Analysis of ANDA Major Bioequivalence Deficiencies

2024 GRx + Biosims

ANDA Deficiency Trends: Common Issues to Improve ANDA Submission Quality

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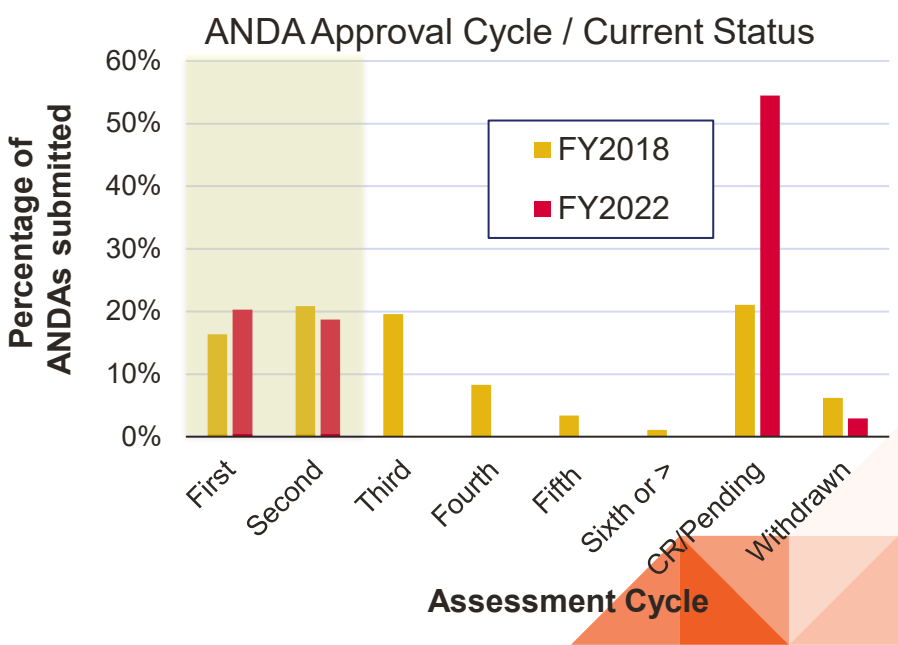
Outline

- Analysis of recent abbreviated new drug application (ANDA) submissions (FY18 to FY23), approval rates, and major deficiency trends based on size of generic industry (number of approved ANDAs in company portfolio) and generic drug product complexity.
- Major bioequivalence (BE) deficiencies and detailed analysis of common BE deficiencies for topical dermatological product ANDAs.
- FDA initiatives and programs to address common issues and facilitate more first and second cycle ANDA approvals.

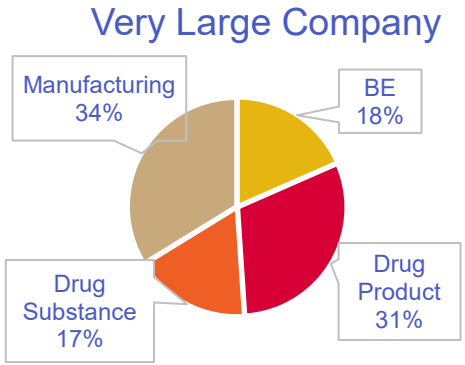
FY2018 & FY2022 ANDA Submissions

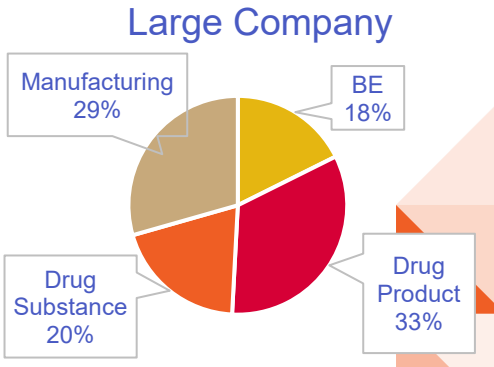
- Approximately 38-40% of FY18 and FY22 ANDAs were approved by the second assessment cycle (applicant has received one complete response (CR) letter before approval). FDA and generic industry should strive to increase the percentage of ANDAs approved by second cycle.
- Complex products accounted for ~14% and ~17% of ANDA submissions in FY18 and FY22, respectively. Approximately 25% of these complex product ANDAs were approved by the second cycle.
- ANDAs submitted in FY18 and FY22 provide sufficient time for at least two assessment cycles. Most FY18 ANDAs should be close to final action status (e.g., approved or withdrawn / abandoned) where most FY22 ANDAs in CR will come back for third cycle.

