Putting it all together: Building a Defensible, Totality-of-Evidence Approach for the Demonstration of Bioequivalence for Locally-Acting Drugs

Charles E. DiLiberti
Montclair Bioequivalence Services, LLC
charlie@montclairbe.com
Chair, Generic Pharmaceuticals Focus Group

Disclaimer

• All information provided here, in any form, represents the opinions of Montclair Bioequivalence Services, LLC and may not, in any way, be construed as legal, regulatory, investment, medical, or pharmacological advice.

• Montclair Bioequivalence Services, LLC and Charles E. DiLiberti make no representation or warranty, express or implied, as to the accuracy or suitability for any purpose of any of the information presented here.

• Montclair Bioequivalence Services, LLC and Charles E. DiLiberti may not be held liable for any losses incurred as a result of any use of any of the information presented here.
Legal definitions of bioavailability and bioequivalence (21 CFR 320.1)

(a) **Bioavailability** means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

(e) **Bioequivalence** means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

- These definitions hinge on drug availability at the site of action

Systemic vs. Local Action

- **Systemically acting drug product**
  - Site of drug absorption (e.g., gut wall) → Bloodstream → Site of drug action (e.g., brain)
  - Drug concentrations in blood (plasma) easy to measure and good proxy for drug concentrations at site of action

- **Locally acting drug product**
  - Site of drug application (e.g., skin-epidermis) → Site of drug action (e.g., skin-dermis) → Bloodstream
  - Drug concentrations at site of action difficult or impossible to measure
  - Historical reluctance to use drug concentrations in plasma as proxy for drug concentrations at the site of action – not always quantifiable, and blood is downstream from site of action
Conventional tools for establishing BE for locally acting drug products – 1

• Clinical endpoint BE studies
  ▪ Measure clinical response (efficacy) in patients
  ▪ Test product (T) vs. Reference product (R) vs. Placebo (P)
  ▪ T must be superior to P
  ▪ R must be superior to P
  ▪ T must be equivalent to R:
    ▪ 90% CI for ratio of T/R clinical responses within 80 – 125% (quantitative endpoints: e.g., scores, lesion counts) or
    ▪ 90% CI for T – R difference in cure rates within ± 20% (dichotomous endpoints: cure rates)
  ▪ Mainstay for most locally-acting drug products

• “Pharmacodynamic” (PD) studies
  ▪ Measure acute pharmacological effect [topical corticosteroids, inhalation (bronchodilators), GI (orlistat)]
  ▪ Normal healthy volunteers or patients (case by case)

Conventional tools for establishing BE for locally acting drug products – 2

• Tissue PK BE studies
  ▪ Aqueous humor PK studies on ocular drugs used in conjunction with cataract surgery
  ▪ One concentration/time point per patient

• Systemic PK BE studies
  ▪ Used where feasible and applicable, e.g., inhalation, vaginal, some GI, some topical, etc.
  ▪ Often aimed at ensuring safe systemic exposure levels
  ▪ Sometimes used to ensure comparable distribution of drug to target tissues (e.g., mesalamine)
Conventional tools for establishing BE for locally acting drug products – 3

- In vitro BE studies – used to:
  - Ensure equivalent delivery from delivery/metering device (e.g., inhalation)
  - Ensure comparable drug product performance at site of action (e.g., in vitro binding studies for locally acting GI products, particle size, etc.)
  - Ensure equivalent drug product distribution [e.g., inhalation, in vitro dissolution testing for locally acting GI (e.g., mesalamine, vancomycin)]
  - Ensure equivalent arrangement of matter within drug product (Q3) (comparative in vitro characterization of complex formulations)

Conventional BE strategies – 1

- Clinical endpoint BE study-based
  - Sometimes together with PK study and/or in vitro BE studies
  - By far, the most common approach, however:
    - “This approach is the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence.”
    - 21 CFR 320.24(b)(3)
- PD study-based
  - Standard approach for topical corticosteroids
  - Rarely used elsewhere [e.g., inhalation (bronchodilators), orlistat]
  - Sometimes used together with PK study and in vitro BE studies (e.g., bronchodilators)
- Non-systemic tissue/fluid PK study-based (e.g., aqueous humor)
  - Together with in vitro BE studies
  - Common for ophthalmic products used in conjunction with cataract surgery
- Combined approaches for multiple actives
  - Bronchodilator/corticosteroid inhalation products
  - Corticosteroid/other agent topical (dermatological) products
Conventional BE strategies — 2

