FDA Drug Topics: The Safety Evaluation and Surveillance of Generic Drugs

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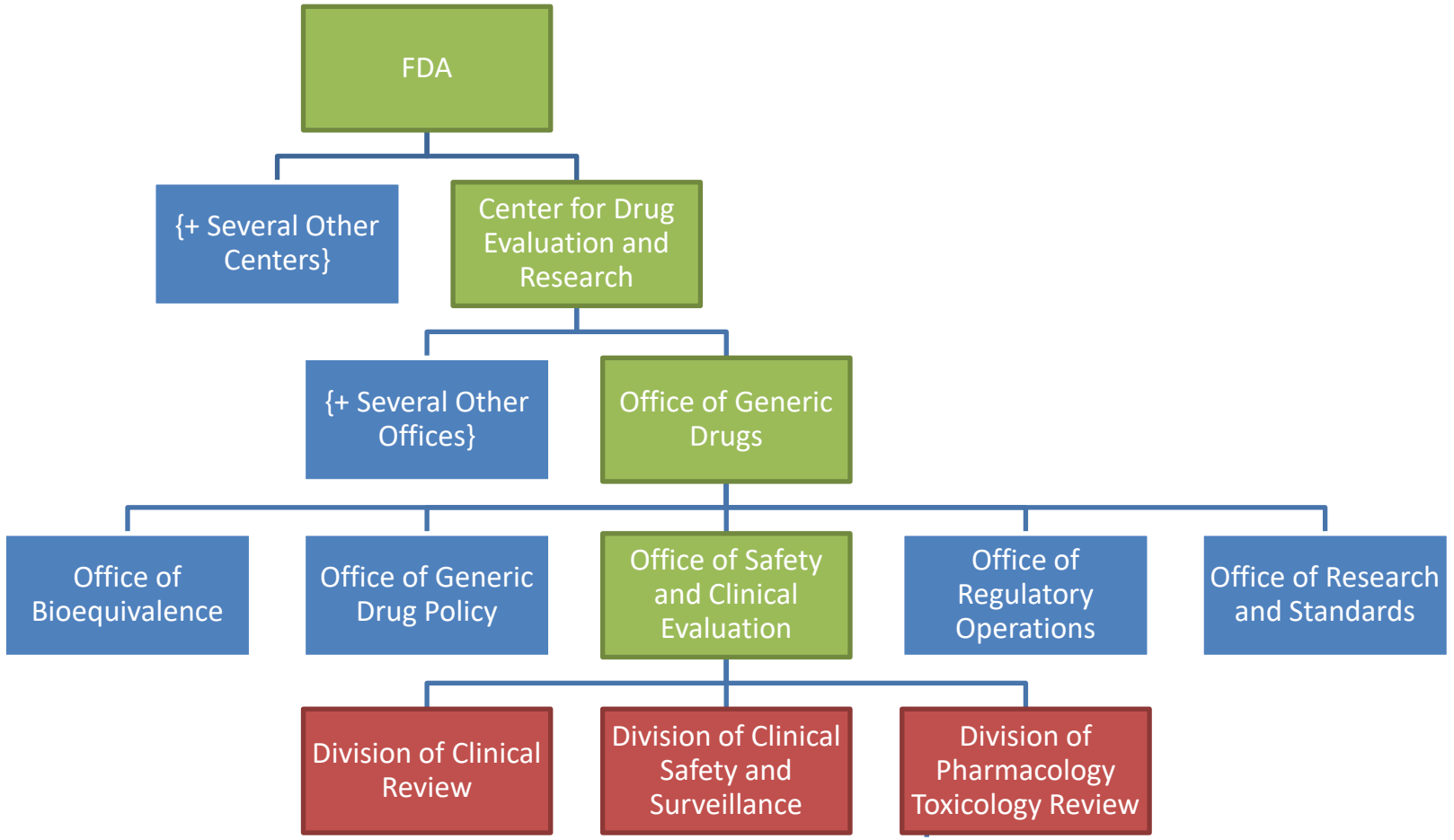
Disclaimer

This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.

