

Generic Drug Development and Safety Evaluation

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Outline



1. Basis for Generic Drug Approvals
2. Contents of an Abbreviated New Drug Application (ANDA)
3. Generic Drug Development
 - Pharmaceutical Equivalence
 - Bioequivalence
 - Therapeutic Equivalence
4. Generic Drug Safety Surveillance
 - Premarket
 - Postmarketing

Generic Drug Approval

- Approval of generic drug starts with a “listed drug” – generally an “innovator” or “brand name” drug.
 - This is the reference listed drug (RLD)
- Abbreviated New Drug Application (ANDA) relies on FDA’s finding of safety and effectiveness for the RLD during the Investigational New Drug (IND) and New Drug Application (NDA) phases of drug review.
- Requires demonstration of “sameness” of a number of characteristics + additional information to permit reliance on the RLD

Modern Generic Drug Approval Pathway



Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)

- First statutory provisions expressly pertaining to generic drugs.
- Created the basic scheme under which generic drugs are approved today.
- Allowed FDA to approve - under new section 505(j) - generic applications for duplicates of drugs submitted under 505(b).



Hatch-Waxman Amendments

- Brand Industry Gains:
 - 5-year New Chemical Entity (NCE) Exclusivity
 - 3-year New Clinical Studies Exclusivity
 - Patent Term Extension to account for time patented product is under review by FDA
- Generic Industry Gains:
 - ANDA pathway
 - Ability to challenge brand drug patents in court prior to marketing
 - 180-day Generic Drug Exclusivity



Contents of an ANDA: 505(j)(2)

- Identify Single RLD
- Same Conditions of Use
- Same Active Ingredient
- Same Route of Administration
- Same Dosage Form
- Same Strength
- Same Labeling
- **Bioequivalence**
- Safety of Inactive Ingredients

Contents of an ANDA (cont.)

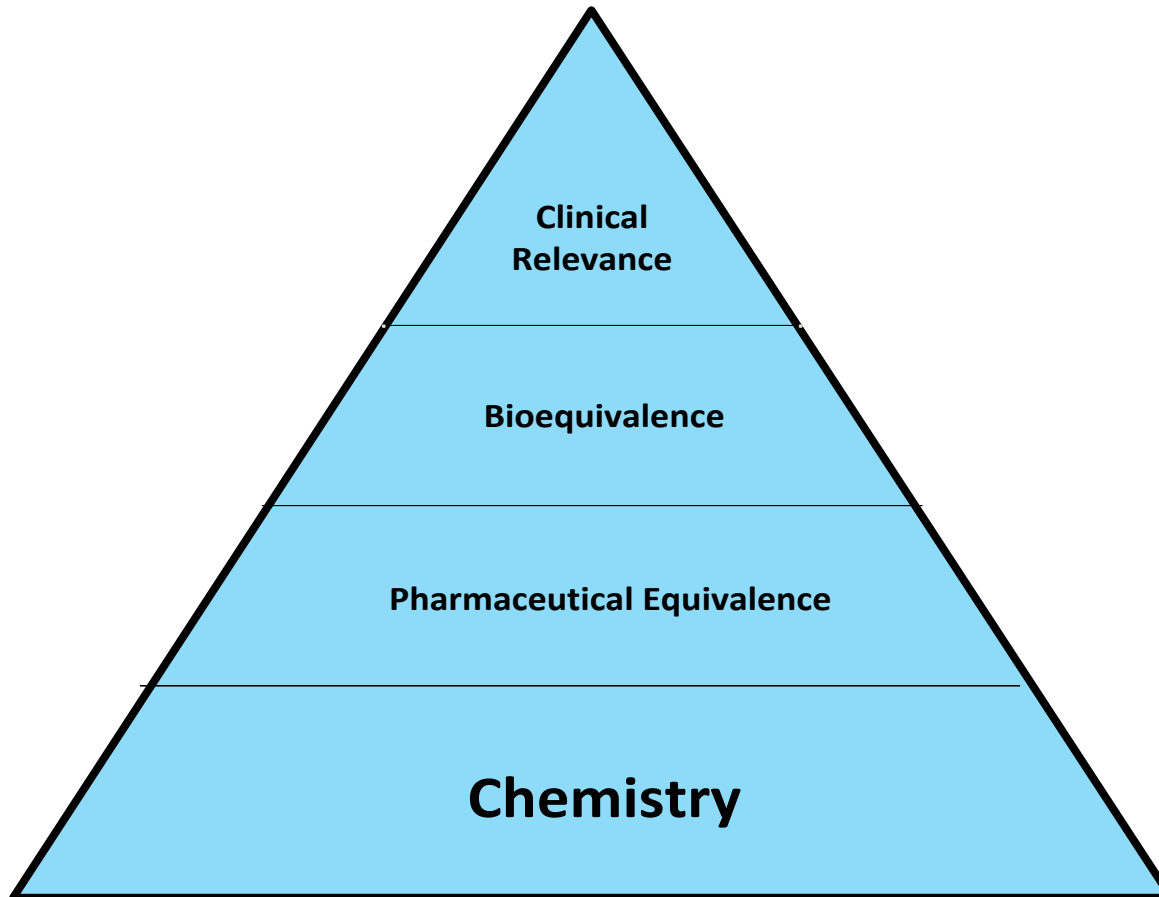
- Patent Certifications, Exclusivity Information
- Chemistry, Manufacturing, and Controls (CMC) Information – same standards as new drugs
- Basis for **Pharmaceutical Equivalence (PE)**
 - Components and composition
 - Manufacturing and controls
 - Batch formulation and records
 - Description of facilities
 - Specifications and tests
 - Packaging
 - Stability

