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## The Path to Bioequivalence – Great Progress, Great Opportunities

Charles E. DiLiberti, President, Montclair Bioequivalence Services, LLC

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# Pre-GDUFA (where we were)

- Difficult bioequivalence matters languished unresolved for years
- Heavy reliance on one-size-fits-all using limited number of conventional bioequivalence pathways
- Little development of novel bioequivalence approaches
- Bioequivalence pathways for many complex products extremely difficult or impossible
- Development of many generic products were, in effect, blocked
- Fewer product-specific bioequivalence guidances

# GDUFA regulatory science research

- Meteoric increase in research needed to develop viable pathways to demonstrate bioequivalence for difficult/complex products
- Vigorous development of novel bioequivalence approaches for historically challenging products
- Dramatic increase in biopharmaceuticals understanding underpinning assessment of bioequivalence

# GDUFA regulatory science research – cont'd

- Defensibility of bioequivalence approaches
- Fountain of product-specific bioequivalence guidances
- Trend away from reliance on clinical endpoint BE studies toward *in vitro*-only approaches
- Development and approval of historically impossible ANDAs

**Great progress – thank-you!!!!**

# GDUFA regulatory science priorities

- Outlined in annual GDUFA performance reports and elsewhere:
  - Post market evaluation of generic drugs
  - Equivalence of complex products (active ingredients, formulations, dosage forms, routes of delivery, drug-device combos, etc.)
  - Equivalence of locally acting products
  - Therapeutic equivalence evaluation and standards (BE and substitutability evaluations)
  - Computational and analytical tools
- Heavy emphasis on bioequivalence and related matters
- Stated priorities and feedback from public meetings/dockets guide internal and external FDA research

# GDUFA regulatory science research activities

- Annual lists of GDUFA-funded external research contracts and grants:
  - FY 2013: 33 new grants/contracts in 20 subject areas
  - FY 2014: 37 new grants/contracts in 27 subject areas
  - FY 2015: 22 new grants/contracts in 18 subject areas
  - FY 2016: 17 new grants/contracts in 15 subject areas
  - FY 2017: 8 new contracts in 8 subject areas
  - Additional funded research opportunities open for bidding
- Vast majority of grants/contracts in some way related to bioequivalence
- Grants/contracts provide insight into what's coming down the pike

# Industry sentiment

- Gratitude for progress so far
- Lingering issues:
  - Unmet historical & new/emerging needs
  - Unintended consequences of rapid progress
- Palpable fear:
  - Dockets/public meetings good, but do not effectively gauge true industry needs because of the “fear factor”
  - FDA doesn’t always get the feedback it needs
  - Need vehicle to anonymize feedback from industry

# My methods

- Objective: gauge key unmet needs/uncertainties in the realm of bioequivalence
- My own collected thoughts/observations from working with industry
- Informal survey of cross-section of manufacturers/developers, CROs, and other contacts
- Raw data: over 70 specific issues/suggestions identified
- Consolidated individual items, eliminated duplicates, organized by subject
- Not intended to be scientific study or comprehensive analysis of industry needs



# How best to address unmet needs/uncertainties?

- Improve communication (easy)
- Change policies/practices (easy – hard)
- Regulatory (scientific) research (hard)

**DISCLAIMER: SUGGESTIONS PROVIDED ARE INTENDED TO STIMULATE DISCUSSION ONLY, AND ARE NOT NECESSARILY VIABLE APPROACHES!**

- ✓ - **FDA research contract/grant active**
- ✓ - **FDA research open bid or on priorities list**

# The “bucket list” (great opportunities!)

- Administrative & procedural matters
- Pre-submission advice, guidance, insight, feedback, etc.
- Reference products
- *In vitro*-only BE approaches
- Specialized BE approaches & issues
- Dosage form-specific BE issues
- Miscellaneous BE issues

Administrative &  
procedural matters

# ANDA content, organization, and formatting

- Data standards (CDISC, ADaM, STDM, etc.) – required for all studies started on or after 12/17/16
- Significant uncertainties regarding how to implement for ANDA's:
  - Which data sets are expected?
  - Scope for ANDAs vs. NDAs?
- Is the content/organization/formatting of ANDA's optimized for preparation efficiency, review efficiency, and consistency with global submission standards? Necessary versus nice-to-have?