- Systemic PK study-based
  - Rarely used as primary basis for BE without clinical endpoint or PD studies (e.g., mesalamine, lidocaine topical patch)
  - Usually supported with *in vitro* BE studies
- *In vitro*-only approaches (no human studies)
  - Common for locally-acting GI products (binding agents, vancomycin)
  - Isolated use elsewhere, e.g., budesonide inhalation suspension, acyclovir topical ointment, cyclosporine ophthalmic emulsion, dexamethasone/tobramycin ophthalmic suspension, ciprofloxacin/dexamethasone otic suspension, ophthalmic antibiotic ointments (biowaivers), some topical (derm.) antibiotic products, etc.
  - Sometimes requires Q1/Q2 formulation

Dose-response curve (log dose scale)

Log(dose) scale conveys the familiar sigmoidal shape
Dose-response curve (derived from clinical effect vs. drug concentration at site of action curve)

Maximum possible clinical effect (infinite dose)

Shallower slope → poorer sensitivity toward dose at higher dose levels

\[ E_R = E_0 + E_{max} \frac{D_R}{(ED_{50} + D_R)} \]
(assumes concentration \( \propto \) dose)

- \( E_0 \) = clinical effect of zero dose (placebo)
- \( E_{max} \) = maximum possible clinical effect (infinite dose) – \( E_0 \)
- \( ED_{50} \) = dose yielding clinical response midway between \( E_0 \) and \( E_{max} \)
- \( E_R \) = clinical effect of RLD at dose administered, \( D_R \)

Relating 80 – 125% equivalence criteria for clinical effect to corresponding limits on test/reference product drug concentrations at site of action

Conc. corresponding to 80% of RLD effect

Conc. corresponding to 125% of RLD effect

Conc. at site of action
Spacing of limits on test/reference product drug concentrations at site of action corresponding to 80 – 125% BE limits on clinical effect varies along dose-response curve.

Equivalence margins are not adjusted for placebo response.

Same equivalence limits for both cases based on 80 – 125% of total clinical response.

Case A: low placebo response
Case B: high placebo response

Clinical Response

125%
80%
Constraints imposed on T/R ratio of drug concentrations at site of action by 80 – 125% BE limits on clinical effect ($E_0 = 0$)

- **80 – 125% BE limits for clinical response only translate to 80 – 125% limits for drug (active moiety) concentration at the site of action when total clinical response is zero!**

Constraints imposed on T/R ratio of drug concentrations at site of action by 80 – 125% BE limits on clinical effect (moderate $E_0$)

- **Dose corresponding to 125% of RLD clinical response**
- **Dose corresponding to 80% of RLD clinical response**
Constraints imposed on T/R ratio of drug concentrations at site of action by 80 – 125% BE limits on clinical effect (high $E_0$)

Variability on clinical effect scale is always magnified on concentration (at site of action) scale
Dichotomous endpoint example (cure rates)

• T = 32.8%, R = 32.8%, P = 20% (n = 750, 1:1:1)

• Study passes all three BE criteria:
  ▪ T superior to P
  ▪ R superior to P
  ▪ T equivalent to R

• Placebo also passes equivalence criterion vs. RLD: 90% CI for P – R is within ±20% (-19.6% to -6.0%)

• Clinical endpoint equivalence criteria can sometimes tell us literally nothing about drug concentrations at the site of action!

Placebo control ensures that the bioequivalence test is sufficiently sensitive toward formulation differences

• Statements like this appear in many product-specific BE guidances and FDA presentations
• They are, however totally incorrect!
• Placebo responses are not used to adjust the equivalence margins, so superiority of T and R to P provides no added assurance that the equivalence criterion can distinguish T/R differences
• In some cases, equivalence margins are so wide as to declare the placebo to be equivalent to the RLD
• In most cases, clinical endpoint BE studies provide little or no information on the relative concentrations of drug (active moiety) at the site of action resulting from application of the test and reference products
  ▪ Superiority of R to P: no info on T/R effect site concentrations
  ▪ Equivalence of T and R: little or no information on T/R effect site concentrations
• Typically, the only statistically valid conclusion regarding the test product effect site concentration that can be drawn from a clinical endpoint BE study is that it is > 0 (from the superiority of test to placebo criterion)
• In some cases, a clinical endpoint BE study comparing different RLDs (same indication) could easily pass as bioequivalent, even if RLDs have different active ingredients!
Why clinical endpoint studies are poor tools to assess bioequivalence – 1

