Fundamentals of Bioequivalence

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This presentation represents the personal opinions of the speaker and does not necessarily represent the views or policies of US FDA

Intent of Talk

- **Present basics of bioequivalence for the non-scientist**
- **Review fundamental terms, definitions, and concepts**
- **Provide tools for improved interactions**

What will we cover?

- Meaning and context of "bioequivalence"
- How bioequivalence is assessed
- Examples
- Challenges today
- Common deficiencies

What are generic drugs?

"… therapeutically equivalent drug products that can be substituted at the pharmacy level for the reference listed drug (RLD), and each other, without any adjustment in dose or other additional therapeutic monitoring."

Reference listed drug (RLD)

- Drug against which proposed generic must be compared
- Usually the "innovator drug" (but sometimes another generic drug)
- RLDs listed in the "Orange Book"
  - ("Approved Drug Products with Therapeutic Equivalence Evaluations")

Substitutability

- **Generic drugs must be:**

  –*pharmaceutically equivalent*

  –*bioequivalent*

Pharmaceutical equivalence

- same active ingredient(s)
- same dosage form
- same route of administration
- identical in strength or concentration

Pharmaceutical equivalence is not enough!

Pharmaceutical equivalence does not necessarily mean equivalent performance

Generics not necessarily identical

- **Certain differences allowed**
  - **excipients can be different**
  - **manufacturing differences**
  - **different formulations**
  - **shape, color can vary**

Role of Bioequivalence

- **Demonstrates the pharmaceutically equivalent drug product performs the same way as the RLD**

- **Reaches the intended site of action at the same *rate* and *extent of absorption* as the RLD.**

Bioequivalence

"Pharmaceutically equivalent drug products whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions in either single or multiple doses."

To reiterate:

Bioequivalence means that the formulation of the pharmaceutically equivalent generic drug performs in the same way (same efficacy and safety profile) as the RLD

No worse and no better!

Science of bioequivalence

- **Developed over the last few decades**
- **Continues to evolve**
- **Specific approaches depend on many factors**
- **Can be straightforward or quite complex**

What do the regulations say?

- **According to 21 CFR 320.24(b), the ways to assess bioequivalence are:**
  - **In vivo measurement of active moiety or moieties in biologic fluid**
  - **In vivo pharmacodynamic comparison**
  - **In vivo limited clinical comparison**
  - **In vitro comparison**
  - **Any other approach deemed appropriate by FDA**

The regulations also state that:

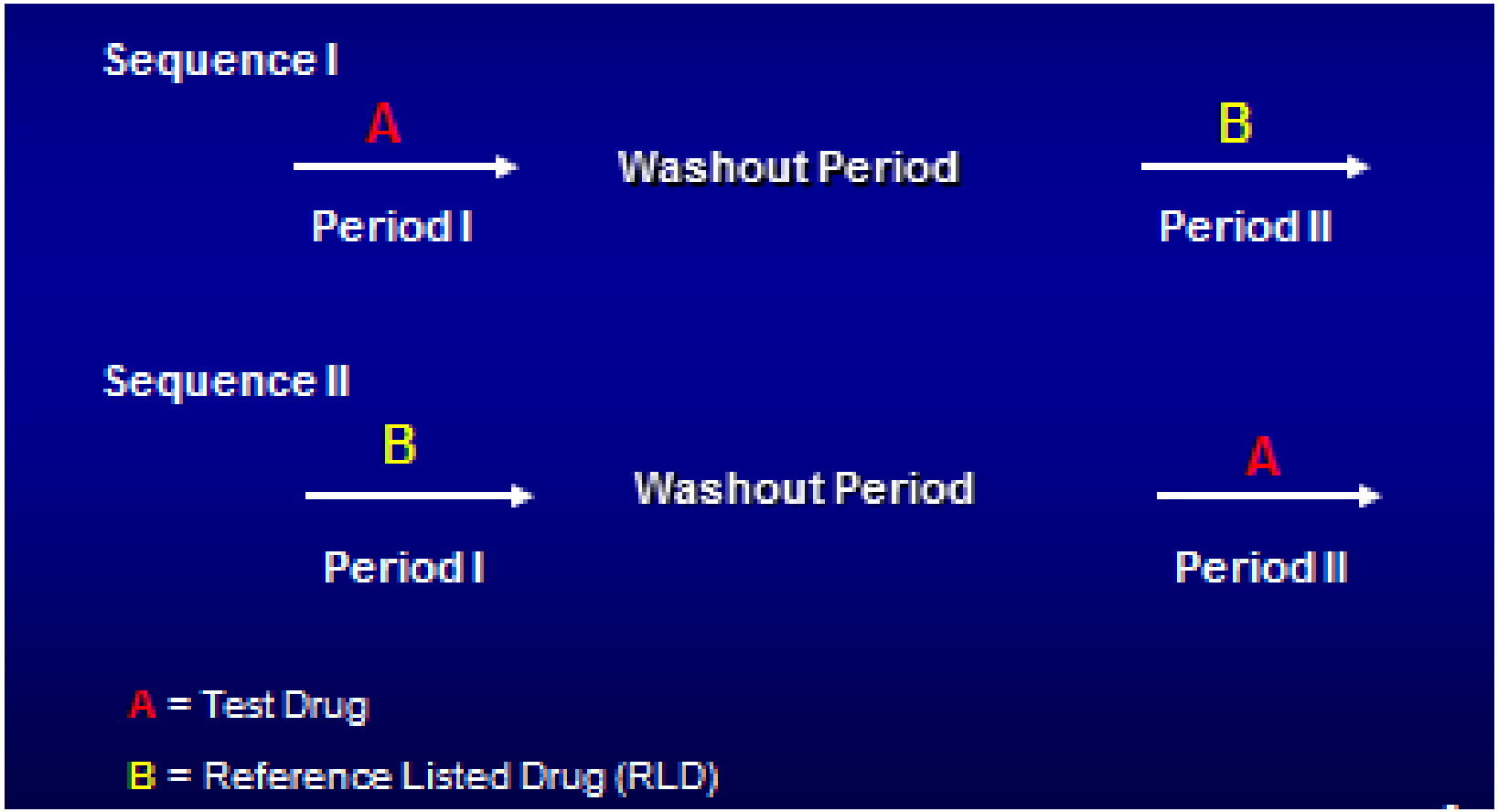
- **Applicants must conduct bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in 21 CFR 320.24.**