# ANDA review process

- “Inappropriate” BE deficiencies:
  - ANDA BE content missed/misunderstood by reviewer
  - BE deficiencies markedly out of line with long-standing FDA policies/practices and/or current science
  - Attempts to enforce draft guidances
  - Overreaction to relatively minor BE matters (RTR, “repeat your BE studies”), etc.
- Not only disruptive for the ANDA under review, also misleads industry as to true FDA policies/practices

# ANDA review process (cont'd)

- Suggestion: enhance internal FDA reviewer training, including examples in which the original FDA comment was inappropriate and was reversed following feedback from applicant
- Suggestion: institute process for automatic higher level review of all very serious decisions like RTR, “repeat your BE studies,” etc. to prevent inappropriate issuance of such serious demands
- Suggestion: implement QA process much like that required for industry

Pre-submission advice,  
guidance, insight, feedback,  
etc.

# FDA guidances – issues

- Rationale sometimes unclear, surprises, disruptions to industry when guidances are changed, uncertain acceptability of legacy BE approaches, disorderly implementation, e.g.:
  - Sudden change in language regarding patch reinforcement in transdermal PK studies (unclear, “tape” = “overlay”?)
  - Frequent, major revisions to some product-specific BE guidances (unintended consequences of rapid improvements)
  - What is a sponsor to do if it has already started or finished a BE study and the guidance changes?



# FDA guidances – issues (cont'd)

- Product-specific BE guidances that are formally withdrawn or simply disappear without a trace – what does this mean to sponsors already following the prior BE approach?
- Confusion over the enforceability of draft versus final guidances

# FDA guidances– suggestions

- Publish list of product-specific BE guidances under development and anticipated issuance dates (much like list of FDA guidances under development, but separate from it)
- Publish list of broad product-specific BE guidance initiatives likely to affect multiple products – e.g.:
  - Retrospective initiative to add fed studies where current product-specific BE guidance specifies fasting only
  - Initiative to tighten requirements for AT-rated topical products
  - Development of model product-specific BE guidances

# FDA guidances– suggestions (cont'd)

- When product-specific BE guidances are issued, revised, or withdrawn, please:
  - Specify the effective date of the new/revised BE approach (i.e. required for all studies started on or after XX/XX/XX)
  - State whether legacy BE approach is still acceptable
  - If guidance deviates from established FDA policy/practice, please explain why
  - Please include consistent notification of whether a bio-IND is required – definition of cytotoxicity (a common trigger for a bio-IND) is fuzzy

# FDA guidances– suggestions (cont'd)

- Please stop trying to enforce draft guidances as if they represent binding requirements – note language:
  - “Contains Nonbinding Recommendations”
  - “This draft guidance, once finalized, will represent the Food and Drug Administration’s (FDA’s) current thinking on this topic.”
- Frequent issue with general guidance on bioanalytical method validation, various product-specific BE guidances

# FDA meetings for ANDAs

- The standards for pre-ANDA meetings (novel BE approach supported by actual study data, ~100 page briefing package) are far too onerous, making the bar far higher than for pre-IND meetings for NDAs
- Historically, the high bar pre-GDUFA was understandable, but industry is now paying (hefty) GDUFA fees and should be entitled to readily-available, detailed, product-specific advice similar to that available under PDUFA
- Agency concerns about getting flooded with meeting requests underscore the tremendous unmet need

# FDA meetings for ANDAs (cont'd)

- Product-specific BE guidances for many complex drug products do not provide sufficient detail to enable an applicant to develop the product properly, resulting in RTRs and significant review issues. Often not feasible to craft a guidance with sufficient detail that would address all contingencies.
- Suggestion: open up pre-ANDA meetings to any applicant seeking approval of a complex drug product, even if using BE approach specified in the product-specific BE guidance, as long as applicant has reasonable uncertainties regarding implementation/requirements of the BE approach

# Enforcement

- FDA's historical enforcement policies have sometimes created uncertainty in the industry – should industry be worried? Will the “other shoe drop” suddenly, as it did during the sudden implementation of ISR requirements? For example:
  - Gender ratios in mixed-gender BE studies: will it continue to be acceptable if only men actually enroll in a study that is open to both men and women? Will enforcement policy change suddenly when the December 2013 draft guidance on BE for ANDA's (with more stringent language on gender) is finalized?
- Suggestion: FDA should provide industry with plenty of advance warning regarding anticipated changes in its enforcement policies (e.g., studies started after XX/XX/XX must comply with....)

Reference products



# “Unobtainium” RLDs – issues

- Preventing generic drug developers from obtaining RLD product it needs to conduct BE studies has been one of the most successful anti-generic tactics ever used
- Implemented via REMS and/or restricted distribution programs
- Procedure for getting protocols reviewed by FDA for REMS products can be slow, painful, and often does not succeed because it does not compel the RLD manufacturer to provide product to the sponsor

# “Unobtainium” RLDs – suggestions

- Possible workaround? – qualify use of foreign (e.g., EU) reference product as a comparator in BE studies:
  - Sponsor procures a particular lot of the foreign reference product, and sends a sample of this lot to FDA labs
  - FDA procures US RLD and does comparative dissolution, forensic testing etc. on the US and foreign products
  - If found to be comparable, FDA would issue a letter to the sponsor certifying that the particular lot of foreign reference product submitted would be acceptable for use as a comparator in BE and in vitro studies supporting an ANDA

# “Unobtainium” RLDs – suggestions (cont’d)

- Sponsor would never have to obtain the US RLD directly
- Similar process could be used for non—REMS/restricted distribution products to support global development programs (conduct a BE study on one reference product for regulatory approval in multiple markets)
- This is untested, and FDA would need to agree to it!

