Common Deficiencies with Bioequivalence Submissions in ANDAs

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This presentation represents the personal opinions of the speaker and does not necessarily represent the views or policies of US FDA
Generic Drugs Make Up 86 Percent of U.S. Retail Prescriptions: GPhA

• Generic drugs account for **86% of all prescriptions dispensed in the U.S. market**, according to a new study.

• Generics has skyrocketed over the past 10 years, from 57 percent in 2004 to 84 percent in 2012, according to a new IMS Health study commissioned by GPhA.

• Helping precipitate the expected drop over the next decade in Medicare and Medicaid spending.

We should all be proud of the impact we have made on the public health and practice of medicine!

http://www.gphaonline.org/
“GDUFA is a historic achievement and shared commitment for the FDA and our industry,” said Ralph G. Neas, President and CEO, GPhA.
OGD Perspective

✓ Increased complexity of dosage forms
✓ New approaches at determining BE

What are the practical issues expected in the incoming ANDA submissions?

How do we (OGD) prepare ourselves to solve these issues under tight GDUFA deadlines?
Office of Bioequivalence (OB) Reorg

John Peters
Acting Director

Dale Conner
Acting Deputy Director

Consistency in our review processes within OB
Communication to Industry of the common BE deficiencies


Avoiding common mistakes in BE submissions will help expedite ANDA review
Outline

• Deficiency types from DBs
  – Dissolution
  – ECD
  – Complete Response (CR)
• Common Deficiencies from each type
• Recommendations for improving application quality
• Summary and Conclusions
Types of BE deficiencies and % of total deficiencies in each category

- Dissolution methods: 16.55%
- Dissolution other: 10.30%
- Bio-summary tables: 14.70%
- Unjustified exclusion of subjects: 12.50%
- Potency, formulation, content uniformity: 10.80%
- Long-term storage stability: 9.20%
- Analytical issues: 7.30%
- General others: 0.90%

1. Types of deficiencies: dissolution-only reviews

- Deficiencies related to Dissolution Testing

  - The dissolution portion of the ANDA submissions are reviewed separately from the bioequivalence studies

  - Does not include dissolution testing for biowaiver or other purposes (e.g., BCS-based waiver, lower strength waivers, alcohol dose dumping, multi-media testing for MR products, etc.)

  - Completed early in review calendar in order to establish a dissolution method and specification for stability testing
Historical Perspective: Importance of Dissolution Database

- Created November 2005
- Provides information about the *in vitro* dissolution methods to be tested for incorporation into a drug product’s stability and QC program
- Since implementation of database, dissolution deficiencies have gone down

Dissolution reviews completed in past 3 months (07/01 – 09/30/2014)

- Originals: 47%
- Amendments: 53%
Dissolution review of originals

* Includes all other dissolution related deficiencies such as typos in tables, clarification questions on method, etc.
Dissolution review of amendments

* Includes deficiencies such as clarification questions on method, etc.
Common Dissolution Deficiencies

• Most common examples:
  – FDA recommends a specification
  – Provide additional comparative dissolution testing data
  – Provide individual unit data
  – FDA does not set specifications based on data collected using aged lots
2. Types of Deficiencies: ECDs

• Easily Correctable Deficiencies (ECDs)
  
  – Can be for dissolution review or full bio-review
  
  – Requires only a modest expenditure of FDA resources
  
  – An applicant should be able to respond to an ECD quickly
  
  – ECD pathway will not be taken if a CR is pending with deficiencies from other discipline(s) and a goal date will be missed otherwise
ECD examples: Electronic table issues

• Not filled out completely
  – Instead of data, information about the relevant volume and page number inserted
  – Not all strengths listed in formulation tables
  – Missing information (e.g. COA is missing information; RLD COA not included)

• Not prepared properly
  – File created by scanning tables rather than by creating a PDF file
ECD examples: Electronic table issues (cont.)

- Not submitted in both Word and PDF formats
- Summary tables are not submitted in one location
  - Module 2
- Inaccurate or incomplete information
  - Formulation: include quantitative breakdown of inks, colorants, capsule shells, etc.
  - Non-standard meal composition
ECD examples: SAS® file issues

• Not submitted in proper format
  – Data should be in .xpt file

• Data in SAS file does not match data presented in study report
  – Data is from another study for an unrelated ANDA
  – Sampling times in report and file do not match
  – Data for fasting study is the same as data for fed study
Additional Common ECDs

• Generally, any deficiency that does not require new data to be generated, for instance:
  – 20% chromatograms
  – Raw data
  – Reports (clinical, bioanalytical, statistical)
  – SOPs (informational)
3. Types of Deficiencies: CRs

• Deficiencies included in a Complete Response (CR) letter
  – Includes comments from all involved disciplines
  – Requires more expenditure of FDA resources
BE reviews completed in past 2 months (08/01 – 09/30/2014)

Note: LTSS is included in bioanalytical issues.
Statistics on common bioanalytical deficiencies

- Data collected over a 10-year period (2001 – 2011)
- 4028 ANDAs were surveyed
- Purpose: ID commonly occurring bioanalytical deficiencies
- Three categories: method, validation, and report

Number of bioanalytical deficiencies in ANDAs

![Bar chart showing the number of bioanalytical deficiencies from 2001 to 2011.](chart.png)
Global bioanalytical deficiencies statistics

- Bioanalytical method: 62%
- Bioanalytical method validation: 35%
- Bioanalytical report: 3%
Percentage of applications that contained bioanalytical deficiencies

![Bar chart showing the percentage of applications with bioanalytical deficiencies over years. The chart indicates a trend with the highest percentage in 2011 at N = 461.](image)
Percentage of deficiencies issued where one of the deficiencies was for LTSS
Deficiencies related to bioanalytical methodology

- Metabolite/parent not measured
- Calibration and quality control (QC) values not within range of subject samples
- Method cannot differentiate isomers

A: Inappropriate method
B: Inadequate measurement
C: Assay methodology is missing
D: Differentiation of isomers is not specified
E: Back-conversion of parent/metabolite is not reported
Deficiencies related to bioanalytical method validation

- Inadequate long-term storage stability
- Recovery data missing/miscalculated
- No anti-coagulant effect study

A: LTSS
B: Dilution Integrity
C: Missing validation data
D: Missing assay dates
E: Anticoagulant used is not specified
Deficiencies related to bioanalytical report

- Sample re-assays data missing/needs clarification
- Raw data not submitted for all subjects
- Missing dates of analysis

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<th>C: Missing or inadequate justification for reassayed samples</th>
<th>D: Missing dates of sample analysis</th>
<th>E: Acceptance criteria for batch runs missing</th>
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Summary and conclusions

• DBs provide deficiencies specific to dissolution early in review cycle.

• ECDs require only a modest expenditure of FDA resources, and an applicant should be able to respond to an ECD quickly.

• CRs often contain bioanalytical deficiencies, and many of these deficiencies are related to method validation.

• Avoiding common mistakes in BE submissions will help expedite ANDA review.
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Thank you for your attention!