• Clinical endpoint BE studies do not directly measure drug concentration at site of action
• Cannot relate BE limits (clinical effect scale) to corresponding effect-site concentrations:
  ▪ Use of a single dose level makes it impossible to know location along concentration-response curve (or corresponding slope)
  ▪ Spacing of effect-site concentrations corresponding to 80 – 125% BE limits for clinical effect is always wider than 80 – 125%, and sometimes wildly so
  ▪ No adjustment of equivalence margins for placebo response

Why clinical endpoint studies are poor tools to assess bioequivalence – 2

• Clinical endpoint BE studies are often conducted at steady state – accumulation in clinical response and/or drug concentrations obscures:
  ▪ T/R differences otherwise apparent with single dosing, i.e., changes in clinical effect over short time frames (e.g., dosing interval)
  ▪ Absorption rates
• Most clinical endpoint studies have tremendous variability:
  ▪ Due to inherently variable endpoints, parallel design, etc.
  ▪ CV magnified greatly on effect-site concentration scale
  ▪ Other common complications, e.g., lack of homogeneity among clinical sites, difficulty in powering, difficulty in estimating clinical effect/cure rates a priori
  ▪ If high variability in a BE metric necessitates the use of hundreds or thousands of patients to assess BE (as is the case with most clinical endpoint BE studies), then that BE metric has inherently poor discriminating power
• Lose – lose situation: clinical endpoint BE studies are very costly for sponsors, yet provide FDA with little assurance of product equivalence
Other BE approaches involving measurement of clinical effect

• Dose-scale method takes placebo response and location along dose-response curve into account when calculating equivalence margins:
  ▪ Orlistat equivalence limits: 80 – 125%
  ▪ Inhalation (bronchodilator) PD (dose-scale) equivalence limits: 67 – 150%
  ▪ Statistically valid, but difficult/impossible to implement for most products

• Vasoconstrictor PD studies for topical steroids address location along dose-response curve with pilot study, and do adjust for null response (no treatment)

• Ophthalmic products for glaucoma have fixed equivalence margin for change in intraocular pressure (IOP) and are not placebo-controlled

A better way: deductive reasoning

• Ultimate goal – compare rate and extent of drug delivery to site of action:
  ▪ Practically speaking, impossible to measure directly
  ▪ Clinical endpoint studies do NOT measure rate and extent of drug delivery to the site of action; instead they measure these indirectly via their downstream effects

• Deductive reasoning approach:
  ▪ Assemble group of indirect tests that collectively force the conclusion that T and R must exhibit equivalent rates and extents of drug delivery to the site of action, otherwise one or more of the indirect tests would not have matched
  ▪ Most of these indirect tests will have much better precision and formulation-discrimination than clinical endpoint studies
  ▪ Compare T and R across all critical product attributes that could affect product performance in vivo
Totality of Evidence (TOE)

• No single test is a magic bullet test of bioequivalence
• Collectively, different pieces of evidence support the conclusion of bioequivalence
  ▪ Composition
  ▪ Structure
  ▪ In vitro performance tests
  ▪ In some cases, other types of tests (ex vivo, animal studies, human PK, etc.) could be useful components of TOE
  ▪ Devise tests and interpret results in light of how T and R products will actually be used by patients
• Historical precedents:
  ▪ In vitro-only BE options in some guidances: e.g., cyclosporine ophthalmic emulsion, acyclovir topical ointment, dexamethasone/tobramycin ophthalmic suspension, budesonide inhalation suspension, etc.

External vs. internal drug application – topology counts!

• Imagine human body as infinitely stretchable object → body is topologically equivalent to a torus (donut) with the GI tract lumen as the donut hole
• If drug at the application site needs to pass through a contiguous layer of cells to get into the body, the application site is topologically outside the body
  ▪ Valves and sphincters can open and thus, don’t count as contiguous layers of cells
• Most locally acting drugs are applied to outside surface of the body (topologically speaking):
  ▪ Topical (dermatologicals), inhalation, ocular, gastrointestinal (orally administered, rectal), vaginal, otic, gingeval, etc.
• A few are applied inside the body (topologically speaking):
  ▪ Intra-vitreal, intrathecal, intra-articular, injectable local anesthetics, locally-acting implants (e.g., intracranial, stents), etc.
Rethink BE from the beginning

