Common Bioequivalence Deficiencies in Abbreviated New Drug Applications for Extended-Release Drug Products

Juhyun Kim, Ph.D.
Division of Bioequivalence III, Office of Bioequivalence,
Office of Generic Drugs
CDER | US FDA

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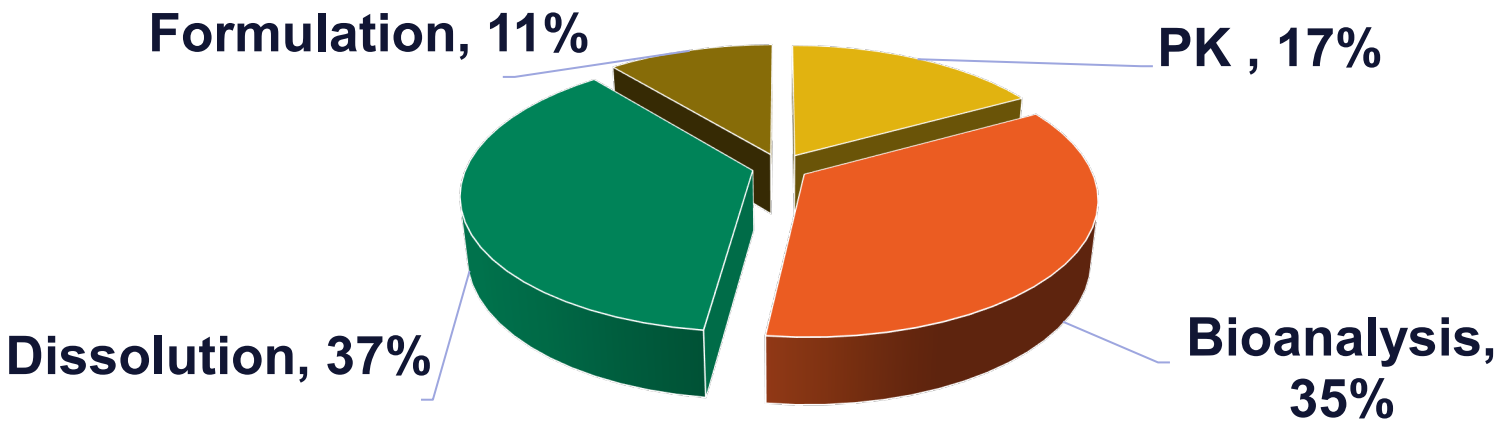
Outline

- Common bioequivalence (BE) deficiencies identified for extended-release (ER) drug product
- First-cycle BE adequacy rate and review time for ER drug product
- Case study for BE deficiencies on dissolution testing using scored tablets
- Recommendations for avoiding BE deficiencies

Learning Objectives

- Summarize common first-cycle BE deficiencies in ANDAs for ER drug products
- Learn from a case study on BE deficiencies in ER formulations to better understand the common BE deficiencies impacting 1st cycle approval for ER products
- Identify strategies to prevent some of these deficiencies

Common BE Deficiencies for ER Drug Product



157 ANDAs[1] were submitted until 12/31/2024.
224 first cycle deficiencies were identified.

[1] **Evaluated ER Tablet Drug Products**: (1) Memantine, (2) Oxymorphone, (3) Tramadol, (4) Metoprolol Succinate, (5) Paliperidone, (6) Glipizide, (7) Oxybutynin Cl, and (8) Quetiapine Fumarate.

Common BE Deficiencies for ER drug Product (cont'd)

- **Dissolution (37%)**
  - ✓ Missing/inadequate multi-pH media dissolution - 9%
  - ✓ Missing/inadequate dissolution data for scored tablets – 9%
  - ✓ Lack of discriminatory ability for the dissolution method – 9%
  - ✓ Missing/inadequate alcohol dose-dumping data – 6%
- **Pharmacokinetics (17%)**
  - ✓ Subject exclusion without proper justification – 4%
  - ✓ Missing/inadequate information on failed/pilot study – 4%
  - ✓ Incomplete SAS Transports files – 4%

Common BE Deficiencies for ER drug Product (cont'd)

- **Bioanalysis (35%)**
  - ✓ Missing analytical raw data and chromatogram - 10%
  - ✓ Inadequate sample re-analysis – 8%
  - ✓ Missing Standard Operating Procedure and/or validation – 6%
  - ✓ Missing/inadequate stability data – 5%
- **Formulation (11%)**
  - ✓ Exceed excipient level – 4%
  - ✓ Missing information on colorant, flavor or shell – 4%