# Which product to use as the comparator in BE studies?

- Assignment of RS product is not always clear when innovator (RLD) has been withdrawn
- Suggestion: FDA could clarify RS designations
- Suggestion: May be better to select RS based on GMRs from its BE studies (i.e., closest match to RLD) rather than market share to minimize bioequivalence “creep”
- Suggestion: FDA should explicitly state its policy with regard to which strengths to use in BE studies when ANDA for subset of strengths is sought

# Reserve/retention samples for BE

- Dr. Nagesh Thudi is presenting on reserve/retention sample requirements for non-traditional dosage forms – will not discuss
- With tremendous advancements in forensic analytical methodology, 5 x full release testing requirement or 300 tablet/capsule minimum is outdated and should be changed
- Exorbitant costs for some RLDs (particularly orphan drugs) can make current BE reserve sample costs prohibitive (> \$1 MM)
- ✓ FDA evaluates contr. corr. justifying reduced quantities of reserve sample on a product-specific basis – see Dr. Suman Dandamudi presentation from October 20, 2017 FDA workshop on topicals
- Suggestion: for high-cost RLDs, FDA could provide relief by putting reduced safe harbor reserve/retention sample requirements into product-specific BE guidances

*In vitro*-only BE approaches

# BCS class I waivers – issues

- Currently can only avoid permeability studies based on RLD labeling, not FDA's own BCS determination (e.g., in Clinical Pharmacology/Biopharmaceutics FDA review)
- Requirement to run permeability studies frequently dissuades sponsors from using this approach
- Permeability studies can cost more than human BE studies
- Results in unnecessary human BE studies

# BCS class I waivers – suggestions

- FDA could revisit its inability to rely on its own previous BCS determination.
- FDA could consider relying on BCS class determinations by other regulatory agencies, e.g., EMA (BCS class is often published in EPARs).
- If FDA determines that a drug is BCS class I, it could state that in the product-specific bioequivalence guidance, which could then be referenced by all generic applicants.



# BCS class III waivers

- Currently, the requirement for the generic formulation to be Q1/Q2 with respect to the RLD formulation (Q1: list of excipients must be identical to the list used in the RLD, and Q2: each excipient must be within  $\pm 5\%$  of the amount present in the RLD formulation) is onerous and a significant impediment to use of the BCS class III waiver pathway
- The Q1/Q2 criteria arose from SUPAC guidance that is more than two decades old, and is not supported by current scientific understanding

# BCS class III waivers (cont'd)

- Reverse engineering RLD products to the required level of accuracy/precision can be very challenging. Amounts of some excipients carried through to the RLD finished dosage form may not reflect what the RLD manufacturer actually puts into its formulation (e.g. due to excipient process loss)
- Need to address intentional formulation differences (non-patent-infringing formulations)
- ✓ Suggestion: could relax the Q2 requirement to reflect *bona fide* concerns regarding the potential for bioinequivalence (Q1.9?); Potential to justify such relaxation based on RLD manufacturers' successful development of IVIVC?

# Other *in vitro*-only approaches

- Increasing number of *in vitro*-only BE options are appearing in product-specific BE guidances
- Often, these have Q1/Q2 requirement (as for BCS class III drugs) – same issues often apply, but are often worse:
  - Increasingly applied to non-solid oral dosage forms, for which reverse engineering may be even more challenging than for solid oral dosage forms
  - Patented RLD formulations may necessitate intentional formulation differences
  - Stakes may often be much higher than for solid oral dosage forms, because the alternative may be a difficult/expensive clinical endpoint BE study, instead of conventional NHV PK-based BE studies

# Other *in vitro*-only approaches

- Simple suspensions (injectable, ophthalmic, otic, topical) represent low hanging fruit for the development of *in vitro*-only BE approaches
- AA, AT products - suggestion: communicate policy clearly so that any applicants don't waste a lot of time

# Specialized BE approaches & issues

# Specialized BE approaches/issues

- ✓ NTI drugs – onerous scaled BE criteria when observed reference product within-subject CV is very low
  - Suggestion: implement mixed scaling approach as is done for RSABE
- Switchability (subject X formulation interaction) BE criteria – currently included in one draft methylphenidate ER tablet guidance - plans to include in other guidances beyond methylphenidate?
- Address issues of lot-to-lot variability in RLDs, particularly inhalation products