• Simplify/demystify
• Abandon traditional methods (conceptually) – start with clean slate, build BE approach from scratch
• Understand context of bioequivalence comparisons sought in assessing utility of comparative tools:
  ▪ Not a comparison of different chemical entities, different routes of administration, considerably different formulations, etc. (BE tools would be less valid under such circumstances)
  ▪ Same drug, same route of administration, very similar formulations, etc. (BE tools much more valid)
• Evaluate importance/closeness of formulation composition
• Define critical clinical performance attributes
• Devise tests and acceptance criteria that are consistent with how products are actually used by patients
• Use deductive reasoning as the basis for a totality-of-evidence based BE approach

Key strategic points – 1

• Create comprehensive TOE strategy addressing all reasonable concerns about product performance
  ▪ Suggestion: internal question-based review (QBR) type process can help think through strategy
• Compare novel TOE approach with existing clinical endpoint study paradigm – which provides better evidence of comparable T/R drug concentrations at site of action?
• Don’t dismiss PK as automatically irrelevant to BE – in context of other tests, it might be valuable BE metric
• Critical to understand rate-limiting step in absorption process:
  ▪ If rate-limiting step occurs before/upstream from site of action, then systemic PK will likely be good surrogate for drug concentrations at the site of action
Systemic vs. Local Action

Systemically acting drug product

Site of drug absorption (e.g., gut wall) → Bloodstream → Site of drug action (e.g., brain)

Drug concentrations in blood (plasma) easy to measure and good proxy for drug concentrations at site of action

Locally acting drug product

Site of drug application (e.g., skin-epidermis) → Site of drug action (e.g., skin-dermis) → Bloodstream

Drug concentrations at site of action difficult or impossible to measure

Rate limiting step

Slow → Fast

Systemic (plasma) concentrations could serve as valid surrogate for drug concentrations at site of action

Key strategic points – 2

- Taking chances is critical – blazing new territory, new analytical methods, new strategies
  - Can mitigate risk via OGD meetings
- Check FDA GDUFA Regulatory Science web site – relevant FDA-funded research may already be done or underway: [www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm370952.htm](http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm370952.htm)
- If TOE BE strategy without clinical endpoint BE study is not acceptable to FDA, consider clinical endpoint BE study with novel, much more sensitive endpoints than conventional endpoints
- “Conservative approach” (following the letter of the product-specific BE guidance) may carry its own risks (e.g., guidance could change or competitor could successfully implement novel in vitro-only approach after you have invested millions in the traditional clinical endpoint BE study)
Critical Clinical Performance Attributes

• Dose applied (dose metering)
• Distribution of drug product across application site
• Retention/permanence at application site
• Physiological processes acting on drug product at application site
• Local PK/PD (microdialysis, TEWL, etc. if feasible and warranted)
• Systemic PK (if feasible and warranted)
• Devise suite of tests and acceptance criteria in light of how patients actually use the product

Dose metering

• Well-controlled dose metering:
  ▪ Oral dosage unit (pill, liquid measuring cup, etc.)
  ▪ Inhalation (MDI, DPI, metered nasal spray)
  ▪ Vaginal (pill, ring, cream/gel applicator syringe, suppository)
  ▪ Ocular (liquid dropper)
  ▪ Metered foam
  ▪ Suppository

• Little or no metering:
  ▪ Ophthalmic ointments
  ▪ Most topicals (creams, ointments, gels, lotions, shampoos)
  ▪ Do we assess equivalence of dose metering/delivery under real-life use conditions? Should we? Much easier, more precise, more relevant than clinical endpoint BE studies.
Distribution of drug product across application site

- Inhalation (pulmonary) – active distribution through mouth, throat, respiratory tree (large central airways, small peripheral airways, alveoli, etc.), changes to particles/droplets emitted from mouthpiece en route to final destination (propellant/solvent evaporation, hydration, aggregation/deaggregation, etc.)
- Inhalation (nasal) – active distribution throughout nasal passages/sinuses
- Topical (derm) – active spreading by patient across application site
- Ophthalmic – passive spreading across cornea, sclera (whites), eyelids, etc.
- GI – passive regional release/delivery within GI tract
- Vaginal – passive spreading across vaginal epithelium, cervix
- Rectal – passive spreading throughout rectum/colon
- Etc.