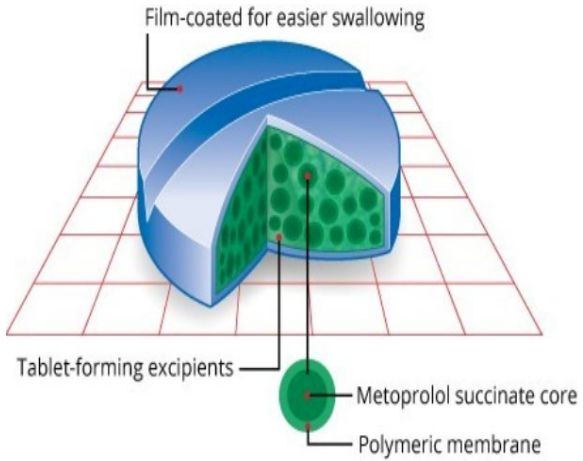
First-Cycle BE Adequacy Rate and Review Time for ER Drug Product

Received Date	Number of ANDAs	1st Cycle BE Adequacy Rate	Review Time*
Prior to GDUFA (≤ 9/30/2012)	63	11%	22.4 months
GDUFA I (10/1/2012 – 9/30/2017)	63	52%	17.0 months
GDUFA II (10/1/2017 – 9/30/2022)	25	76%	7.0 months
GDUFA III (10/1/2022 – 12/31/2024)	6	83%	8.1 months

* **Review Time**: Time from FDA received the application to the first complete BE review with an outcome of either BE adequate/BE inadequate (CRL).

Case Study: Dissolution using Scored Tablets

Metoprolol Succinate ER Tablets, 100 and 200 mg



https://www.toprol-xlhcp.com/02-patented-tech.html

- TOPROL-XL (RLD) was designed as
  - The tablets comprise a multiple unit system containing metoprolol succinate in a multitude of controlled-release pellets
  - Each pellet acts as a separate drug delivery unit
  - A scored tablet and can be divided

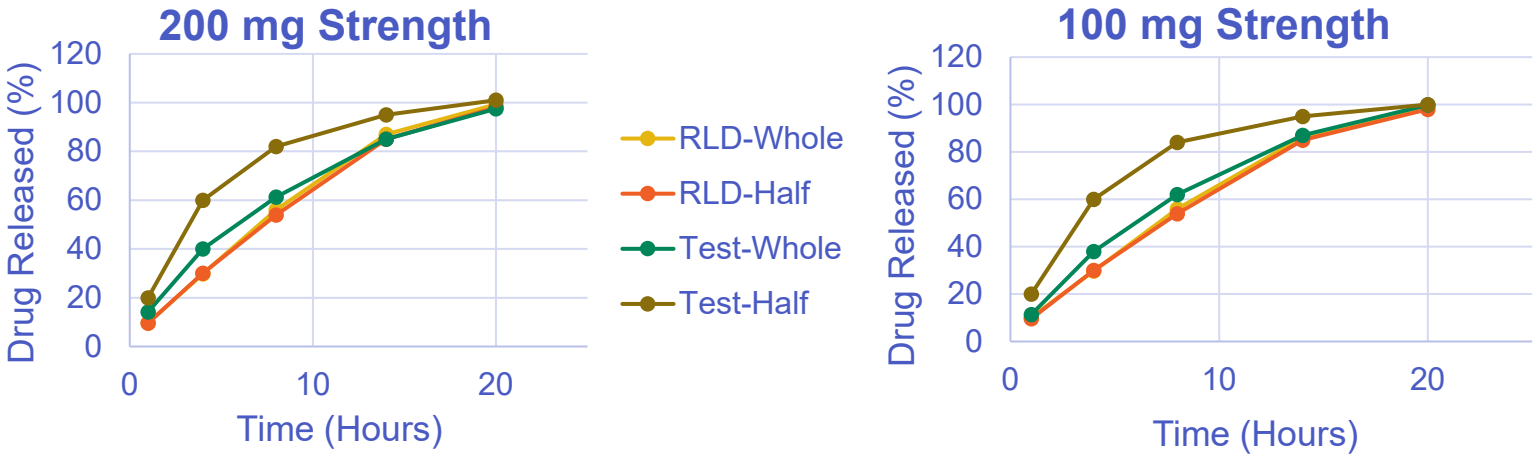
Product Specific Guidance (PSG) Recommendation: (1) *In vivo* fasting and fed BE studies on the 200 mg strength, (2) Compendial dissolution testing: whole tablets and half tablets, (3) Multimedia dissolution testing, (4) In vitro alcohol dose-dumping testing

PSG on Metoprolol Succinate ER tablets: https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_019962.pdf.