Current Good Manufacturing Practices



- ANDAs are held to same high standards for current good manufacturing practices (cGMPs) as NDAs
- Purpose - to assure quality of marketed drug products
- Mechanisms - Product Testing
 - Surveillance inspections
 - Manufacturing/Testing plant inspections
 - Assess facility compliance with good manufacturing practices

Foundation for Identity of Generic Drugs



Same Active Ingredient

- **Active Ingredient** - component intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man
- What does “same” active ingredient mean?
 - Different polymorphic forms (crystalline & amorphous forms, solvates & hydrate forms) are generally same active ingredient; different salts and esters are different active ingredients
 - Complex drug substances
 - New analytical technologies critical to new generic approvals



Pharmaceutical Equivalence (PE)

Pharmaceutical equivalence means:

“Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are formulated to contain the same amount of active ingredient, and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity).”

Source: Approved Drug Products with Therapeutic Equivalence Evaluations (“The Orange Book”)



Allowable Differences

The definition for PE allows for differences between generic drugs and the RLDs in “...characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients, expiration time, and, within certain limits, labeling.”

Excipients are any inactive ingredients that are added to drugs during manufacturing.

- Examples - fillers, extenders, solvents, preservatives, flavors and colors.
- Not specifically intended to exert a therapeutic effect
- Could aid in delivery by enhancing absorption or release



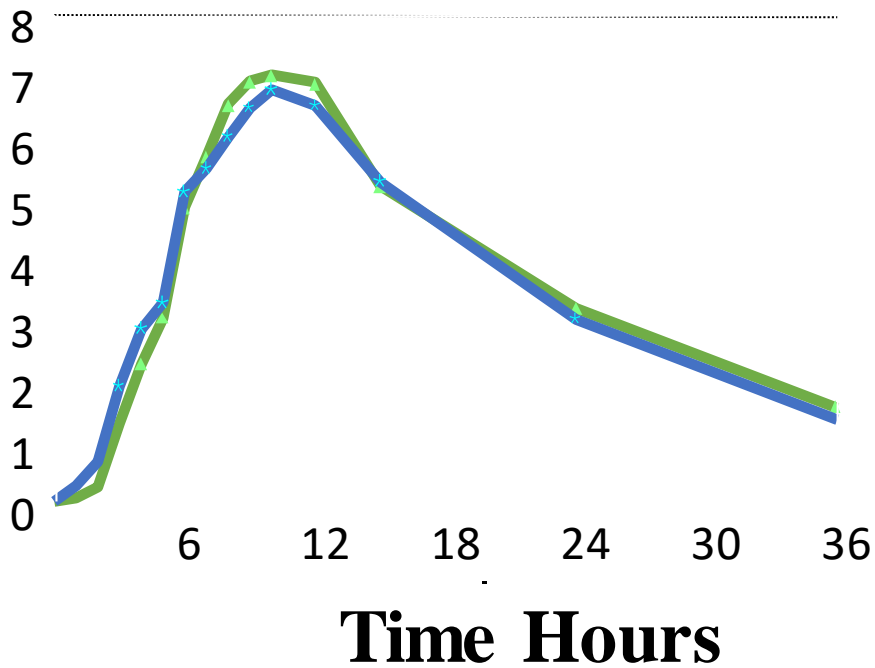
Bioequivalence (BE)

