Clinical Endpoint Bioequivalence Study Review in ANDA Submissions

Ying Fan, Ph.D.

Disclaimer

This presentation constitutes an informal communication that represents the **best judgment of the speaker** at this time but does not constitute an advisory opinion, does not necessarily represent the **formal position** of U.S. FDA, and does not bind or otherwise obligate or commit the U.S. FDA to the views expressed.

Outline

- Background
  - Generic drug approval, ANDA vs. NDA, Bioequivalence (BE)
- Clinical endpoint bioequivalence study
  - What is it?
  - When to do it?
  - Who review it?
  - How do we review it?
- Special case: nasal sprays
- Questions

FDA U.S. FOOD & DRUG ADMINISTRATION

Background

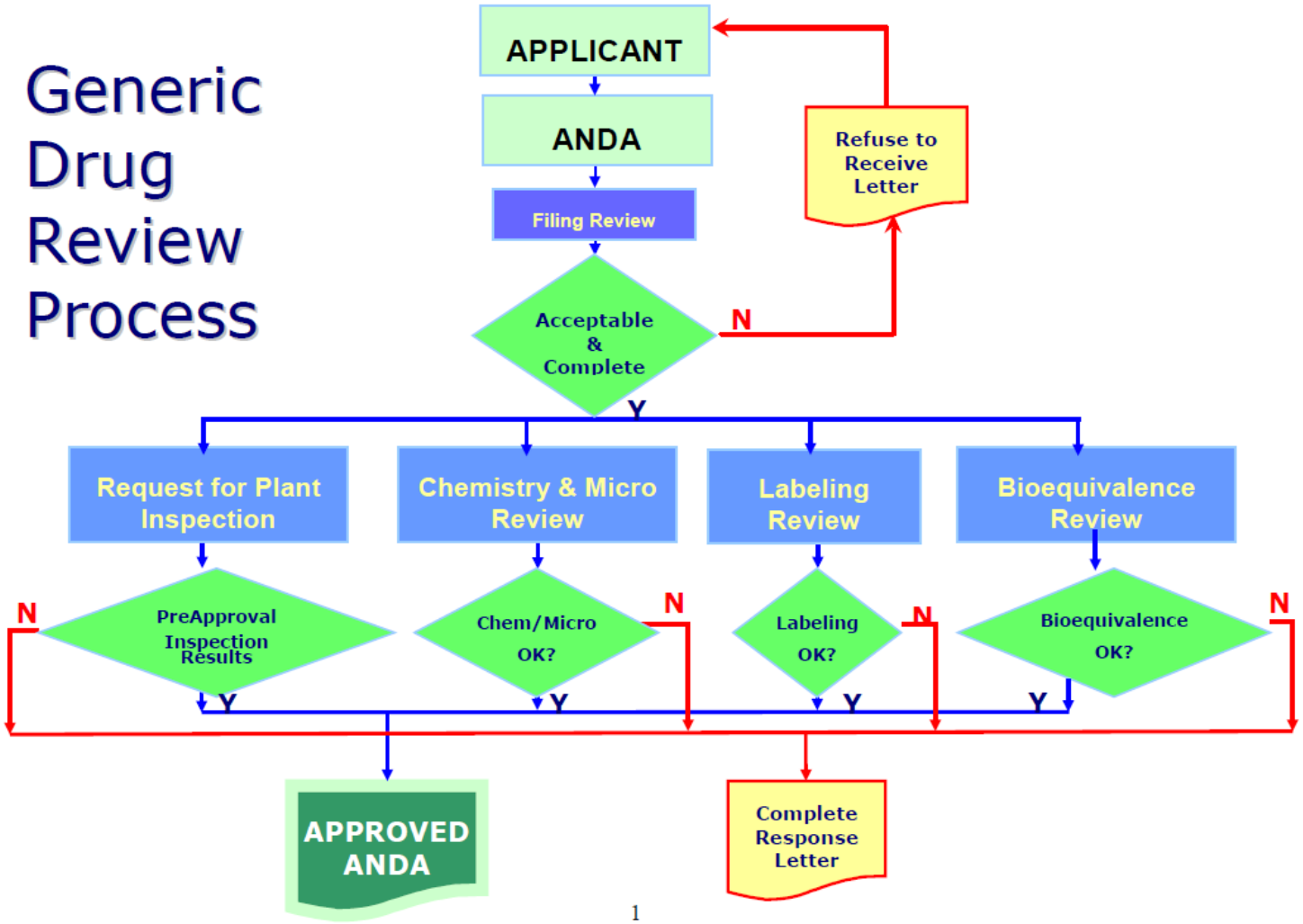
What is ANDA vs. NDA?

