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A Division of the Association for Accessible Medicines

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Old, New, and Future Challenges in Bioequivalence

September 7, 2018

Charles E. DiLiberti

Engineering the Future
of Generic + Biosimilar Medicines

Objectives and approaches

- Facilitate robust dialogue on the most pressing bioequivalence-related issues facing generic drug developers, sponsors, and CROs
- Based on informal feedback of “please fix it” wish-lists from stakeholders
- Identify issues as being old, new, or future Olde New Future
- Most serious/widespread issues summarized and presented first (~ 15 min) to stimulate audience participation and panel discussion (~ 45 min)
- Backup slides show details, suggested fixes, and less serious/widespread issues; for later review and reference

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Panel

- Charlie DiLiberti, MS, President, Montclair Bioequivalence Services, LLC (Moderator)
- Keith Gallicano, PhD, Chief Scientific Officer, Novum Pharmaceutical Research Services
- Russ Rackley, PhD, Head, Global Pharmacokinetics/Drug Metabolism, Mylan Inc.
- Nageshwar Thudi, PhD, Senior Director, Clinical End Point Studies – Global, Teva Pharmaceuticals
- William Zarycranski, PharmD, Director Clinical Development – Early Phase, Sandoz Inc., A Novartis Company

Guidances – clarity, consistency, rationale, implementation issues

- Many guidances lack clarity:
  - Interpretation is uncertain
  - No quick way to resolve uncertainties
- Inconsistencies exist across guidances:
  - Between product-specific and general guidances
  - Among product-specific guidances for similar products
- FDA rationale behind its product-specific BE guidances is often a mystery

Olde New

Olde New

Olde New

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Guidances – clarity, consistency, rationale, implementation issues – cont'd

- Lack of guidances where they are needed — Olde
- Implementation/enforcement issues: — New
  - New product-specific BE guidances are issued without warning, and without implementation schedule
  - Adversely affects products under development and already-filed ANDAs under review
  - FDA improperly attempts to enforce draft guidances

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Biowaivers and *in vitro* BE methods to reduce or eliminate clinical burden

- Suggestions/questions on extension of *in vitro* approaches for various types of locally acting drug products: *New*
  - Injectable, ophthalmic, nasal suspensions, topicals, implants
- Challenges meeting Q1/Q2 requirements to qualify for *in vitro* BE approaches for locally-acting drug products: *New* *Future*
  - New guidances + Q1/Q2 response opacity + Q1/Q2 policy opacity = stuck
- BCS biowaivers: overcoming obstacles *New*
  - Literature support for high permeability rather than CACO-2 studies
  - Q1/"Q2" similarity issues

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Clinical endpoint BE studies: challenges

- High variability with untransformed change-from-baseline endpoints Olde
- High placebo response rates (especially if unexpected) Olde
- Too many primary endpoints Olde
- Need alternatives for many more products: *in vitro*, PK, etc. Olde

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BE reserve (retention) samples

- Costly, difficult-to-obtain RLDs (note FDA waiver program) — *New*
- Requirements for clinical endpoint BE studies are often onerous — *Olde / New*
  - Each-site for multi-site studies
  - Exacerbated when IVRS/IWRS are used
- Requirements for *in vitro* BE studies are unclear and potentially excessive — *Future*
- Lack of clarity for dosage forms other than solid orals — *Olde*

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Patient PK studies

- FDA guidances sometimes specify patients when *New*
  - NDA sponsor conducted multiple studies in healthy volunteers
  - EMA guidances recommend healthy volunteers
- Inferior BE comparisons in patients: Olde
  - Steady state vs. single dose conditions
  - Confounding factors (disease state, con meds, different dose levels)
- Significant challenges with patient studies (recruitment, large amounts of Olde RLD needed – high cost, duration, etc.)

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ANDA review frustrations

- Frivolous citation of minor issues, seemingly to invoke a Refuse-to-Receive (RTR) or meet a GDUFA performance metric *New*
- Seemingly over-zealous/inexperienced reviewers: *New*
  - Demanding inappropriate application of guidances/regulations
  - Issuing unreasonable comments/deficiencies
  - Out-of-step with historical FDA policies/practices

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CDISC data standards

- These are expensive and onerous to prepare *New*
- Poor guidance/clarity on details of how to apply CDISC to ANDAs *New*
- FDA demands perfection in structure/formatting *New*
- Is there any way to streamline these, e.g., for certain drug classes, formulations and/or types of study (patients vs NHVs)? *New*
- Are the new CDISC data files/formats even utilized by FDA? FDA sometimes asks for data in the old formats! *New*

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Reference Listed Drug (RLD) issues

- Obtaining RLDs: REMS and restricted distribution programs *New*
  - FDA protocol review for REMS compliance is of limited utility
- Considerable lot-to-lot variability in RLD *Olde*
  - Inherent, and/or aging-related
  - Complicates generic development (moving target)
  - Justifies adjustment of BE criteria?
  - For products significantly affected by administration technique, are differences technique or formulation-related?

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Reference Scaled Average Bioequivalence (RSABE)

- When can/can't RSABE be used? PD, anticoagulants, etc. *New*
- Questions on details of implementing RSABE method: handling missing data, multiple dosing groups, passing unscaled average BE but not RSABE, etc. *New*
- Extension of RSABE principle to two-period designs (Balaam's: RR, RT, TR)? Olde
- Use of 2 different RLD lots to address high lot-to-lot RLD variability? Olde *New*

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Outliers and anomalous data

- Need to re-think outlier/anomalous data policies — Olde
  - Humans are biological organisms subject to inherent and sometimes erratic variability
  - Many good studies are thrown out when the RLD is the bad actor
- Re-dosing study policy has morphed from routine to unclear/unacceptable — New
- Need better approaches for dealing with PK “flatliners” (all zero concentrations): expected for some types of products — Olde
- Recent FDA comments on alleged cross-study inconsistencies in absolute concentrations are concerning — New

Transdermal/topical patches

- PK studies: taping was OK but now is not – consequences — *New*
- Adhesion: — Olde *New*
  - New guidance helps, but still residual issues
  - Scoring scale rationale, performance issues
  - Revised adhesion guidance under development
- Irritation: — Olde *New*
  - New guidance under development
  - Scoring scale rationale, performance issues
  - SLS positive control patch issues
  - Policy on sites in different climatic regions?

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Global harmonization of BE requirements

- Needed to minimize BE study redundancy for global registration — Olde
- Reference product issues across different regions — Olde
  - Ideally, would like to conduct one BE study against a reference product from one region, and file it in multiple regions, but not accepted by most regulatory authorities
  - Inequivalent reference product formulations in different regions
- BE approaches differ among different regions — Olde
- Global Bioequivalence Harmonization Initiative (GBHI) – limited success — New

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Upcoming event of interest:

Streamlining Generic Drug Development by Matching Reference Product Composition and Performance, *In Vitro* and *In Vivo*
October 18 – 19, 2018
Baltimore, MD

Scientists Advancing Affordable Medicines, Inc.
https://saamnow.com

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THANK YOU

With special thanks to my industry colleagues who contributed their current issues and valuable suggestions under conditions of anonymity, and to the outstanding panelists.

BACKUP SLIDES

(available post-conference)

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