- BE studies demonstrate that the generic drug and the RLD deliver the same amount of the active drug and any active metabolites into the blood stream at the same rate for distribution to the drug's pharmacological site of action.
- The goal of premarket BE studies is to establish that a PE generic drug will perform in the same way as the RLD in vivo.

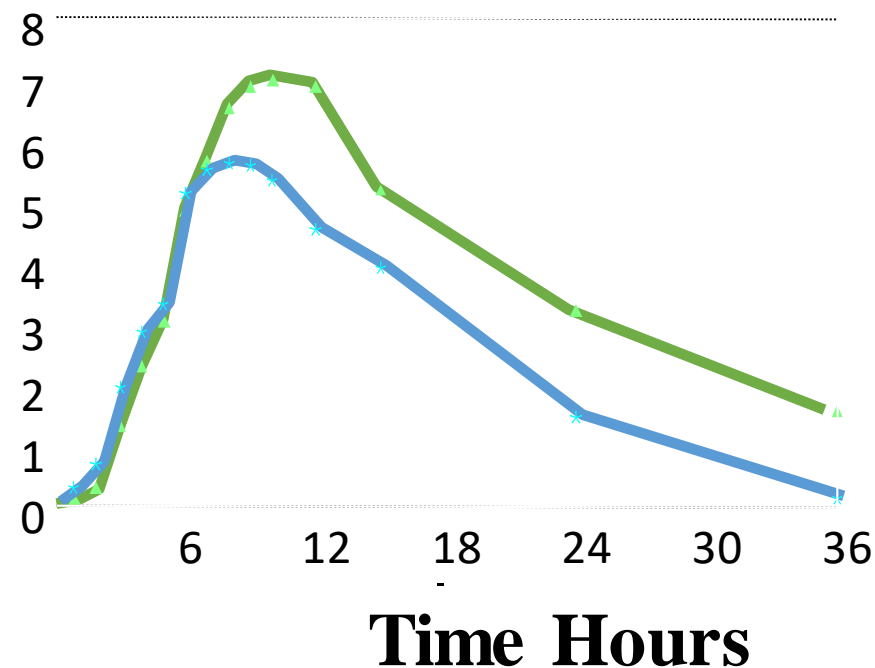
Bioequivalence (BE)

- BE analysis includes a robust statistical comparison of pharmacokinetic data for the generic and the RLD, including maximum concentration (C_{max}) and area under the curve (AUC).
- These measures serve as surrogates for the rate and extent of absorption.
- To demonstrate BE, the statistical analysis must show that the ratios (generic to RLD) of these parameters remain strictly within a 90% confidence interval of 0.80 to 1.25.

Bioequivalent



Inequivalent




Test/Generic

Reference/RLD

NDA vs. ANDA Requirements

Brand Name Drug NDA Requirements

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing

6. Animal Studies
 7. Clinical Studies
 8. Bioavailability
- 

Generic Drug ANDA Requirements

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing

6. Bioequivalence

Clinical Relevance

- A drug that is both PE and BE must be able to deliver the active ingredient to the site of action in the body **in the same clinically relevant way** as does the RLD to the indicated target population.
- **Therapeutic Equivalence (TE)** means that the criteria used to assess both PE and BE are relevant to the clinical intent of the design of the reference drug, as well as the specific target population, duration of use, and indication(s).

