

# 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

(April 10, 2025)

Disclaimer: This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

# Outline



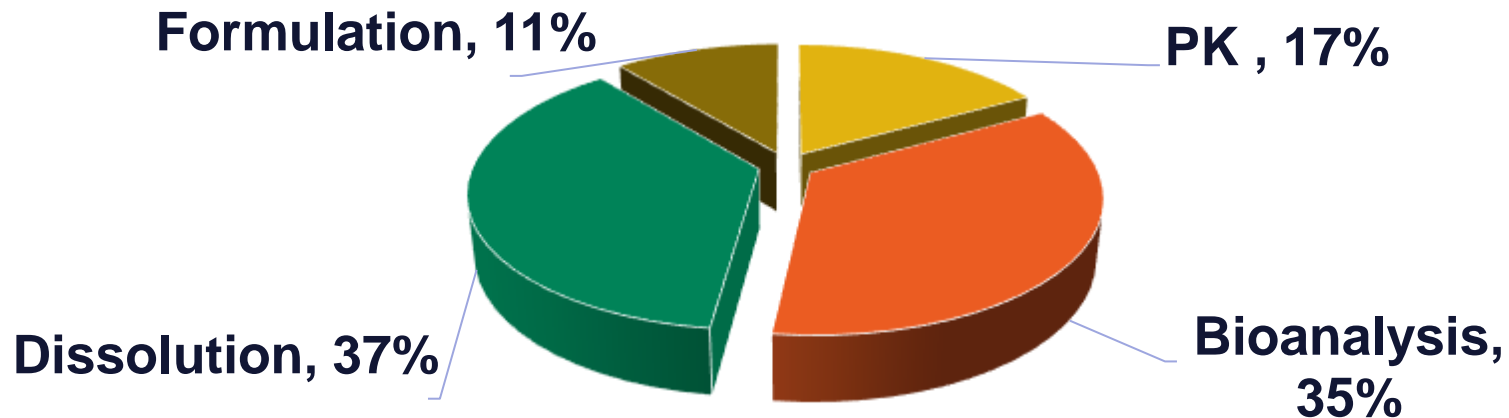
- Common bioequivalence (BE) deficiencies identified for extended-release (ER) drug product
- First-cycle BE adequacy rate and review time for ER drug product
- Case study for BE deficiencies on dissolution testing using scored tablets
- Recommendations for avoiding BE deficiencies

# 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 1<sup>st</sup> cycle approval for ER products
- Identify strategies to prevent some of these deficiencies

# Common BE Deficiencies for ER Drug Product



**157 ANDAs<sup>1</sup>** were submitted until 12/31/2024.  
**224 first cycle deficiencies** were identified.

<sup>1</sup> **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

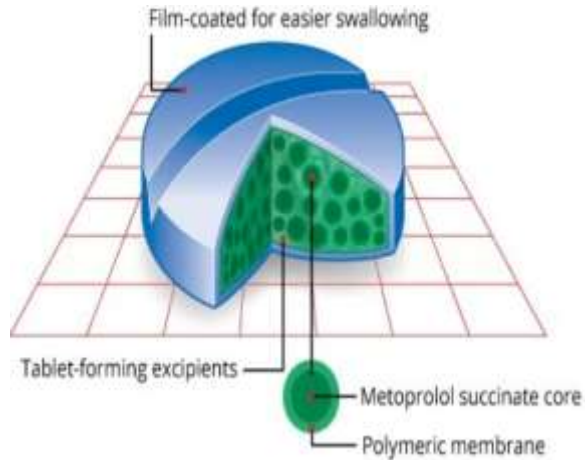


Received Date	Number of ANDAs	1 <sup>st</sup> Cycle BE Adequacy Rate	Review Time*
<b>Prior to GDUFA</b> (≤ 9/30/2012)	63	11%	22.4 months
<b>GDUFA I</b> (10/1/2012 – 9/30/2017)	63	52%	17.0 months
<b>GDUFA II</b> (10/1/2017 – 9/30/2022)	25	76%	7.0 months
<b>GDUFA III</b> (10/1/2022 – 12/31/2024 )	6	83%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



- 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

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

**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](https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_019962.pdf).  
[fda.gov/cdersbia](https://www.fda.gov/cdersbia)

