e.g., RLD, Test, Placebo (if applicable))

E. All of the above

Challenge Question #2

Which of the following guidances will be helpful to check prior to conducting irritation, sensitization and adhesion studies?

A. Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs

B. Assessing Adhesion with Transdermal and Topical Delivery Systems for ANDAs

C. Product specific guidance of the study drug product

D. All of the above

Questions?

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