Why worry about generic drug safety?

- So why should we worry about the safety of generic drugs if they are PE, BE and TE?
- Shouldn't all generic drugs be safe if the RLD has been vigorously tested with animal studies and human clinical trials for safety through the NDA review process?



Bottom Line

- Although PE and BE analyses, along with inference of TE, build a coherent and concise model for generic drug assessments, there can still remain **unexpected safety considerations and concerns** that occur both before and after marketing of a generic drug.
- This is especially true when the generic drug begins to replace the RLD in the marketplace and use of the generic drug increases in a larger, more diverse patient population.
- But we can consider the safety of generic drugs both premarket and postmarketing

Premarket Safety Reporting Requirements for Generic Drugs



- Regulation: 21 CFR 320.31(d)(3) [Final Rule: 09/29/2010]
- Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (amended December 2012)
 - Pages 25-27: Requirements for BA/BE Studies
 - <https://www.fda.gov/downloads/Drugs/Guidances/UCM227351.pdf>
- Applies only to expedited serious adverse events in studies conducted within the United States
- The remaining adverse events that occur during BE studies conducted outside the United States are submitted with the final study report in the ANDA

Postmarketing Surveillance of Generic Drugs



Provides assurance that unanticipated factors or unanticipated variability causing **therapeutic inequivalence** will be identified early, allowing for corrective action.

Examples include:

- Reports of generic drug adverse events
- Quality problems
- Presumed product inferiority
- Suspected contamination
- Concern for difference in safety profile compared to the RLD



Scope of Generic Surveillance

Generic surveillance does NOT focus on complaints related to the active ingredient.

Generic surveillance DOES involve:

- Therapeutic inequivalence with complaints of lack of effectiveness
- Problems with quality - odor, taste, rapid oral disintegration
- Problems related to new unanticipated safety concerns not seen with the RLD
 - Problems related to off label use of the generic drug
 - Problems with packaging/device - dropper, cap, syringe, injector

Quality Issues and Complaints

- Treatment failure or excess adverse events
- Tablets breaking apart
- Scored tablets breaking unevenly or crumbling when split
- Tablets sticking in the throat
- Unusual odor, taste, smell, or texture
- Precipitates in oral liquids and injectables
- Patches not sticking
- Errors in packaging (wrong quantity)
- Container/closure issues
- Device issues
- Suspected contamination
- Dropper issues with ophthalmologic products
- Abnormal solubility
- Large size tablet/capsule



Potential Postmarketing Safety Signal Sources



- Contacts from the public directly communicated to FDA
- MedWatch reports submitted to FDA
- Identified in CDER's Office of Generic Drugs (OGD) and Office of Surveillance and Epidemiology (OSE) databases
- Sponsor reports
- Scientific literature

OGD definition of a potential signal may be different from that of OSE



Drug Quality Reporting System (DQRS)

- A subset of MedWatch reports that contain complaints related to quality or inequivalence are entered into DQRS.
- These reports may also contain adverse events (AEs) and thus the same reports would also be in FAERS.
- Largely spontaneous reports - enriched in cases of product inequivalence and quality problems
- Approximately 600 MedWatch reports per month
- Searchable for multiple fields with dynamic reporting

101B DQRS Report



- Main report used is the 101B that was designed by OGD staff to accommodate the periodic surveillance reports

The screenshot displays the SAP BusinessObjects interface for the 101B DQRS Report. The browser address bar shows the URL: <http://bi.fda.gov/BOE/portal/1402080552/InfoView/listing/main.do?bttoken=MDAwRE06OEYxSDdQZEJhQ2VYVz9PbEYyYVJhP0FXODAEQ&appKind=InfoVie>. The SAP BusinessObjects header shows the user is logged in as OSTERHOUT JAMES. The main window displays the report title "DQRS REPORT" and a "Prompts" dialog box. The dialog box contains a "Prompts Summary" list with the following items:

- Enter Firm Name:
- Enter Narrative Keyword:
- Enter Product Name:
- Enter Received Date (Start) (MM/DD/YYYY):
- Enter Received Date (End) (MM/DD/YYYY):

The "Enter Firm Name:" prompt is currently selected, showing a text input field with the placeholder "Type values here" and a search help icon. Below the input field, there is a text box with the following instructions: "Use search criteria to retrieve values. The search is case sensitive. Here are examples of search criteria: Search = a* -> retrieves all values". The dialog box also includes "Run Query" and "Cancel" buttons.