- ANDA:
  - Abbreviated New Drug Application
  - Application for approval of a generic drug
  - Reviewed by the Office of Generic Drugs (OGD) and Office of Pharmaceutical Quality (OPQ)
- NDA:
  - New Drug Application
  - Application for approval of a brand name drug
  - Reviewed by the Office of New Drugs (OND) and OPQ

What are the requirements for a generic drug?

- Same active ingredient(s)
- Same route of administration
- Same dosage form
- Same strength
- Same conditions of use
- Compared to reference listed drug (RLD) - (brand name product)

Generic Drug Review Process



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	

Bioequivalence (BE)

- 21 CFR 320.33 (a)(3)(b):
- "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".

Definitions relevant to generic drugs

Orange Book: A list of FDA approved drug products, including therapeutic equivalence (the basis for generic drug substitution) codes.

Bioequivalent Drug Products. Bioequivalence refers to equivalent delivery of the **same drug substance, in the same amount, to the intended site of action at an equivalent rate and extent as the RLD**.

Pharmaceutical Equivalents. Contain the **same active ingredient(s), in the same dosage form and route of administration, and are identical in strength or concentration**

Therapeutic Equivalents. Therapeutic equivalents are **pharmaceutical equivalents and can be expected to have the same clinical effect and safety profile** when administered to patients under the conditions specified in the labeling. Therapeutic equivalence may not be relevant for off-label uses.

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

Hatch-Waxman Act: US federal law which encourages the manufacture of generic drugs by the pharmaceutical industry and established the modern system of government generic drug regulation in US. (1984)

There were 3 basic mandates 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

Purpose of Bioequivalence (BE)

- Therapeutic equivalence (TE)
- Bioequivalent products can be substituted for each other without any adjustment in dose or other additional therapeutic monitoring
- The most efficient method of assuring TE is to assure that the formulations perform in an equivalent manner

Generic Drugs in Clinical Use

Therapeutic Equivalence = Substitutability

This decision is based on the Pharmaceutical Equivalence (same API, same dose form and route of administration) and Bioequivalence in the context of Clinical Use (delivery to the same site of action for the same indication).

Only when both factors are equivalent can the product be acceptable as a generic equivalent.

BE Evaluation of Generic Products

There are various approaches to demonstrate bioequivalence including:

- **Waiver**—for drugs that are qualitatively (Q1) and quantitatively (Q2) equivalent.
  - Q1: qualitative similarity (same components);
  - Q2: quantitative similarity (same amounts of the same components)
- **Pharmacokinetic Equivalence**—for drugs having a measurable plasma concentration curve.
- **Pharmacodynamic Equivalence**—for drugs where a PK evaluation is impossible or not relative to the therapeutic effect.
- **Clinical Endpoint BE —**for topically active 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 Clinical Endpoint BE studies

FDA U.S. FOOD & DRUG ADMINISTRATION

Clinical Endpoint BE Study

What is it clinical endpoint 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.

- Applies 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

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)

When to do a clinical endpoint BE study?

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

Study design

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

Design: a blinded, randomized, parallel study. A placebo arm is usually included in these studies in order to demonstrate that the study is sufficiently sensitive to identify a clinical effect.