- **FDA is also mindful of the feasibility of our recommended approaches**

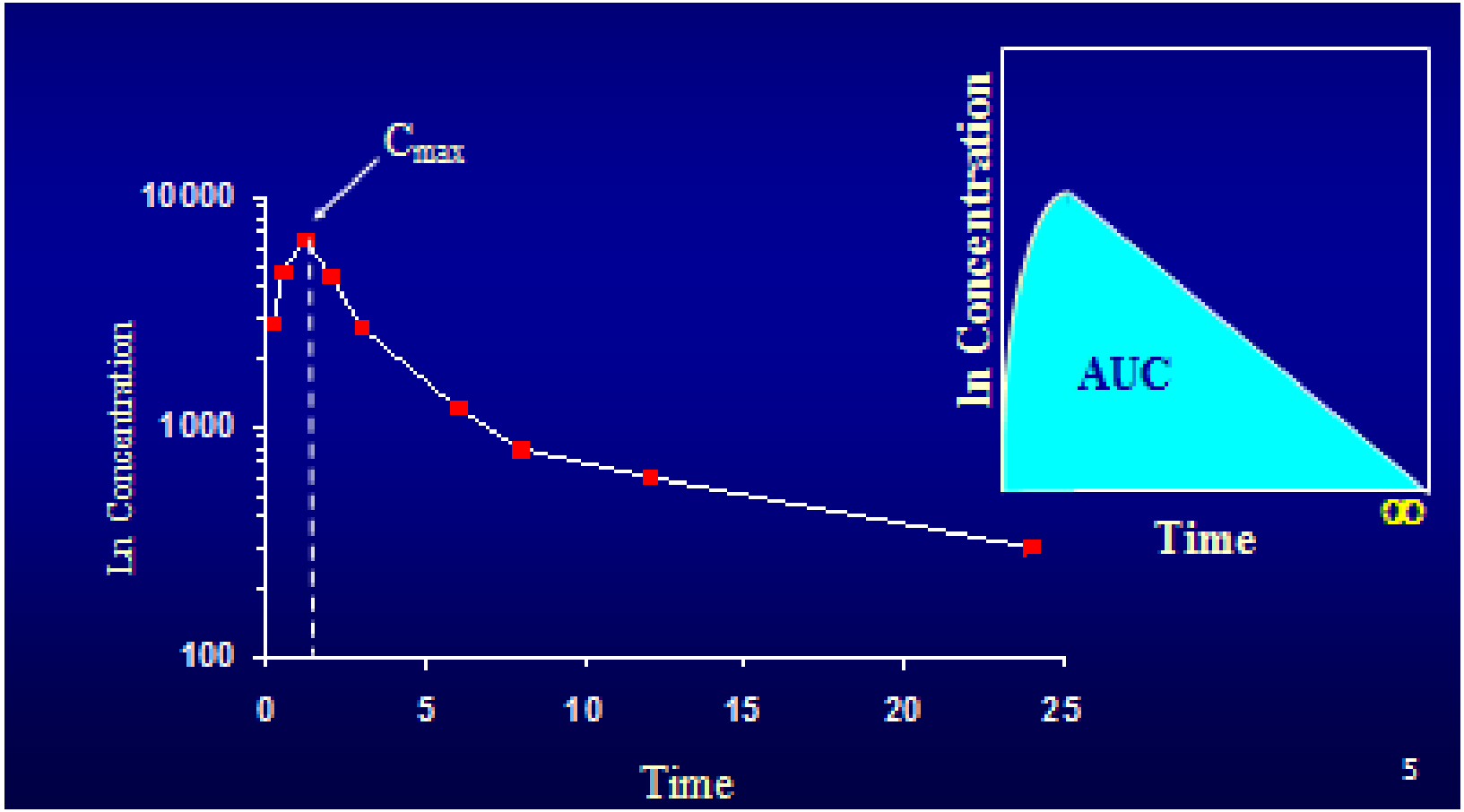
In vivo measurement of active moiety or moieties in biologic fluid