Retention/permanence at application site (“sticktuitiveness”)

- Drug applied does not necessarily remain at application site long enough to have clinical effect
- Inhalation (pulmonary) – drug not deposited sufficiently deeply is cleared by the mucociliary escalator
- Inhalation (nasal) – portions of the dose drip out through the nose and into the back of the throat
- Topical (derm) – drug product may be lost from the site of application by flaking, contact with clothing, etc.
- Ophthalmic – drug lost by tearing
- Vaginal – large volumes of creams, gels can drip out
- Etc.
Physiological processes acting on drug product at application site

- Diffusion of drug out of formulation
- Diffusion of excipients out of formulation
- Evaporation of water from formulation, e.g., topical (derm)
- Diffusion of water into formulation, e.g., vaginal, rectal
- Melting (suppositories)
- Interaction with body fluids, e.g., GI, vaginal, rectal
  - Chemical environment at application site (pH, osmolality, ions, etc.)
  - Enzymatic activity at application site
- Agitation/movement, e.g., GI, topical/derm, vaginal
- Drug uptake/absorption/permeation/active transport

The context of a BE comparative tool is critical – systemic PK example – 1

- Consider four products: conjugated estrogens oral tablets, conjugated estrogens vaginal cream, estradiol oral tablets, estradiol vaginal cream
- All four result in the appearance of estrone sulfate (parent drug from conjugated estrogens, major metabolite from estradiol) in plasma
- Some PK comparisons of plasma estrone sulfate levels would be of little utility to evaluate new generic product:
  - Comparing different drugs/APIs (generic conjugated estrogens vs. RLD estradiol)
  - Comparing different routes of administration (generic oral vs. RLD vaginal)
The context of a BE comparative tool is critical – systemic PK example – 2

• PK comparisons within same drug/API and same route of administration provide much more useful info on suitability of new generic formulations:
   Generic estradiol oral tablets vs. RLD estradiol oral tablets
   Generic conjugated estrogens vaginal cream vs. RLD conjugated estrogens vaginal cream

• Take concept a step further – require similar formulations, comparable T/R results on battery of performance tests, etc.
   Systemic PK becomes even more valuable tool to assess equivalence of product effect site concentrations.
   Would be very hard to envision how T and R product could match in composition, structure, extensive in vitro comparisons, systemic PK, and still somehow yield materially different drug concentrations at the site of action.

• Critical to consider all of the other available information in evaluating the utility of a given BE tool to assess the clinical significance of formulation differences

Compositional/structural requirements: Q1/Q2/Q3 – definitions

• Q1: Qualitatively the same
   Same ingredients/excipients

• Q2: Quantitatively the same
   Stringent criterion – each excipient must be within ± 5% of corresponding amount in RLD (i.e., 95 – 105% of RLD amount)
   Very challenging for some minor components

• Q3: Same arrangement of matter/structure
Q1/Q2/Q3 – comments and questions

- Some FDA compositional requirements may be too strict – should we temper by the particular product and route of administration?
  - Is strict Q2 always necessary? Is “Q1.9” reasonable?
    - e.g., vancomycin capsules
    - Minor excipients in topical (derm), vaginal, etc. products – difficult to quantitate precisely
    - Potential for processing loss of minor excipients in RLD, high variability in RLD content of minor excipients, etc. – need leeway
    - Could we justify minor compositional differences by demonstrating that varying amounts of certain minor excipients does not have any meaningful effect on product Q3 or critical performance characteristics, thereby avoiding need for strict Q2?
  - Should strict Q3 really be needed when product structure is destroyed during application process, e.g., topical (derm) products?
- Other issues:
  - Q1/Q2 letters for products not ordinarily requiring Q1/Q2 sometimes not answered by FDA (can be addressed in ODG meetings, though)

Which locally-acting generic drug product would you rather take?

**Generic product A**
- Approved via conventional clinical endpoint BE approach
- Formulation may be materially different from RLD
- Limited comparative testing vs. RLD
- No PK vs. RLD
- Clinical endpoint BE study passes usual criteria
- Could not pass novel TOE BE approach

Allow generics to be deemed bioequivalent by accident

**Generic product B**
- Approved via novel TOE BE approach
- Formulation/structure must be nearly identical to RLD
- Extensive comparative testing shows excellent match to RLD on all critical performance qualities expected to affect BE
- PK passes BE vs. RLD
- No clinical endpoint BE study
- Very likely to pass clinical endpoint BE study if tested

Forces generics to be bioequivalent by design

Testing into compliance?
Miscellaneous issues

Some important factors in justifying a novel BE approach

- Conventional BE paradigm:
  - Lower cost, more defensible conventional clinical response metrics will probably not be displaced by \textit{in vitro}-only methods: little motivation to change
    - Vasoconstrictor studies for topical corticosteroids
  - Very expensive clinical endpoint BE studies with poor formulation discrimination more likely to be replaced with less burdensome BE methods
  - Have generics already been approved using conventional BE approaches?