- 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.

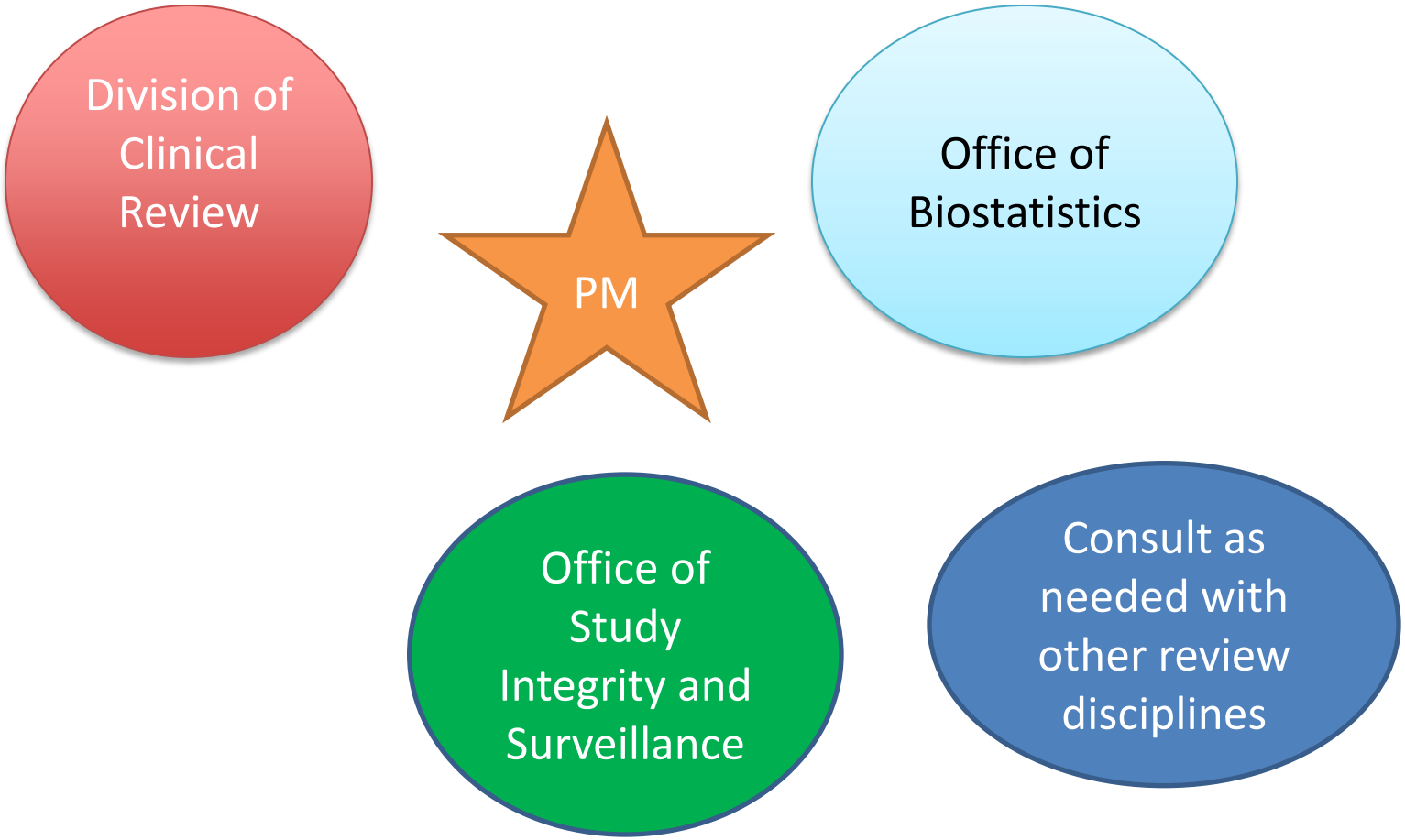
Study population

- Per Protocol (PP) Population: Used in the BE analysis
- Intend to Treat (ITT)/Modified ITT (MITT) Population: Used in the superiority analysis
- Safety Population: Used in the safety assessment