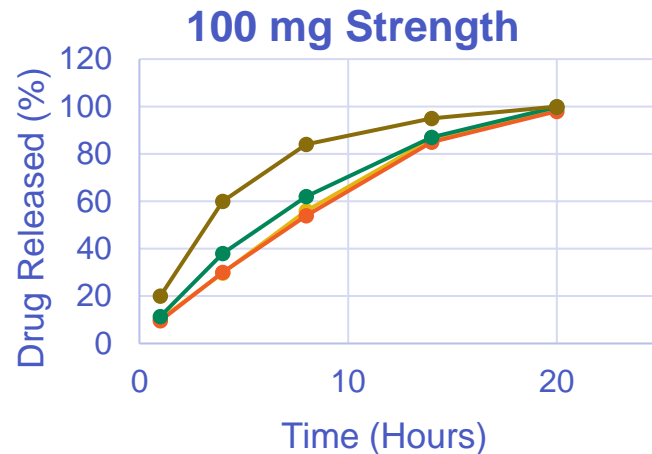
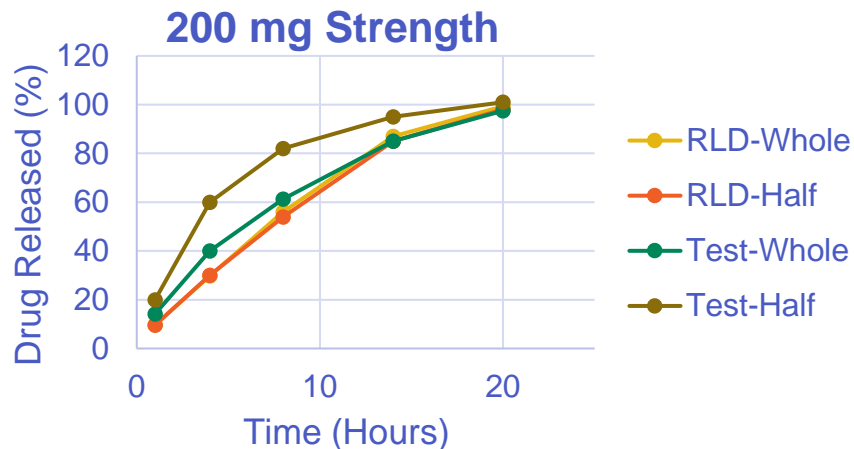


# Case Study: Dissolution using Scored Tablets (hypothetic)

Metoprolol Succinate ER Tablets, 100 and 200 mg



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

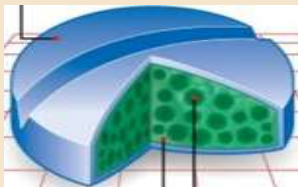



- Fasting and fed BE studies on the 200 mg whole tablets: Acceptable**
- Dissolution testing on whole tablets for both strength: Acceptable**

# Case Study: Dissolution using Scored Tablets (hypothetic)

Metoprolol Succinate ER Tablets, 100 and 200 mg



Reference Product (TOPROL-XL)	Test Product
<ul style="list-style-type: none"><li>• Multiple unit system</li><li>• No functional coating</li></ul>  <p>A 3D perspective diagram of a white, oval-shaped tablet. The tablet is scored down the middle. One half is shown in cross-section, revealing a green matrix with numerous small, dark green circular units embedded within it. The other half of the tablet is shown in its entirety, with a red line indicating the score.</p>	<ul style="list-style-type: none"><li>• Core: Drug loaded matrix</li><li>• Functional coating</li></ul>  <p>A cross-sectional diagram of an oval tablet. It features a central blue region with a stippled texture, labeled "Core" in bold black text. This core is surrounded by a thin orange layer, which is in turn surrounded by a thicker green layer, representing the functional coating.</p>
<ul style="list-style-type: none"><li>• Comparable dissolution profile for half and whole tablets for both strength</li></ul>	<ul style="list-style-type: none"><li>• Half tablets released <b>faster</b> than whole tablets for both strength</li></ul>

**1<sup>st</sup> 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 1<sup>st</sup> 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 C<sub>max</sub> did not fall within the limits of 80.00-125.00% (failed in the upper limit).

- **2<sup>nd</sup> 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



- **Dr. April Braddy**, Director of Division of Bioequivalence III (DBIII)/Office of Bioequivalence (OB)/Office of Generic Drugs (OGD)
- **Dr. Ke Ren**, Deputy Director of DBIII/OB/OGD
- **Dr. Yi Zhang**, Associate Director of DBIII/OB/OGD
- **Dr. Li Gong**, Lead Pharmacologist of DBIII/OB/OGD
- **Dr. Fang Lu**, Lead Pharmacologist of DBI/OB/OGD
- **Dr. Bing Li**, Associate Director of OB/OGD
- **Dr. Partha Roy**, Director of OB/OGD

# Thank you!

