U.S. FOOD & DRUG ADMINISTRATION

Common Bioequivalence Deficiencies for Orally Inhaled Drug Products in ANDAs

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Common Deficiencies for In Vitro, Pharmacokinetic and Pharmacodynamic Bioequivalence Studies for Orally Inhaled Products in ANDAs

Outline

- Overview of Agency's bioequivalence (BE) recommendations for orally inhaled drug products
  - Metered dose inhalers (MDIs)
  - Dry powder inhalers (DPIs)
- Common BE deficiencies and BE comments for future studies for MDI and DPI ANDAs
  - General
  - In vitro studies
  - Pharmacokinetic (PK) studies
  - Pharmacodynamic (PD) studies

FDA BE Recommendations for MDI: weight-of-evidence approach

Equivalent In Vitro Performance

1. Single actuation contents (SAC)
2. Aerodynamic particle size distribution (APSD)
3. Spray pattern
4. Plume geometry
5. Priming and repriming

Equivalent Systemic Exposure

PK study

Equivalent Local Delivery

PD study
or
Comparative clinical endpoint study

Formulation and Device Design

FDA BE Recommendations for DPI: weight-of-evidence approach

Equivalent In Vitro Performance

1. Single actuation contents (SAC)
2. Aerodynamic particle size distribution (APSD)

Equivalent Systemic Exposure

PK study

Equivalent Local Delivery

PD study
or
Comparative clinical endpoint study

Formulation and Device Design

Study Design Recommendation

- Follow recommendations in the product-specific guidance
- Differences from product-specific guidance needs justifications, and the acceptability is evaluated on a case-by-case basis.
- May discuss in pre-ANDA communications

Common BE Deficiencies

- General deficiencies
- In vitro studies
- PK studies
- PD studies
- Comparative clinical endpoint studies

Common BE Deficiencies

- General deficiencies
- In vitro studies
- PK studies
- PD studies
- Comparative clinical endpoint studies

Common BE Deficiencies – General Deficiencies

- The test lots used in BE studies do not represent the proposed to-be-marketed/commercial products.
  - e.g., changes in formulation, device, manufacturing process, etc.
  - Specify differences between the test product used each BE studies and the to-be-marketed product
  - Additional bridging studies may be requested.
  - May discuss in pre-ANDA communications
- Retention samples

Common BE Deficiencies

- In vitro studies

SAC, APSD, spray pattern, plume geometry, priming and repriming

- Method validation
  - Testing method validation (all 5 studies)
  - Analytical method validation for HPLC (SAC, APSD, priming and repriming)
- Pivotal studies

Common BE Deficiencies for In Vitro Studies – Testing Method Validation

- Asked to provide method validation data using unexpired reference product
- Asked to use the method that is representative of the method used in the pivotal study
  - e.g. actuation method, analytical procedure

Common BE Deficiencies for In Vitro Studies – Testing Method Validation (cont'd)

- Asked to provide intermediate precision (by date and by analyst) data
- The acceptance criteria should be defined in the method validation standard operating procedure (SOP).
- If method validation and pivotal studies were conducted at different sites, method transfer studies (conducted using unexpired reference product) are needed.

Common BE Deficiencies for In Vitro Studies – HPLC Method Validation

- Incomplete method validation studies
  - Asked to validate
    - Accuracy
    - Precision/intermediate precision
  - Lower limit of quantitation (LOQ) was not covered by the linearity study.
    - Additional data/justification was requested
- If method validation and pivotal studies were conducted at different sites, method transfer studies are needed.

Common BE Deficiencies/Comments for In Vitro Studies - General

- Missing study information/document, asked to
  - Clarify the device orientation setup
  - Provide SOP that is effective at the time of the study
  - Provide the study data as SAS Transport files (i.e. .xpt format)

Common BE Deficiencies/Comments for In Vitro Studies – General (cont'd)

- Missing supporting information/document
  - For sample repeat (e.g. reinjection, repeat using the next actuation), asked to provide
    - SOP that pre-defined objective data acceptance criteria
    - Detailed reason of why the original assay was rejected
      - not just e.g. "minor analytical error"
    - Supporting documents for sample rejections
      - e.g. investigational report

Common BE Deficiencies for In Vitro Studies – SAC, APSD, and Priming and Repriming

- Missing study information/document, asked to
  - Provide 100% raw numerical data for all analytical runs (accepted and rejected) conducted during the HPLC sample analysis
  - Provide 20% of serially selected sample HPLC chromatograms
  - Specify how many quality control (QC) samples were used in each analytical run and at what concentration

Common BE Deficiencies for In Vitro Studies – Spray Pattern and Plume Geometry

- Missing study information

Example: Product-specific Guidance for Albuterol Sulfate MDI (Recommended Apr 2013; Revised Jun 2013; Dec 2016) – spray pattern study

Type of study: Spray pattern
Design: The spray pattern test should be performed at the B lifestage of the product and at two different distances from the actuator orifice. The selected distances should be at least 3 cm apart and based on the range of 3 to 7 cm from the R actuator mouthpiece.[4] Impaction (thin-layer chromatography plate impaction), non-impaction (laser light sheet technology), or other suitable method may be used to determine the spray pattern.
Additional comments: Spray pattern should be measured quantitatively in terms of

[4] The distance between the actuator orifice and point of spray pattern measurement should be same for T and R.