- Formulation complexity:
  - Solutions, suspensions, ointments: less complex
  - Creams, gels: more complex
OGD has been very proactive in developing novel methods of establishing BE for complex drug products

- Generic Drug User Fee Act (GDUFA) regulatory science research initiatives:
  - FDA now spends millions of dollars each year funding external research, much of it aimed at developing better ways to assess BE
  - GDUFA 2 – massive, all-out effort by OGD to modernize/streamline BE for complex drugs (including locally acting drug products)

- Guidances:
  - OGD has recently introduced a number of streamlined BE approaches for previously difficult or intractable products, including some in vitro only approaches

- Meetings with OGD:
  - Although not (yet) required by law or regulation, OGD has fostered interaction with industry via meetings on complex drug products, which are often focused on advancing novel, more effective BE approaches
  - Strongly advisable to discuss novel TOE approaches with OGD as early as possible in drug development process

- Citizen petition responses:
  - OGD has vigorously defended its streamlined BE approaches for complex drugs in responses to citizen petitions from RLD NDA holders

Popular, conventional analytical methods are not necessarily relevant

- In vitro release testing (IVRT, synthetic membrane)
  - Assumes drug particles suspended in thick layer of formulation matrix – Higuchi model – mathematically tractable
  - Codified in 1997 SUPAC nonsterile semisolid guidance
  - Very popular with creams, ointments, etc.

- But what happens when patient spreads topical cream on skin?
  - Becomes very thin layer, probably only a few microns thick
  - Water evaporates
  - Most structure, except solid API particles, is destroyed, (e.g., oil globules, gel)
  - Most API particles end up in direct/nearly direct contact with skin
  - IVRT measurement of diffusion through original matrix may not be relevant

- Measurement process itself may be flawed:
  - Focus on diffusion of drug through matrix into receiver medium
  - Little attention paid to back diffusion of receiving medium into drug product – may disrupt/destroy product structure/composition during test

- IVRT is probably more relevant to vaginal administration (thick application layer, no evaporative loss of water) than topical (derm) administration
Calibrating performance property or surrogate marker response to clinical effect

• Clinical meaning of a given test-reference difference in performance property or surrogate marker for clinical response may be unclear
• Sometimes possible to compare response of similar approved products:
  ▪ Same API, same indication
  ▪ RLD and approved generic
  ▪ Different RLDs
  ▪ Same RLD, different strengths
  ▪ Can they be distinguished clinically? If not, it may support argument that observed T-R difference in performance/surrogate response might not have clinically significance
• Lot-to-lot variability of RLD important determinant of acceptable difference between T and R products

Need better analytical methods for:

• Viscous, high-concentration matrices
• Gels
• Emulsions
• Creams
• Three-phase materials (e.g., hydrophobic liquid/hydrophilic liquid/solid drug particles)
• Insoluble polymers
• Need methods to analyze as is, without dilution
Conclusions

• Traditional clinical endpoint BE paradigm often has poor sensitivity toward formulation differences and provides little information about relative T/R drug concentrations at the site of action

• A totality-of-evidence (TOE) approach combining a comprehensive collection of tests addressing critical clinically relevant attributes can provide greater assurance of product equivalence than conventional clinical endpoint BE-based approaches

• Consideration of how product is actually used by patients is important

• Comprehensive, bottom up rethinking of BE strategy advisable to dispel historical fallacies

• Novel TOE BE approach should be supported with comprehensive justification addressing all critical factors potentially affecting BE

• Discuss novel TOE BE approaches with FDA in advance wherever possible

Thank-you!
Acknowledgements

• AAPS Program Committee
• Workshop organizing committee, speakers, and moderators
• Generic Pharmaceuticals Focus Group Steering Committee
• Elizabeth Scuderi for AAPS operational support
• Generic Pharmaceutical Association (co-sponsor)

Questions?

Charles E. DiLiberti, President
Montclair Bioequivalence Services, LLC
charlie@montclairbe.com

also Chair, Generic Pharmaceuticals Focus Group:
https://www.aaps.org/Generic_Pharmaceuticals/