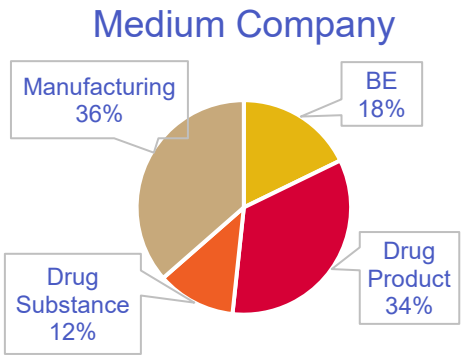


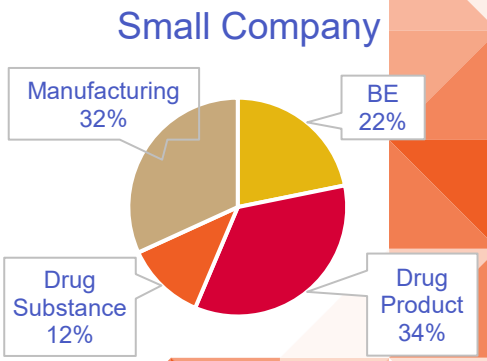
First Cycle Major Deficiencies

- Approximately 300 different companies submitted ANDAs in FY18 & FY22.
  - **Very Large Company**[1] (>100 ANDAs), **Large** (< 100 ANDAs > 20), **Medium** (< 19 ANDAs >6), **Small** (< 6 ANDAs)
- Very large companies submitted half of all ANDAs.
  - Complex product ANDAs make up 18% of ANDAs submitted by Very Large and Small companies. 10% of ANDAs submitted by Large and Medium sized companies are for complex products.
- Manufacturing and Drug Product are most common major deficiencies at the first cycle CR regardless company size.