Learning Objectives

1. Recognize how comparative clinical studies and other assessments are used to evaluate the bioequivalence and comparative safety of new potential generic drug products
2. Identify scenarios and approaches when OGD Pharmacology/Toxicology (Pharm/Tox) assesses the safety of excipients in generic drug products
3. Describe the sources of drug impurities and how OGD Pharm/Tox assesses their safety in generic drug products and drug master files
4. Review the methods used by FDA to monitor the safety and effectiveness of generic drugs in the pre-market and post-market setting

Generic Drug Clinical Safety Presenters



Generic Drug Safety is an Organization-wide priority with many collaborating Centers/Offices/Divisions

U.S. FOOD & DRUG ADMINISTRATION

Background of Generic Drug Evaluation

Benefits of Generic Drugs

- Generic medications saved Americans $373 billion in 2021
- **91%** of U.S. prescriptions filled by generic drugs
- Generic medications accounted for only **18%** of all drug spending
- **93%** of generic prescriptions were filled at under $20
  - the average generic copay was **$6.19** compared to the average brand-name copay of **$56.12**

Reference: AAM Report: 2022 U.S. Generic Drug and Biosimilar Medicines Savings Report (https://accessiblemeds.org/resources/reports/2022-savings-report)

Hatch-Waxman Amendments

Drug Price Competition and Patent Term Restoration Act of 1984

- Created the basic scheme under which generic drugs are approved today
- Allows FDA to approve generic applications using an Abbreviated New Drug Application (ANDA) under section 505(j) of the Federal Food, Drug, and Cosmetic Act
- ANDAs rely on FDA's finding of safety and effectiveness for the reference listed drug (RLD) and require a demonstration of "sameness" of a number of characteristics and additional information to permit reliance on the RLD
- Increases patient access to medication and reduces cost through competition and reduced need to repeat costly animal and clinical (human) studies

Therapeutic Equivalence

1. Products are approved as safe and effective.
2. Products are **pharmaceutical equivalents** in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration and (b) meet compendial or other applicable standards of strength, quality, purity, and identity.
3. Products are **bioequivalent** in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard.
4. Products are adequately **labeled.**
5. Products are **manufactured** in compliance with current Good Manufacturing Practice regulations.

Reference: The Orange Book (https://www.accessdata.fda.gov/scripts/cder/ob/)

Generic vs. Reference Listed Drug (RLD)

Generic drugs must be the **same** as an RLD in:

- Active drug ingredient
- Dosage form
- Strength
- Route of administration
- Safety
- Quality
- Performance characteristics
- Intended use

Generic drugs **may differ** with RLD in:

- Shape
- Scoring configuration
- Release mechanisms
- Certain excipients (e.g., colors, flavors, preservatives)
- Packaging
- Labeling (with certain exceptions)
- Expiration date/time
- Manufacturing and controls (e.g., impurities)

The differences with RLD should not affect the safety and efficacy

Requirements for NDA vs. ANDA

NDA
New Drug Application
{Brand Name}

1. Chemistry
2. Manufacturing
3. Testing
4. Labeling
5. Inspections
6. ***Bioavailability***
7. ***Animal Studies****
8. ***Clinical Studies*****
   - Demonstrate safety and effectiveness

ANDA
Abbreviated New Drug Application
{Generic}

1. Chemistry
2. Manufacturing
3. Testing
4. Labeling
5. Inspections
6. ***Bioequivalence****
   - Demonstrate Bioequivalence
   - Relies on FDA findings safety and efficacy data from NDA
   - No pre-clinical and clinical testing required

* Nonclinical studies may be necessary to determine the safety of excipients or impurities in the proposed products
** Efficacy/Safety

Safety and Efficacy vs. Bioequivalence

- For a New Drug Application (NDA) drug **Safety and Efficacy** must be established. **This often requires a randomized clinical trial.**

- For an Abbreviated New Drug Application (ANDA) drug **Bioequivalence** must be demonstrated against the reference standard. There are four options to do this:
  - Pharmacokinetic (PK) studies
  - Pharmacodynamic (PD) Studies
  - Comparative clinical endpoint studies
  - In vitro studies

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Clinical Review of Generic Drugs

Evaluation of Safety in Bioequivalence Studies

Evaluate concerning safety data from any bioequivalence study

Assessment of data from all Comparative Clinical Endpoint Bioequivalence Studies:

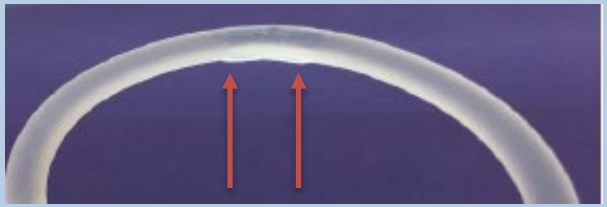
- Treatment
- Endpoints
- Timing of endpoints
- Method of measurement
- Statistical Analysis
- Outcome
- **Adverse Events**

Bioequivalence

Comparative Safety

Safety Evaluation in a Bioequivalence Study

Adverse events in the Bioequivalence study	
2% Menorrhagia	20% Menorrhagia

Vaginal Contraceptive Ring	
Brand Name Product: 	**Generic Product:**  Do burrs at ring joint lead to vaginal irritation?