← Asked to specify whether this is the case for their ANDA

Common BE Deficiencies for In Vitro Studies – Spray Pattern and Plume Geometry (cont'd)

- Missing study information/document, asked to
  - Provide intensity profile for spray pattern and plume geometry studies
    - The intensity profile should include the formation and dissipation of the spray
    - For plume geometry study, the intensity profile should also include the frame selected for measurement
  - For plume geometry study, provide pre-specification of how plume angle and width were determined

Common BE Deficiencies

- General deficiencies
- In vitro studies
- PK studies
- PD studies
- Comparative clinical endpoint studies

Common BE Deficiencies for PK Studies

- Asked to address the impact of protocol deviations (e.g. dosing error) on the study outcome
- Other common BE deficiencies are similar to those for PK studies in ANDAs of e.g. solid oral dosage forms.

Common BE Deficiencies

- General deficiencies
- In vitro studies
- PK studies
- PD studies
- Comparative clinical endpoint studies

Common BE Deficiencies for PD Studies

- Incomplete study information, asked to
  - Specify the formulation of the test/reference placebo products used in the PD study
  - Provide case report forms of all subjects in the safety population
- For protocol deviations, asked to address the impact of protocol deviations on the study outcome

Summary

- Common BE deficiencies for in vitro, PK, and PD BE studies
- Many BE deficiencies are preventable by providing more complete supporting information/study data.

Review of Comparative Clinical Endpoint Studies for Orally Inhaled Drug Products

Outline

- General study design recommendations for comparative clinical endpoint studies
- Common deficiencies and helpful tips for comparative clinical endpoint studies

Why a Comparative Clinical Endpoint Study

- Incomplete understanding of relevance of results from in vitro studies to drug concentrations at local site of action (lung)
- Uncertainties regarding the correlation of in vitro and in vivo PK data to the clinical effects at site of action

Comparative Clinical Endpoint Study

- Patients with asthma or chronic obstructive pulmonary disease (COPD)
- Placebo run-in period
- Primary endpoint based on spirometry
  - Example: Forced expiratory volume in 1 second (FEV_1)
- Rescue medication use

Study Design Recommendations

- Follow recommendations in the product specific guidance
- Differences from product specific guidance may be acceptable but require justification and must be pre-specified
- Discuss comparative clinical endpoint study in pre-ANDA process

Differences from product specific guidance

- Study population
  - Age, required predicted FEV_1, percent FEV_1 reversibility criteria for asthma, non-US population
- Treatment duration
- Statistical analysis
  - Primary endpoint including baseline
  - Study population definitions
- Retention samples

Common Deficiencies

- Prohibited concomitant medications
- Rescue medication use
- Treatment failures
- Percent predicted FEV_1 inclusion criterion

Common Deficiencies

- Study drug compliance calculation
- Out of window study visits
- Bridging information
- Retention samples

Prohibited Concomitant Medications

- Use the product specific guidance
- Consider other concomitant medications that may affect evaluation of primary endpoint
  - Examples: Roflumilast, Montelukast, Ipratropium, Omalizumab, other medications indicated for asthma or COPD, etc.
- Medications listed as PRN – specify if subject actually used the “as needed” medication

Rescue Medication Use

- Pre-specify rescue medication use
  - Name and type
  - Amount and dose
  - Frequency
  - Reason(s) for use
  - Maximum allowable amount of rescue medication use
  - Limits on rescue medication use (example: prohibited within 6 hours of primary endpoint evaluation)
  - How subjects who exceed maximum allowable amount will be handled in statistical analysis

Rescue Medication Use

- Must control for rescue medication to avoid confounding variable
- Proper limits on rescue medication use
  - Consider recommendations in product specific guidance for wash-out period (6 hours for short-acting beta-agonist)
- Subjects who use rescue medication within 6 hours before spirometry evaluation that is used for *inclusion and exclusion criteria* and *primary endpoint evaluation* should be **excluded** from the Per Protocol population

Rescue Medication Use

- Provide “rescue medication data set” that includes date/time of each use of rescue medication for each subject

Subject ID	Rescue Medication	Rescue Medication Dose	Study Date	Study Day	Time Used	PP Population	MITT Population	Safety Population
10000000	Albuterol 90 mcg	1 puff(s)	2015-01-17	-1	0816	Y	Y	Y
10000000	Albuterol 90 mcg	1 puff(s)	2015-01-18	1	1626	Y	Y	Y
10000000	Albuterol 90 mcg	2 puff(s)	2015-01-18	1	1723	Y	Y	Y
10000001	Albuterol 90 mcg	6 puff(s)	2015-03-14	14	0931	N	Y	Y
10000001	Albuterol 90 mcg	1 puff(s)	2015-03-14	14	1115	N	Y	Y

- If rescue medication use is included in concomitant medication data set, clearly document which listings are rescue medication use