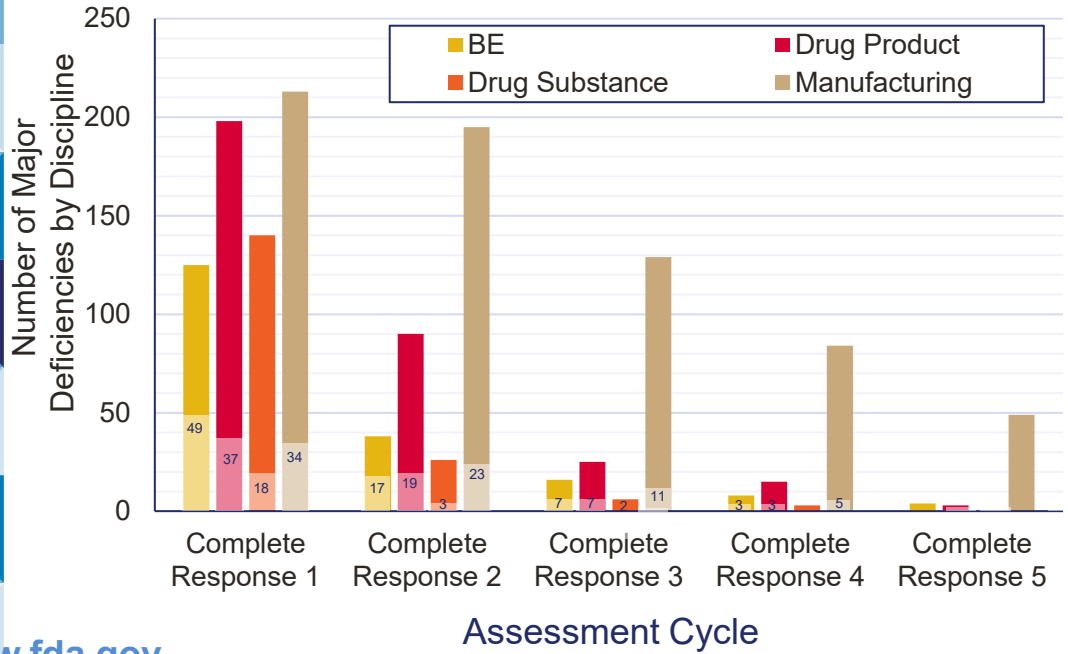




1. Company size is based on number of approved ANDAs held by the parent company in 2023. GDUFA Program Fee does not include a very large company definition/category. Very large was arbitrarily defined as having more than 100 ANDAs.

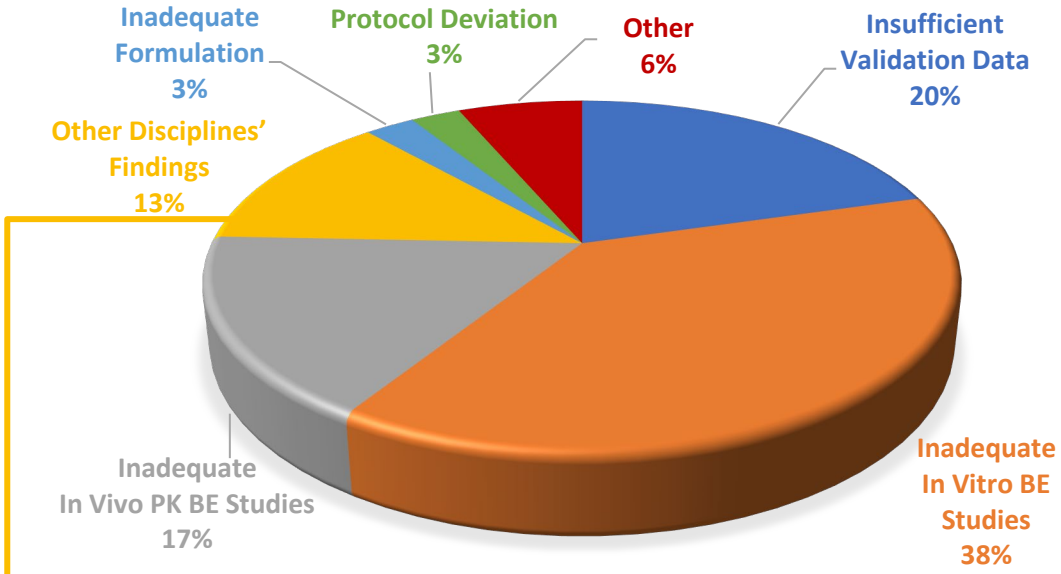
Major Deficiencies by Discipline

- ANDAs submitted in FY18 were more likely to have a major manufacturing deficiency at each review cycle. Other major deficiencies were generally resolved by second or third assessment cycle.



- Complex products (lighter shaded data with labels) generally make up a larger percentage of major BE (~40%) and Drug Product (~20%) deficiencies in the first CR even though they are ~14% of ANDA submissions in FY18.
- Manufacturing deficiencies do not appear to be dependent on product complexity
  - Manufacturing major for complex products is ~14%, which is similar percentage of complex ANDA submissions (~14%) in FY18.