- **"A BE study with pharmacokinetic (PK) endpoints."**
- **Measurements of the active moiety (or metabolite) in a biological fluid in humans.**
- **the most common, sensitive, accurate, reproducible, and efficient method**
- **the gold standard**

Single Dose Two-Way Crossover Design



What is measured: Cmax and AUC



Bioanalytic Considerations

- **Critical that proper methods used, validated, and all data submitted**
- **Considerations of the assay used include:**
  - **Accuracy**
  - **Precision**
  - **Selectivity**
  - **Sensitivity**
  - **Reproducibility**
  - **Stability**

Critical aspect of the review

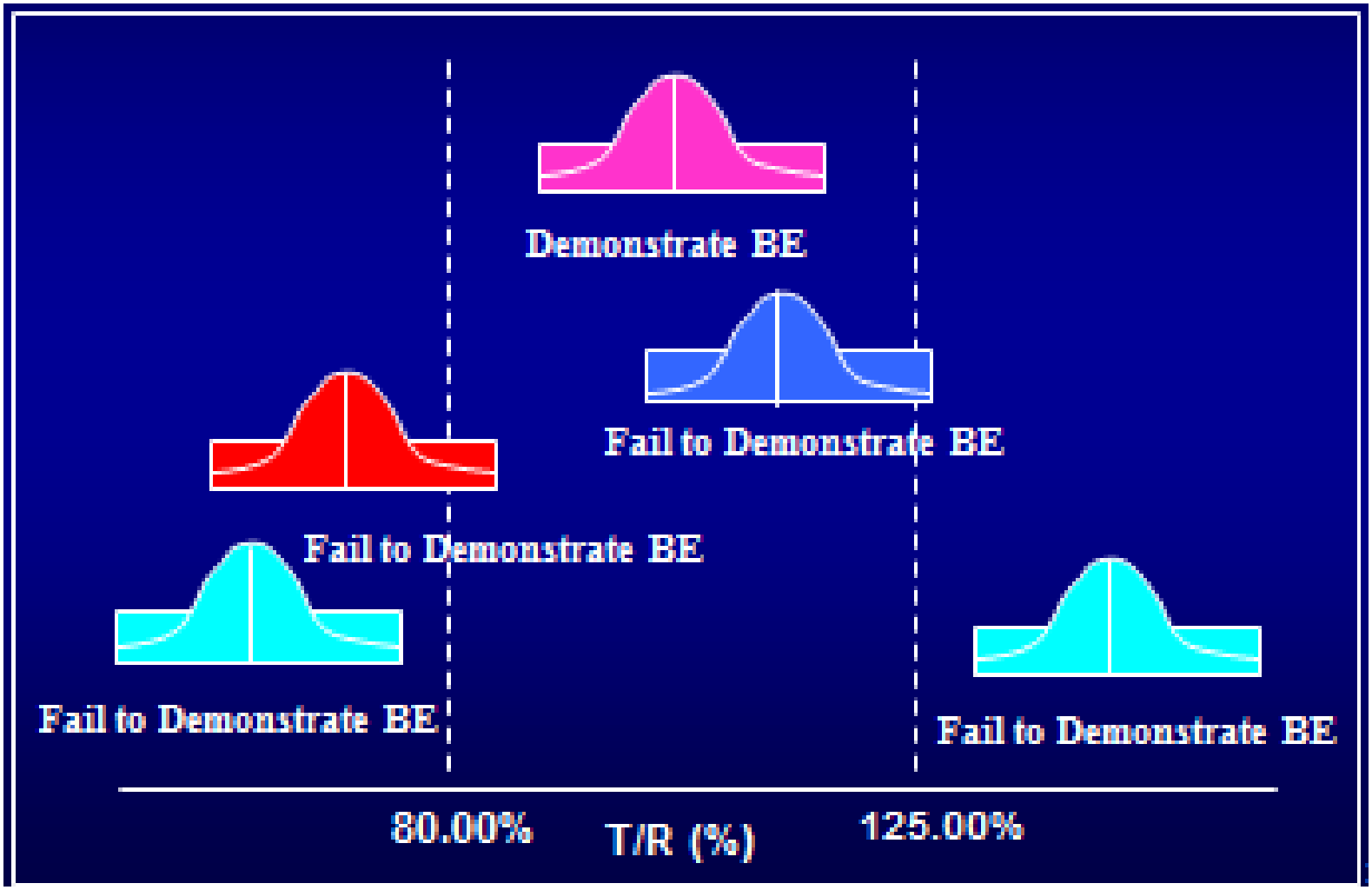
Statistical considerations

- **Critical that data analyzed properly**
- **Unique stat approaches used for BE studies**
- **Fundamental approach**
  - **AUC (area under the curve) measured**
  - **Cmax (maximum concentration) measured**
  - **Data often log transformed (LAUC and LCmax)**
  - **90% Confidence Intervals (CIs) calculated**
  - **CI must be between 80-125%**

Typical Summary of PK study data

Drug A Tablets Dose (1 x 100 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. 12345				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng.hr/ml)	6926.21	7073.05	0.98	88.52-108.32
AUC∞ (ng.hr/ml)	7272.94	7442.56	0.98	88.79-107.55
Cmax (ng/ml)	1014.78	1067.66	0.95	87.18-103.62