Applicant changed welding equipment and submitted new proposed product	
	

Differences from reference listed drug (RLD)

Evaluate potential differences to ensure safe substitution to target population

- Devices
- Pill size and color
- Packaging
- Labeling

Drug-Device Combination Products

Generic Combination Products

Evaluate Generic Drug

Same evaluation as other generic drugs:

- Drug Substance
- Drug Product
- Labeling
- Manufacturing and Quality
- Microbiology

Evaluate Device

If new device, evaluate performance

Ex: Nasal spray

- Droplet size distribution
- Distribution of drug in droplets
- Spray pattern
- Plume geometry
- Priming and repriming

Evaluate Combination Product

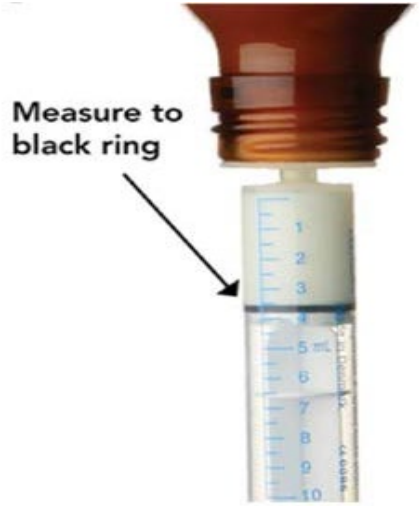
Can the product be safely substituted for the RLD?

- Physical product
- Task analysis
- Labeling evaluation

Comparative Analysis Example

Brand Name Product

Reference Listed Drug Package Insert
Step 6. With the syringe in place, turn the bottle upside down. Pull the plunger to the number of mLs needed (the amount of liquid medicine in Step 4).
Measure the mLs of medicine using the black ring on the white plunger. **See Figure G**



Proposed Generic Product

Applicant's Proposed Package Insert
Step 6. With the syringe in place, turn the bottle upside down. Pull the plunger to the number of mLs needed (the amount of liquid medicine in Step 4).
Measure the mLs of medicine using the top of the white plunger. **See Figure G**

Summary

Clinical Review of Generic Drugs:

- Responsible for a variety of review work and consultations that address clinical concerns and the safety of generic drug products throughout the product life cycle
- Evaluates safety of participants in bioequivalence studies
- Evaluates differences between generic and RLD that may impact safe substitution
- Evaluates the user interface of combination products to ensure no device differences that would impact safe substitution to target population

… works with the other divisions of the Office of Safety and Clinical Evaluation, and the FDA as a whole, to evaluate the clinical safety of generic drugs

Excipient Safety Assessment

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Office of Generic Drugs

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Generic vs. Reference Listed Drug (RLD)

Generic drugs must be the **same** as an RLD in:

- Active drug ingredient
- Amount of drug
- Dosage form
- Strength
- Route of administration
- Safety
- Quality
- Performance characteristics
- Intended use
- Labeling (with certain exceptions)

Generic drugs **may differ** with RLD in:

- Shape
- Scoring configuration
- Release mechanisms
- **Certain excipients** (e.g., colors, flavors, preservatives)
- Packaging
- Expiration date/time
- Manufacturing and controls (e.g., impurities)

A generic's differences from the RLD should not affect its safety and efficacy

What are Excipients?

- **Excipients are** any inactive ingredients intentionally *added* to therapeutic and diagnostic products that are not intended to exert therapeutic effect at intended dosage
- Most generic products may utilize different excipients from the RLD
- Generic ophthalmic, otic, and parenteral products must contain the same excipient at same concentration as the RLD [per 21 CFR 314.94]
  - Exceptions: buffers, antioxidants, preservatives, tonicity adjusters*, or thickening agents*
- Differences in excipients may change the safety profile of a drug product under the proposed ***Context of Use*** (e.g., dose, route of administration, duration of exposure, patient population)

*Applicable to ophthalmic and otic products

What are Excipients?

Excipients may include:

- Absorption enhancers
- Coloring agents
- Diluents
- Emulsifiers
- Extenders
- Fillers
- Flavors
- Preservatives
- Solvents
- Sustained-release matrices
- Wetting agents
- Macromolecular substances (e.g., albumin, sugars, amino acids)

Not Excipients:

- Process or product-related impurities (e.g., degradation products, leachates, residual solvents)
- Extraneous contaminants

How is Excipient Safety Evaluated in Generics?