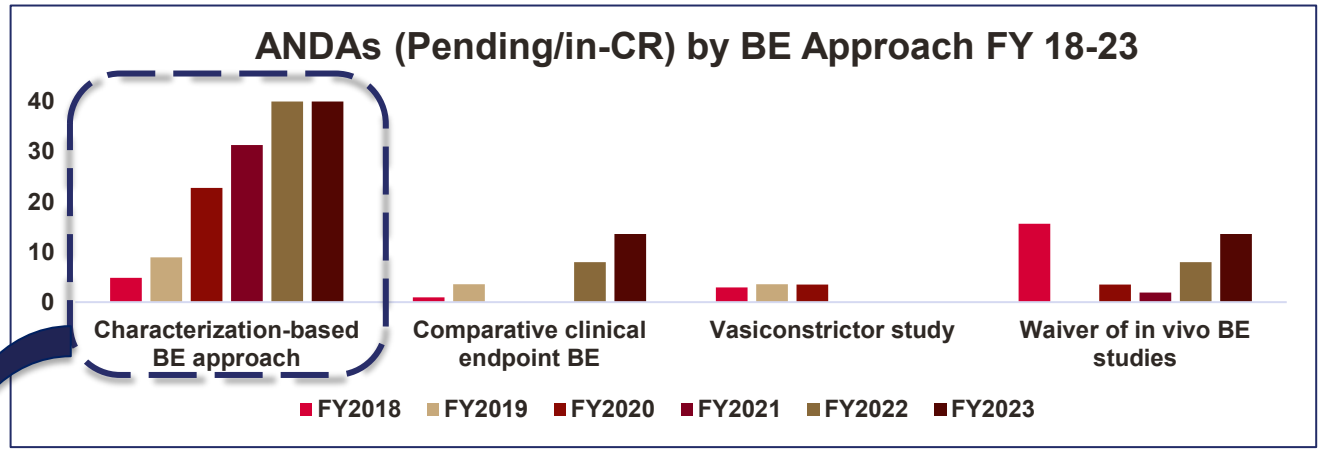
FY23 Bioequivalence Major Deficiencies

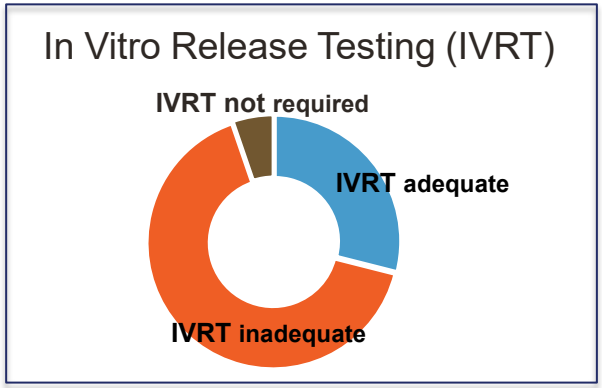


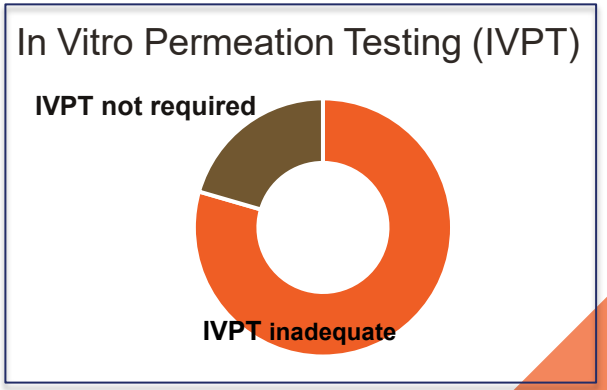
Impacts From Other Disciplines' Findings Include:
Inadequate RRA (Remote Regulatory Assessment) Findings
Inadequate Bio-batch due to API (Active Pharmaceutical Ingredient) Sameness Issues
Inadequate Formulation due to Excessive Excipients' Amounts Causing Safety Concerns
Inadequate Formulation due to Excipients with Unknown Safety Profiles
Bioequivalence Waiver Request Denied due to Unacceptable User Interface Design