Possible BE Results (90% CI)



Bioequivalence study with pharmacokinetic (PK) endpoints

- **Two PK studies usually recommended:**
  - **One in the fasting state.**
    - **The most sensitive and accurate way to evaluate the formulation**
  - **One is in the fed state.**
    - **Assures the drug product performs the same way in the presence of food**
- **Sometimes BE in presence of alcohol (alcohol dose dumping studies)**

Alternative PK study designs

- **Replicate designs**
  - **3 way crossover**
  - **4 way crossover**
- **Parallel designs**
  - **No crossover; two separate populations compared**
- **Multiple dose steady–state studies**
- **Studies in patients (rather than healthy volunteers)**

Alternative statistical analyses

- **Alternative statistical approaches**
  - **Adjustments must be made for alternative study designs**
  - **Partial AUCs**
  - **Reference scaling**
  - **Other techniques and permutations on basic approach**

In vivo pharmacodynamic (PD) comparison

- **"A BE study with PD endpoints."**
- **Used when PK study is not possible or not relevant**
- **Carefully chosen biological or physiological response measured**
  - **e.g. air flow into the lungs after administration of an asthma drug**
- **Not commonly done; not as sensitive to formulation differences**

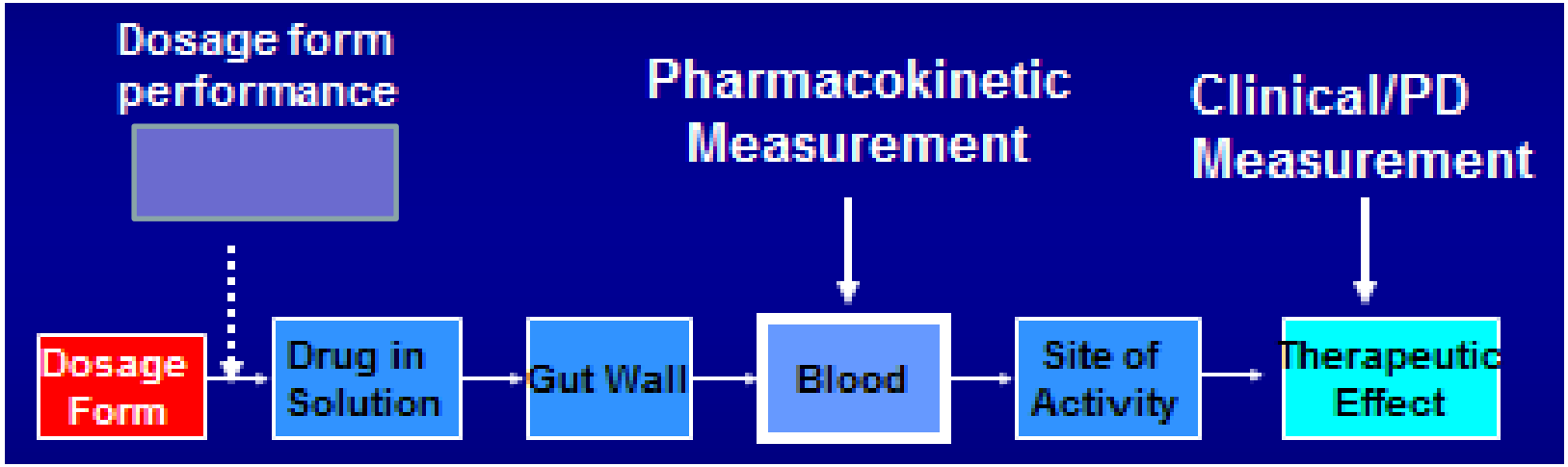
In vivo limited clinical comparison

- "A BE study with clinical endpoints"
- Usually done when PK and PD studies not possible
- Clinical outcome measured
  - e.g. reduction in allergy symptoms from a nasal spray
- Less precise and accurate than previous approaches
- Time consuming and expensive

BE studies with a PD or clinical endpoint also have unique:

- Study designs
- Methodological issues
- Statistical analyses
- Analytic issues

Measuring Oral Dosage Form Performance



In vitro comparisons

- **Variety of laboratory tests**
  - **Measures and compares some attribute of drug product in laboratory conditions**
  - **e.g. dissolution testing measures how fast a drug product dissolves into solution**
- **In vitro testing can help establish bioequivalence**
- **An in vitro test may be correlated with in vivo performance (“IVIVC”)**
  - **When available, IVIVC powerful tool**

Any other approach deemed appropriate by FDA

- Broad, open ended category
- Provides FDA wide latitude in developing and utilizing other methods or combinations of methods
- Increasingly important today with new more complex drug products

Biowaivers

- **In certain situations in vivo BE testing can be waived:**
  - **Parenteral solutions**
  - **Opthalmic and otic solutions**
  - **Gasses administered by inhalation**
  - **Solutions for application to the skin, oral solutions, elixirs, syrups, nasal solutions**
- **Different strengths (provided the same formulation and proportionally similar)**
- **A few other situations**

Not re-evaluating safety and efficacy!