Case Study: Dissolution using Scored Tablets (hypothetical)

Metoprolol Succinate ER Tablets, 100 and 200 mg

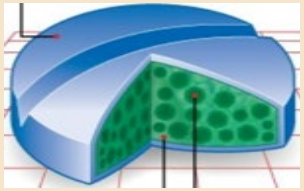
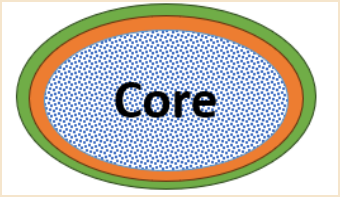
- **Compendial Dissolution Testing: Whole Tablets and Half Tablets**



- **Fasting and fed BE studies on the 200 mg whole tablets**: Acceptable
- **Dissolution testing on whole tablets for both strength**: Acceptable

Case Study: Dissolution using Scored Tablets (hypothetic)

Metoprolol Succinate ER Tablets, 100 and 200 mg

Reference Product (TOPROL-XL)	Test Product
• Multiple unit system • No functional coating 	• Core: Drug loaded matrix • Functional coating 
• Comparable dissolution profile for half and whole tablets for both strength	• Half tablets released faster than whole tablets for both strength

1st cycle deficiency: 1) fasting and fed BE studies on the 200 mg strength *half tablet*; comparative multi-pH dissolution testing and in vitro alcohol dose dumping testing on *half tablets* of both strengths; or 2) alternatively reformulate the test products

Case Study: Dissolution using Scored Tablets (hypothetic)

Metoprolol Succinate ER Tablets, 100 and 200 mg

- **Applicant's Response to 1st Cycle Deficiencies**
  - ✓ Applicant conducted fasting and fed BE studies on the 200 mg half tablet for test and reference standard drug product.
  - ✓ Both fasting and fed studies on half tablets failed due to 90% CIs of Cmax did not fall within the limits of 80.00-125.00% (failed in the upper limit).
- **2nd Cycle Deficiency**: Applicant was asked to reformulate.
- **Tip for Avoiding Deficiencies**: understand formulation design of RLD drug product

Recommendations for Avoiding BE Deficiencies

- **Dissolution**
  - ✓ Check the product-specific guidance (PSG) and relevant general guidance for identify adequate dissolution testing
  - ✓ Generate dissolution data using a discriminating method
  - ✓ Conduct dissolution testing on fresh lot or ensure the test product stability at the time of the dissolution study
- **Bioanalysis**
  - ✓ Submit 100% analytical raw data including rejected and repeat runs and chromatograms from 20% of serially selected subjects
  - ✓ Provide justification with supporting documentation/data for sample re-analysis

Recommendations for Avoiding BE Deficiencies

- **Formulation**

✓ Provide quantitative breakdown of colorants, ink, flavors, capsule shells etc.

✓ Submit a Control Correspondence if you need clarification on whether the proposed levels of inactive ingredients in the test product are acceptable

- **Pharmacokinetics**

✓ Submit the investigation report with real-time evidence to support exclusion of concentration data of subject in BE statistical analysis

✓ Provide SAS data in proper format and data in SAS file match data presented in BE study report. All clinical trial studies starting after 12/17/2016 are required to have data submitted in Clinical Interchange Standards Consortium (CDISC) compliant format (https://www.cdisc.org/standards/foundational/sdtmig)

Summary

- Out of 157 ANDA, 224 deficiencies were identified in the first-cycle BE assessment for ER drug products.
- Various deficiencies identified during BE review for oral ER products are avoidable and occur repeatedly.
- Submitting thorough, well-structured, and acceptable BE data for ANDAs will greatly benefit the generic drug industry and the American Public by facilitating faster and wider availability of generic drugs.

Acknowledgements

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Thank you!