- **Insufficient Validation Data:** Bioanalytical method
  - Information on sample stability, changes in matrix, or method may be not suitable (e.g., LLOQ, poor chromatograms)
- **In Vitro BE Studies:** IVRT/IVPT/ in vitro binding studies
  - Method development and validation information to support the in vitro release/permeation testing (e.g., discriminatory ability, justification for conditions), or achieving maximum binding

Common In Vitro BE Deficiencies for Topical Dermatological ANDAs







Identifying and Resolving Issues Before they Become Deficiencies

- GDUFA III initiatives and opportunities for enhanced communication throughout the generic drug process to help identify resolutions to (potential) major deficiencies.
  - Control correspondences, development meetings, discipline review letters (DRL), information requests (IR), Mid-cycle review meetings, post-CR meetings, etc.
- Targeted workshops on development issues for specific classes of products and issues.
  - SBIA workshops and webinars are informational sessions on processes, best practices, and common issues/deficiencies with generic drug development (pre-ANDA) and ANDAs. These are recorded and publicly available: https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/cder-small-business-and-industry-assistance-sbia-learn
  - Center for Research on Complex Generics (CRCG) includes interactive workshops on complex scientific issues and considerations. These are recorded and publicly available: https://www.complexgenerics.org/education-training/
- FDA strives to provide clarity, where possible, through general guidance and product-specific guidance (PSG) as well as make regulatory and scientific research findings publicly accessible through presentations, publications, and white papers.

Targeted Resources: Addressing Common Topical IVRT & IVPT Study Deficiencies

In addition to application specific GDUFA III communication, FDA routinely develops and delivers guidances and publicly available recoded content on common issues and best practices:

- FDA Draft Guidances for Industry:
  - *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs* (Oct 2022)
  - *In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs* (Oct 2022)
- PSGs reflect FDA's current product-specific thinking on IVRT and/or IVPT studies to support BE, FDA forecasts PSGs
- SBIA Presentations/Webinars:
  - In Vitro Bioequivalence Studies of Topical Drug Products: Challenges and Promises of IVRT and IVPT (Sept 29, 2020)
  - Common Issues Identified in IVRT and IVPT Studies Submitted in ANDA to Support BE for Topical Products (Sept 21, 2021)
  - Theoretical Principles and Best Practices IVRT (Sept 21, 2021)
  - Theoretical Principles and Best Practices IVPT (Sept 21, 2021)
  - Practical Considerations Related to IVPT Studies for Topical Products Submitted in ANDAs (Aug 11, 2022)
  - Practical Considerations for IVRT Studies with Topical Drug Products Submitted in ANDAs (Aug 11, 2022)
  - General Guidances Related to Characterization-Based Bioequivalence Approaches for Topical Products (Sept 13, 2023)
  - An Overview of the Current Product-Specific Guidances for Topical Products (Sept 13, 2023)
  - Guidance Development and Regulatory Assessment of Generic Topical and Dermal Drug Products (Oct 3, 2024)
- CRCG Workshops:
  - In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods: Best Practices and Scientific Considerations for ANDA Submissions (Aug 18-20, 2021)
  - Implementing FDA's IVPT Guidance Recommendations: A Step-By-Step Illustration (May 27-28, 2025)

Conclusions

- Approximately 40% of submitted ANDAs are approved by the second assessment cycle. Remaining 60% of ANDAs have continued unresolved deficiencies that require additional cycles and prevent approval.
- Manufacturing (largely facility related), drug product, bioequivalence, and drug substance are the top (sub)disciplines identifying major deficiencies in the first assessment cycle.
- Most common major BE deficiency (38%) are for inadequate in vitro studies.
  - Inadequate IVRT and IVPT studies are most common major BE deficiencies for topical dermatological product ANDAs that utilized a characterization-based BE approach.
- FDA and GDUFA III initiatives have enhanced communication with applicants to improve ANDA assessment efficiency and reduce common deficiencies.
  - PSGs, control correspondences, GDUFA meetings, DRLs, IRs, workshops and webinars
  - More than 175 topical dermatological ANDAs received since FY18, have been approved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Questions?