- **Purpose of bioequivalence often misunderstood**
- **Safety and efficacy already established**
- **Not repeating these studies**
- **Rather, evaluating whether the proposed generic drug product is sufficiently similar**

A different approach from assessing a new drug

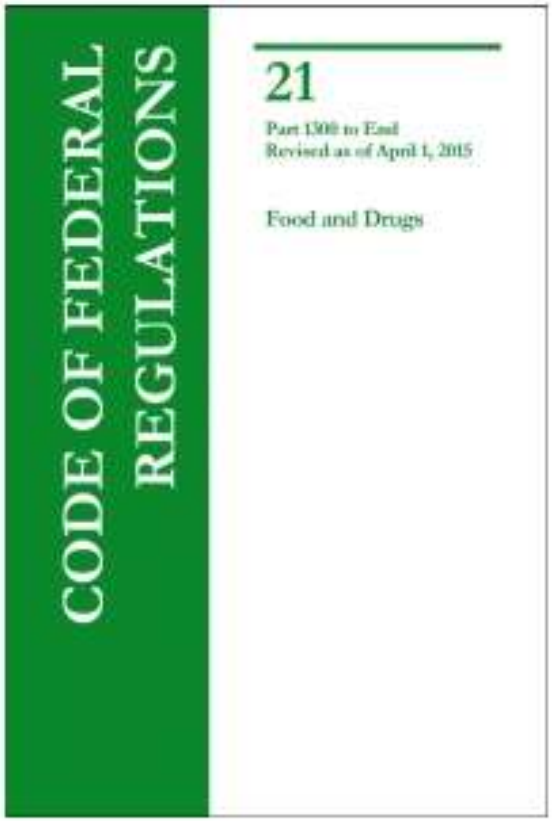
- BE studies designed to evaluate generic drug sameness
- PK studies the gold standard when possible
- Purpose of clinical studies (when necessary) to show drug is reaching intended site of action at the same rate and to same extent as RLD

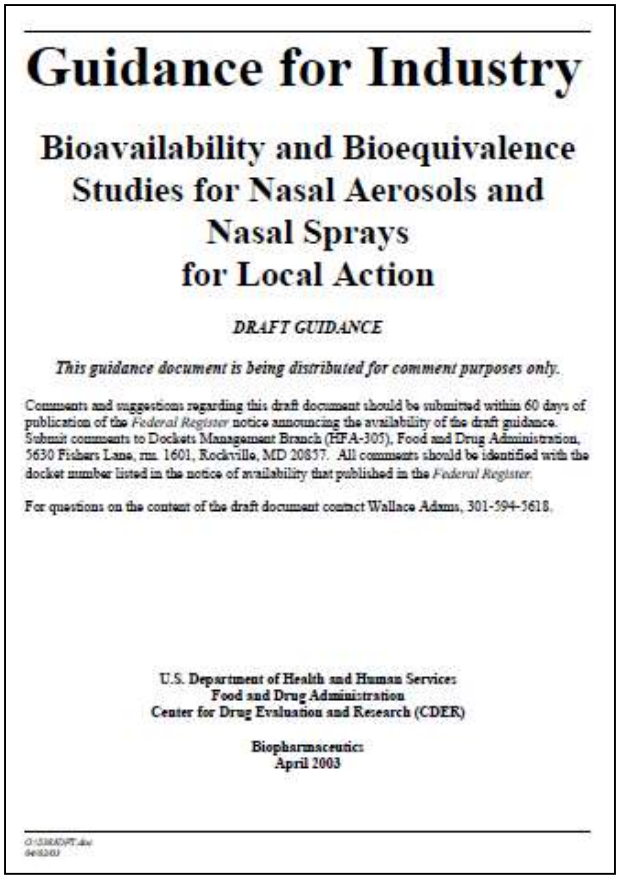
Many different approaches needed

- **Injectable solutions**
- **Solid oral dosage forms--immediate release**
- **Solid oral dosage forms-- modified release**
- **Transdermal systems and patches**
- **Creams and ointments**
- **Nasal and Oral Inhalation Products**
- **Peptide products**
- **Nano-products**

How do you know the best current approach?

- **Regulations (21 CFR 320)**
- **General Guidances**





Guidance for Industry

Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1601, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability that published in the *Federal Register*.

For questions on the content of the draft document contact Wallace Adams, 301-594-5618.

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

Biopharmaceutics
April 2003

Product Specific Recommendations for Generic Drug Development

Contains Nonbinding Recommendations

Draft Guidance on Fluticasone Propionate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Fluticasone propionate

Dosage Form; Route: Metered, spray; nasal

Recommended Studies: In vitro and in vivo studies

The Agency recommends the following in vitro and in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) nasal spray containing fluticasone propionate.