Note: Information is not from an actual ANDA

Treatment Failures

- Subjects discontinued due to “lack of efficacy”
- Important to ensure subjects with worst case scenario are included in statistical analysis and to avoid potential bias
- Important to pre-specify in study protocol
  - Definition (who they are)
  - Inclusion or Exclusion status in study populations (per protocol and modified intent to treat)
  - Statistical analysis (Last observation carried forward)

Treatment Failures Definition

- Need to consider when creating definition
  1) Reason for discontinuation
     - Examples: asthma exacerbation, lack of efficacy, etc.
  2) Adverse event
     - Examples: asthma exacerbation, worsening of asthma
  3) Required alternative therapy
     - Examples: rescue medication use, other prohibited concomitant medications (corticosteroids, etc.)
- Must complete at least X days/weeks of treatment with the study drug

Percent Predicted FEV_1 Inclusion Criterion

- Ensures subjects have the disease of interest and consistent criteria is being used to determine inclusion status
- Provide detailed information including exact formulas used to determine predicted FEV_1
- Formulas should be pre-specified and the same for all clinical sites

Percent Predicted FEV_1 Inclusion Criterion

Approach 1

- Example: "Based on NHANES III – Hankinson 1999"
  - **Not specific enough**
- Pre-specify and provide in study protocol the exact formula(s) based on NHANES III – Hankinson 1999 that investigators should program spirometry machine to use at each clinical site
  - Example: Caucasian male ≥ 20 years: predicted FEV_1 = 0.4678 + (0.1214 * Age^2) + (0.09542*$Height^2$)
- Limits possibility of different interpretation and formulas being used at different clinical sites

Percent Predicted FEV_1 Inclusion Criterion

Approach 2

- Pre-load same formula into spirometry machines and provide all clinical sites with Sponsor provided spirometry machine
- Still need to provide the actual formula(s) used at all clinical sites in study protocol and study report

Study Drug Compliance Calculation

- Improper calculation of expected doses and study drug compliance
- Study drug compliance = $\frac{\text{number of doses received}}{\text{number of expected doses}}$
- Number of expected doses
  - Based on study design
  - Same number for all subjects (does not change if subjects discontinue from study early)

Study Drug Compliance Calculation Example

- Subject received 18 doses of study drug
- Discontinued from study on Day 11
- Study duration is 28 days
- Study drug is taken twice a day

Study Drug Compliance Calculation Example

- Study drug compliance = $\frac{\text{number of doses received}}{\text{number of expected doses}}$
- Number of expected doses is 56 doses (2 doses per day times 28 days)…not 22 doses
- Study drug compliance = $\frac{18 \text{ doses received}}{56 \text{ expected doses}}$
- Study drug compliance = 32.1%

Out of Window Study Visits

- Windows for all study visits should be pre-specified in study protocol

Visits	Visit 0 Screening	Visit 1 Baseline	Visit 2	Visit 3
Days	9±2 Days before Visit 1	Day 0 days	Day 14±2 days	Day 28±2 days

- Pre-specified windows for study visits should be used in statistical analysis

Out of Window Study Visits

- Subjects who did not complete visit in which primary endpoint is evaluated within pre-specified visit window **should not** be included in the Per Protocol population for statistical analysis
- Subjects with out of window study visits for interim visits that *do not contribute* to primary endpoint evaluation may remain in Per Protocol population
- Important to minimize confounding factors

Bridging Information

- Changes in formulation, manufacturing, and device likely to occur during drug development process
- Examples
    - Filling overage
    - Blending process time
    - Individual device components
- Recommend to use the to-be-marketed (commercial) drug-device product in the comparative clinical endpoint study

Bridging Information

- Provide list of all differences in formulation, manufacturing, and any device component for drug-device used in the comparative clinical endpoint study compared to the:
    1) to-be-marketed (commercial) product
    2) other pivotal studies submitted in support of bioequivalence (PK studies, etc.)
- Provide justification including bridging studies in original ANDA submission for all differences
- Recommend to discuss major differences in pre-ANDA program

Retention Samples

- Follow CFR and FDA's for industry on *Handling and Retention of BA and BE Testing Samples (May 2004)*
- Requirements
  - **Quantity**
  - **Retain reserve samples from every shipment to all clinical sites** (including all subsequent shipments)
  - Others as listed in CFR and Retention Sample Guidance
- Potential for large number of shipments but all aspects of guidance and regulations still apply

Guidance for Industry

Handling and Retention of BA and BE Testing Samples

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2004
OGD

Retention Samples

- Develop retention sample process and procedures early on in design of comparative clinical endpoint study
- Discuss alternative approaches to *Retention Sample Guidance* in pre-ANDA program
- Important to ensure study integrity and public's trust in generic drugs

Summary

- Use the product specific guidance
- Discuss alternative approaches and significant differences in pre-ANDA program
- Justify differences from product specific guidance with adequate and scientifically sound justification

References

- Guidance for Industry Bioequivalence Recommendations for Specific Products
- Product Specific Guidances for Generic Drug Development
- Product-specific Guidance for Albuterol Sulfate MDI (Recommended Apr 2013; Revised Jun 2013; Dec 2016)


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