Below the dialog box, the report content is partially visible, showing "Selection Criteria:" with fields for "Firm Name:", "Narrative Keyword:", "Product Name:", "Received Date:" (with "From:" and "To:" sub-fields), and "Sort Order:" (with "Priority, File Number" sub-fields). A blue link at the bottom of the report area reads "<< Reports start from Page 2 >>".

DQRS



- Search results are exported into Excel for sorting and analysis for any potential signals
- The report output contains manufacturer and lot if available, defect and a full narrative from the reporter.
- A custom SAS program written by CSSS is used to analyze the complaints and identify and potential signals.
- Individual narratives are reviewed to identify any single report that may need further review by a medical officer.

Drug Distribution Data

- Two sources of distribution (marketing) data are used
 - IMS Smart
 - National Sales Perspective (NSP)
 - National Prescription Audit (NPA)
 - Symphony
- Drug distribution data are considered when investigating a potential signal in an attempt to compare multiple generic manufacturers by calculating a relative rate.

Retrospective Generic Surveillance

- Short-term emerging signals
- Safety Evaluator reviews 1 month of DQRS complaints to identify any single report warranting further scrutiny by safety team
- Reports sorted by manufacturer/product to identify clusters for a single manufacturer indicating a possible emerging problem
- Any problems or potential signals identified are forwarded for discussion at the Monthly CSSS Committee Meeting.



Prospective Generic Surveillance

“Newly Approved” Generic Watch List

- Anticipates future safety signals
- Each surveillance period, the Safety Evaluator reviews the list and searches for complaints on newly approved and marketed generics
- DQRS complaints in initial weeks/months of marketing are documented
- New generics that meet signal criteria are added to the New Generic Watch List and monitored over time.

Addresses the Weber Effect whereby increased safety signals occur when new generics are on the market or from other stimulated reporting.



Detailed Review of Individual Potential Safety Issues

- Safety Evaluator performs an in-depth evaluation for a safety, quality, or therapeutic inequivalence signal
- Review of ANDA and RLD Information
- Components & Composition, Release Mechanism, Excipients
- CMC changes, recent manufacturing changes
- Relevant FARs (Field Alert Reports) for the product
- Review of BE data for possible areas of concern
- Market Share Determination-IMS Sales Data
- Scientific / Medical literature research

Critical Elements

- **Chemistry (PE)**

- Drug Product
- Dosage Formulation
- Specifications
- Impurities
- Excipients

- **Bioequivalence (BE)**

- Pharmacokinetics
- Pharmacodynamics
- In vitro characterization
- Statistics

- **Clinical intent of product design (TE)**

- Clinical use
- Target populations
- Specific indications
- Chronicity of use

- **Inspections**

- Facility
- Bioanalytical
- Clinical

- **Labeling**

- **Legal/Regulatory**

- FDCA
- CFR
- Hatch-Waxman Amendment
- FDAAA
- FDASIA
- Precedent
- Citizens Petitions



CSSS Committee Meetings

- **Monthly CSSS Safety and Surveillance Committee Meeting** - Coordinates issues with OGD's and OPQ's suboffices
 - Discusses and triages emerging safety surveillance issues
 - Hears presentations
 - Makes preliminary decisions regarding whether or not to open a Tracked Safety Issue (TSI)
- **Bimonthly OGD Safety and Surveillance Committee Meeting** - Coordinates safety issues with representation from all of CDER's offices.
 - Helps to make final decisions on whether or not to open a TSI and discusses other controversial safety issues.



Acknowledgments

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