Example 1: Injectable antibiotic in solution

- Simplest example
- A parenteral solution intended for injection must be “Q1/Q2”
  - Qualitatively the same
  - Quantitatively the same
- Covered in regs; guidance not necessary

21 CFR §320.22(b)(1)

Example 1: Injectable antibiotic in solution

- **Applicant presents evidence of formulation, in vitro studies, manufacturing process, etc.**
- **If criteria met (Q1/Q2), BE is assumed; no BE testing necessary.**
- **A "biowaiver" granted and product approved (from BE standpoint)**

Example 2: Antibiotic in oral solution

- **Similar, but per the regs (21 CFR §320.22(b)(3)) a generic oral solution can contain different excipients**
- **If Q1/Q2, same as previous example**
- **If not Q1/Q2, the different excipients must not impact absorption or safety**

Example 2: Antibiotic in oral solution

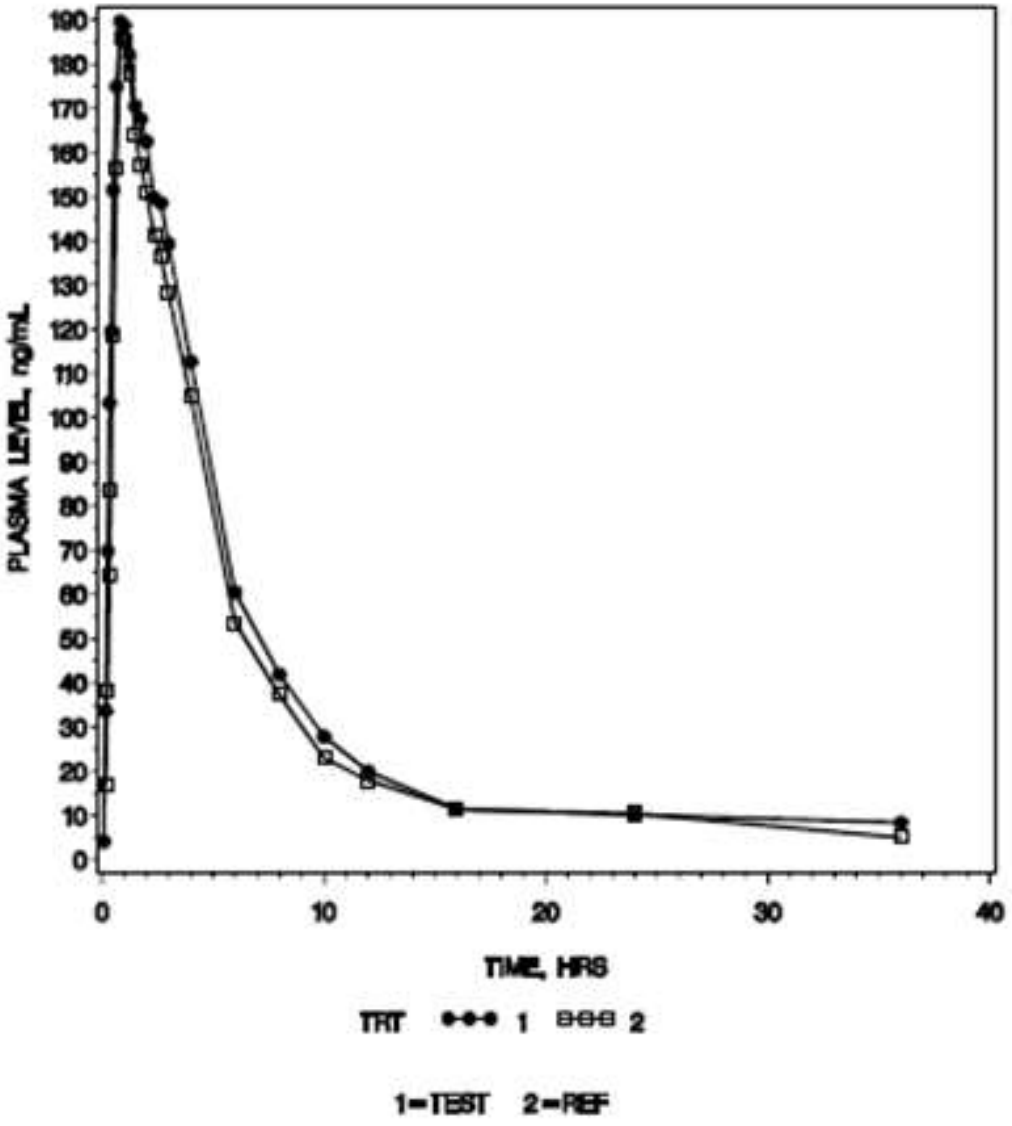
- Again, applicant provides data (and justifications if different excipients used)
- If criteria met, again no BE testing necessary
- A biowaiver granted and product approved
  - If question about excipients, BE testing could be required

Example 3: Tablet A, Immediate release solid oral dosage form for pain relief, 10 and 5 mg

- Most common scenario
- FDA's product specific guidance for Tablet A recommends:
  - Single dose, two way crossover using the 10 mg strength in normal fasting and fed healthy volunteers
  - Active ingredient measured in plasma over time
  - Testing of 5 mg strength can be waived (biowaiver) if certain criteria met

Example 3:

PK curves for Tablet A and RLD



Example 3: Tablet A, Immediate release solid oral dosage form, 10 mg

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	936.40	827.62	1.13	105.56	121.27
LAUCI	962.92	852.37	1.13	105.40	121.09
LCMAX	234.38	215.30	1.09	101.02	117.32

Extent of absorption: AUC-- area under the curve
Rate of absorption: Cmax-- maximum concentration