PK vs. Clinical Endpoint BE

PK Study	Clinical Endpoint BE Study
▪ Blood concentration	▪ Biomarker
▪ Healthy subjects	▪ Patients
▪ Single Dose	▪ Multiple Doses
▪ Test vs. Reference	▪ Test vs. Reference vs. Placebo
▪ AUC, CMAX, TMAX	▪ Primary endpoint
▪ 90% CI T/R	▪ 90% CI T/R or T-R
▪ 80-125% T/R	▪ 80%-125% T/R, +/-20% if T-R
▪ PP population	▪ (M)ITT population and PP population

Who reviews clinical endpoint BE studies?



Challenges

- Product-specific guidance may not be available
- Multiple treatment indications
- Time of measurement may not be sensitive to detect the difference between products
- Rating scale is subjective and variable
- Sample size is large
- Very expensive

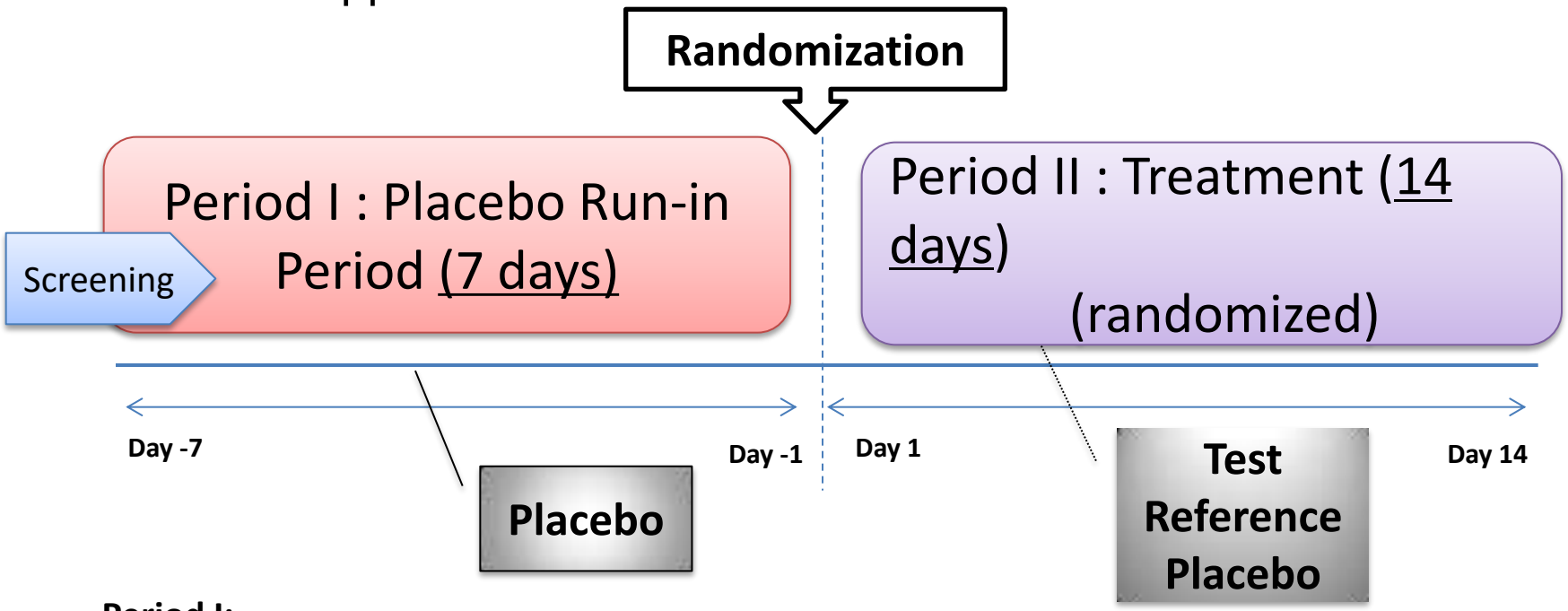
How do we review the clinical endpoint BE study?