# Specialized BE approaches/issues (cont'd)

- ✓ Issues with performance properties of partial AUC metrics - discussed in recent DQMM workshop 10/2/17
  - Group or adaptive sequential BE study designs – acceptability?
  - Parallel design studies – novel approaches to reduce residual variability/sample sizes
- ✓ Outliers in BE studies – longstanding issue – single outlier can shipwreck study

# Specialized BE approaches/issues (cont'd)

- Ongoing issues with BE studies on endogenous compounds
- BE on parent drug vs. active metabolites for pro-drugs – demonstration of BE on parent drug can sometimes be far more onerous than for active metabolite; parent drug concentrations may be far lower than those of metabolite and clinically inconsequential; suggestion: use modeling to justify demonstrating BE on active metabolite instead



# ✓ Abuse-deterrent formulations

- Heightened attention due to opioid abuse epidemic in the US
- General guidance helpful, but uncertainties remain regarding studies needed, designs, and acceptance criteria, particularly in light of frequent need to use non--patent infringing formulations
- Suggestion: Although abuse-deterrent formulations are complex drug products, could loosen requirements (especially data requirement) for pre-ANDA meetings to resolve the abuse-deterrent features

# Bioequivalence study design issues

- Normal healthy volunteers versus cancer patients; additional triggers beyond cytotoxicity and daily dose?
  - Mystifying when product-specific BE guidance specifies the use of patients for drugs where the innovator has conducted multiple normal healthy volunteer studies
  - FDA should explain its rationale, as well as whether or not studies conducted in normal healthy volunteers would be acceptable
- For marginally efficacious locally-acting RLD products, need to address the inability to demonstrate superiority in clinical endpoint studies

# Dosage form-specific BE issues

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- ✓ Transdermals – retrospective evaluation of all PK studies done with tape reinforcement?; continued use of inverse/nonlinear adhesion scoring scale; positive control (SLS) issues for irritation studies; statistical issues for irritation studies
- ✓ Inhalation products – studies too complicated and too expensive; rethink some of the *in vitro* tests – are they really relevant?; issues with subpopulations of slightly defective devices (one slightly defective mold issue)
- ✓ Simple long-acting injectables (simple suspensions) – are the use of patients, long time frames, steady-state designs, etc. really necessary, or are *in vitro*-only approaches possible?

# Dosage form-specific BE issues (cont'd)

- ✓ Complex, long-acting injectables: liposomes, biodegradable microspheres, etc.
- ✓ Ophthalmics – aqueous humor PK studies are themselves onerous and not optimal solutions to the problem
  - Suggestion: *in vitro*-only approach for suspensions
- ✓ Topicals – need better methods for *in vitro* release testing for hydrophilic-drug-in-hydrophobic-ointment products (IVRT doesn't work well), Q3 (microstructure) characterization tools
- ✓ Implants – need better polymer characterization methods

# Miscellaneous BE issues

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- Globalization – avoiding repetition of BE studies for each region
- Post-approval changes for inhalation and other products not covered in SUPAC guidances – BE studies needed?
- Need clearer guidance on statistical methods, e.g., SAS code for vasoconstrictor studies, analysis of 3-way crossover studies with two different test formulations, etc.
- Need more transparency on internal FDA regulatory science research projects

# Conclusions

- Tremendous progress over the last ~5 years under GDUFA
  - Extensive, wide-ranging research activities
  - Many improved, revised, new guidances, including dramatic simplification of BE (clinical endpoint BE study → *in vitro*-only) in some cases
  - Solving some longstanding BE problems
  - Thank-you!!!!



# Conclusions (cont'd)

- Tremendous opportunities to further improve:
  - Communication, policies, BE approaches
  - Get involved in the GDUFA Regulatory Sciences Working Group (biannual meeting with FDA – see GDUFA 2 Commitment Letter)
  - Thanks in advance!!!!

# References/links

## **GDUFA Regulatory Science and Research page:**

<https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm>

## **Regulatory Science Research Reports:**

FY 2015: <https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm500571.htm>

FY 2016: <https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm548872.htm>

## **GDUFA Performance Reports:**

<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm379854.htm>

## **Open GDUFA Regulatory Science Research Grant/Contract Announcements:**

<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm391696.htm>

## **GDUFA 2 Commitment Letter:**

<https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/ucm525234.pdf>

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# Thank-you!

Charles E. DiLiberti

President, Montclair Bioequivalence Services, LLC

[charlie@montclairbe.com](mailto:charlie@montclairbe.com)

+1-973-744-0160