The ratio of the test measurement to the reference listed drug measurement must fall within a confidence interval of 80-125%

Example 3: Tablet A, Immediate release solid oral dosage form for pain relief, 10 and 5 mg

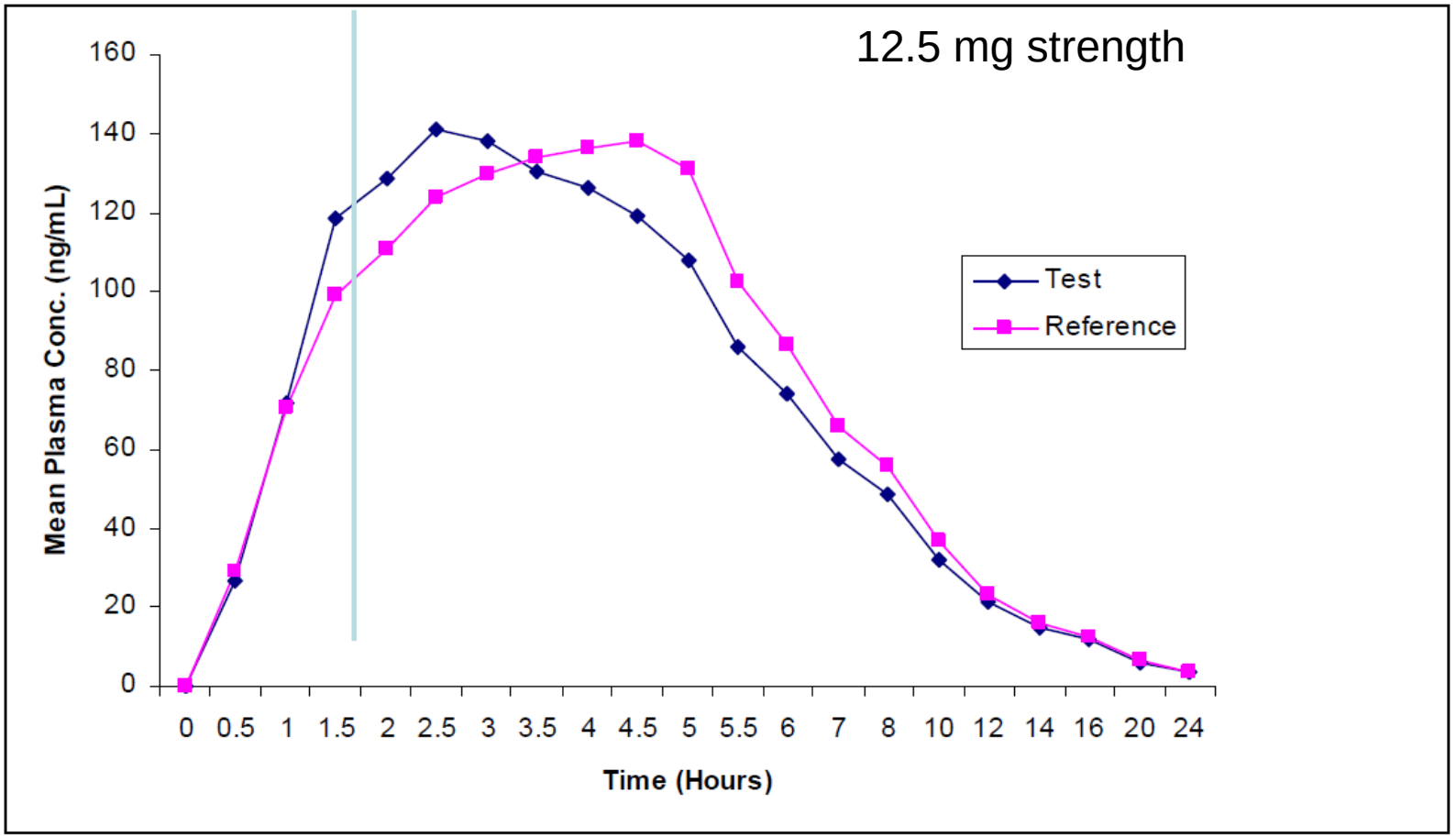
- **Adequate from a BE perspective**
  - **Fasting and fed PK studies adequate**
  - **Cmax and AUC within 80-125 CI**
  - **Bioanalytics in order**
  - **Statistical analysis appropriate**

- **5 mg strength granted biowaiver**

Example 4: Tablet Aex, Extended release solid oral dosage form, 6.25 mg and 12.5 mg

- **Immediate release and extended release components**
- **Per FDA's product specific guidance, similar studies**
  - **except more detailed analysis of PK profile**
  - **"Partial AUCs"– different time periods in the PK curve analyzed separately**

Example 4: Tablet Aex, Extended release solid oral dosage form, 12.5 mg



Example 4: Tablet Aex, Extended release solid oral dosage form, 12.5 mg

[redacted] Tablets Extended Release, 1 x 12.5 mg Fasting Bioequivalence Study No. [redacted] N=15 (Male=10 and Female=5) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
$AUC_{0-1.5}$ (ng·hr/mL)	173.84	169.16	1.03	87.60	120.55
$AUC_{1.5}$-t (ng·hr/mL)	781.91	866.10	0.90	80.49	101.26
AUC∞ (ng·hr/mL)	1094.10	1149.57	0.95	87.05	104.06
Cmax (ng/mL)	203.98	179.08	1.14	107.22	121.00