- Study protocol (original, amendment)
- Study report (study design, inclusion/exclusion criteria, concomitant medications, protocol deviation/violation, adverse event (AE), etc.)
- Study population (PP population adjustment needed?)
- Statistical Review
- Formulation
- OSIS inspection report

Special case-
Nasal sprays

Study Design

Study design: double-blind, randomized, multi-center, placebo-controlled, parallel-group
Indication: Seasonal Allergic Rhinitis (SAR) patients
Treatment: Test; reference listed drug (RLD); Placebo
Dose: lowest approved dose



Period I:
An initial single-blind, placebo run-in period
(why? establish a baseline and to identify placebo responders) (next slide)

Period II:
A double-blind, randomized, placebo-controlled, parallel group

Evaluation
-Score System

- Self-score symptoms twice daily (AM and PM, 12 hrs apart)
- Immediately prior to each dose
- Symptoms: runny nose, sneezing, nasal itching, and congestion

Score	Description
0	absent (no symptom evident)
1	mild (symptom clearly present, but minimal awareness; easily tolerated)
2	moderate (definite awareness of symptom that is bothersome but tolerable)
3	severe (symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

Evaluation
-Terminology

- Total nasal symptom score (TNSS): Sum of each individual symptom rating of runny nose, sneezing, nasal itching, and congestion

- Reflective total nasal symptom score (rTNSS): Total nasal symptom score reflect the previous 12 hr

- Instantaneous total nasal symptom score (iTNSS): Total nasal symptom score at the time of evaluation

Primary and secondary endpoints

- Primary endpoint:
  - Change from the baseline mean rTNSS to the treatment mean rTNSS, expressed in the absolute units
    - Change from Baseline in rTNSS = (Baseline mean rTNSS) – (Treatment Mean rTNSS)

- Secondary endpoint:
  - Change from the baseline mean iTNSS and the treatment mean iTNSS, expressed in the absolute units
    - Change from Baseline in iTNSS = (Baseline mean iTNSS) – (Treatment Mean iTNSS)

Study Population

- Per Protocol (PP) population: all randomized subjects who meet all inclusion/exclusion criteria, take a pre-specified proportion of the scheduled doses, record a prespecified number of qualifying rTNSS scores, and complete the evaluations as prespecified in the protocol, with no protocol violations that would affect the treatment evaluation. (used in BE analysis)
- Modified Intend-to-treat (MITT) population: all randomized subjects who received at least one dose of assigned product. (used in superiority analysis)
- Safety population: all randomized subjects who received at least one dose of study product. (used in safety assessment)

PK vs. Clinical Endpoint BE

PK Study	Clinical Endpoint BE Study
▪ Blood concentration	▪ Nasal symptom score
▪ Healthy subject	▪ Patient
▪ Single Dose	▪ Multiple Doses
▪ Test vs. Reference	▪ Test vs. Reference vs. Placebo
▪ AUC, CMAX, TMAX	▪ rTNSS, iTNSS
▪ 90% CI Test/Reference	▪ 90% CI Test/Reference
▪ 80-125% Test/Reference	▪ 80%-125% Test/Reference
▪ PP population	▪ (M)ITT population and PP population

Summary

- Generic drug approval: ANDA submission
- Clinical endpoint study
  - Definition:
    - 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.
    - Applies 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.
  - Study design: blinded, randomized, parallel study
  - Treatment arms: Test, Reference, Placebo
  - Statistical analysis:
    - BE analysis
    - Superiority analysis

Questions?