Example 4: Tablet Aex, Modified release solid oral dosage form, 12.5 mg

- **Adequate from a BE perspective**
  - **Fasting and fed PK studies adequate**
  - **Cmax and AUCs within 80-125 CI**
  - **Bioanalytics in order**
  - **Statistical analysis appropriate**

- **6.25 mg strength granted biowaiver**

Example 5: "Nasex" steroid nasal spray for allergic rhinitis

- **Challenging to establish BE**
  - **Locally acting product**
  - **Site of action is nasal mucosa**
  - **Minimal (but some) systemic absorption of active ingredient**
  - **Administered by a spray bottle**
    - **thus, a drug-device combination**
- **Basic BE study with PK endpoint not adequate for establishing BE**

Example 5: Nasex nasal spray

- **Per FDA's both general and product specific guidance:**
- **"Weight of Evidence" approach including:**
  - **Series of in vitro studies**
    - **Single Actuation Content. A series of tests to assure the generic spray bottle performs the same as the reference**
    - **Droplet Size Distribution by Laser Diffraction**
    - **Drug in Small Particles/Droplets**
    - **Spray Pattern**
    - **Plume Geometry**
    - **Priming and Repriming**

Example 5: Nasex nasal spray

- **In addition:**
  - **BE study with PK endpoint**
    - **Single dose 2 way crossover design**
    - **Done for safety reasons (potential systemic absorption of steroid)**
    - **Not to evaluate delivery of active moiety to site of action**
  - **BE study with clinical endpoints**
    - **A randomized, double-blind, three-arm, placebo-controlled, parallel group study**
    - **Evaluation of clinical effect**
    - **Only way to evaluate delivery of drug to site of action**

Example 5: Nasex nasal spray

- **Very challenging product**
- **Multi-pronged approach to establishing BE using PK, clinical and in vitro studies**
- **Much data for applicant to generate and for FDA to review**
- **If all of this in order– approved from BE perspective**

Challenges Today

- Other locally acting drug products
- Transdermal systems and patches
- Complex formulations (osmotic pumps, modified release, liposomes, microspheres)
- Drug-device combinations
- Small peptides
- Nano-products

Factors in Determining Approach to Bioequivalence

- **Mechanism of drug delivery and release**
- **Intended site of action**
- **Formulation design and composition**
- **Ability to measure drug availability systemically or at the site of action**
- **Available in vivo and in vitro tests**
- **Others**

Applicants must conduct bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in 21 CFR 320.24.

Recommendations

- **Follow the CFR and FDA's guidances and recommendations**
- **Alternative approaches allowed but require justification**
  - **We recognize that industry has been a partner in developing new approaches, particularly in newer challenging areas**
- **Select quality Contract Research Organizations (CROs) to execute your studies**

Submit Quality Applications

- **Incomplete or faulty applications result in more work for everyone**
  - **In FDA's and your interests to submit high quality applications**
  - **Quickest path to approval**
- **Office of Bioequivalence has evaluated common deficiencies in ANDAs over last decade**

Common BE Deficiencies

- **Bioanalytic Issues**
  - **inappropriate methods used**
  - **failure to validate method (particularly long-term stability)**
- **Data missing, incomplete, or incorrect format**
- **Inappropriate statistical analysis**
  - **Lack of explanation for subject exclusions, determination of outliers, use of alternative methods**
- **Inappropriate reanalysis**
- **Failure to use or follow SOPs**

Summary

- **Generics are pharmaceutically equivalent but not necessarily identical**
- **Bioequivalence assures the generic formulation performs the same**
  - **Active moiety reaches site of action at same rate and to same extent**
- **Thus, a generic drug is therapeutically equivalent and substitutable**

Summary

- **Bioequivalence study with PK endpoints is the best approach for most products**
- **However, wide variety of other approaches**
- **Follow FDAs guidances and recommendations**
- **Avoid common deficiencies and submit quality applications**

Final thoughts

- **References and links attached**
- **Hope this provides insight, terminology, and other material that will be useful**
- **Hope this allows you to work more effectively with your internal science staff, contractors, and FDA**

Links to CFR and Guidances

- **21 CFR 320: BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS**
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=320
- **General Generic Drug Guidances**
  - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064995.htm
- **Product Specific Recommendations for Generic Drug Development**
  - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

Thank You!

Questions?

surveymonkey.com/r/GDF-D1S3

References for BE Deficiencies

- Liu Q, Davit BM, Cherstniakova SA, et al. Common deficiencies with bioequivalence submissions in abbreviated new drug applications assessed by FDA. AAPS J. 2012 Mar;14(1):19-22
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- Chimalakonda K, Saraf P, Patel D et al. Common Deficiencies in Abbreviated New Drug Applications with In vitro Bioequivalence Studies. Poster at AAPS Conference 2015
- Saraf P, Chimalakonda K, Patel D, et al. Common Deficiencies in Abbreviated New Drug Applications for Nasal Spray and Aerosol Drug Products. Poster at AAPS Conference 2015