- Excipient evaluation includes:
  - Comparison with RLD formulation
  - Comparison with approved levels for proposed route using Inactive Ingredient Database (IID)
- Safety evaluation is driven by the context of use, such as:
  - Proposed level > level in IID under same route of administration
  - For a different route (e.g., excipient in approved oral drug product in other routes)
  - For a different duration of exposure (e.g., acute vs chronic use)
  - For a different patient population (e.g., pediatrics)
- If comparison with existing use raises potential safety concern with the proposed use of excipient, additional assessment is conducted on a consult basis

How is Excipient Safety Evaluated in Generics?

- Goal: To ensure the proposed generic drug has the same safety profile as RLD when used according to labeling

- Generic applications do not include large battery of clinical or nonclinical studies, therefore the safety assessment considers
  - Applicant's justification
  - Information in public domain (e.g., published literature)
  - Information in internal databases

How is Excipient Safety Evaluated in Generics?

- Excipients are generally evaluated jointly by Clinical and Pharm/Tox disciplines
  - Clinical: Assess context of use and available evidence of safe use in humans
  - Pharm/Tox: Review existing data for systemic/local toxicity and studies that inform endpoints difficult to assess in humans (genetic toxicity, carcinogenicity, reproductive and developmental toxicology), conduct quantitative toxicological risk assessment based on context of use
- Apply the principles from FDA's Guidance for Industry – Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients
- Consider margins of exposure when evaluating safety
- Identify potential data gaps
- Provide recommendation based on available information
  - Data gap indicates a deficiency and results in non-approval for the ANDA
  - Recommendations to resolve deficiency are provided to ANDA applicant

Some Challenges in Excipient Review

- Complex excipients
  - Mixture of several components
    - Composition can be proprietary (e.g., flavors, fragrances) and dose matters
    - Obtaining composition and identifying compound-specific safety information is challenging
  - May be present as different grades of the same excipient: build “a bridge” with available safety data from similar grades
- Safety in sensitive populations
  - Pediatric patients, particularly in newborns and young infants that may be critically sick or weak
    - Higher exposure (due to greater inhalation rate, body surface area)
    - Immature/Different metabolism, protein binding, volume of distribution
    - Different sensitivity of rapidly developing tissues/systems
  - Elderly patients or patients with conditions needing dosage adjustments (e.g., renal or hepatic impairment)

Some Challenges in Excipient Review

- Certain routes of administration may warrant additional safety assessment
  - e.g., ophthalmic, rectal, vaginal, buccal, sublingual, dermal
  - In addition to systemic exposure, local tissue tolerance is also evaluated
  - Clinical and nonclinical data are considered
  - Occasionally, animal studies may be requested to address excipient-related effects via specific administration route

Summary

- Excipients are inactive ingredients intentionally added to formulations and may alter the safety profile of a proposed generic drug
- Safety assessment of excipients is an important aspect of generic drug review
  - The safety review of an excipient incorporates the proposed drug product's context of use into the assessment
  - The safety of an excipient relies on both nonclinical evaluations and clinical assessment
- Challenges in excipient safety review may be due to the nature of the excipient itself, the potential effects in sensitive patients, potential systemic or local tissue effects
- If a safety gap is identified, a deficiency is issued and the ANDA does not receive approval
- Overall goal of safety review is to ensure that the safety profile of the generic drug is same to the RLD

Impurity Safety Assessment

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What are Impurities?

- Any component of the drug product or drug substance that is not the drug substance or an excipient in the drug product
- Generic drugs may use different manufacturing processes or containers and therefore may have different impurity profiles than their RLD

- **Degradation/Process-related Impurities** –arise during manufacturing or storage
- **Residual Solvents** – organic volatile chemicals used in manufacturing
- **Elemental Impurities** – arise from residual catalysts or interaction with container
- **Extractables and Leachables** – Organic or inorganic chemicals that are extracted/leached from the container

RLD = Reference Listed Drug

Overview of Impurity Review in Generics

- Office of Pharmaceutical Quality (OPQ) oversees impurity review
- OGD Pharmacology/Toxicology reviews the safety of impurities that exceed established safety levels in generic drugs upon request by OPQ
  - Safety assessment approaches align with what were used for the RLD and recommendations in FDA and internationally harmonized guidances
- The level of an impurity in drug substance or drug product is considered acceptable if it:
  - Does not exceed safety thresholds for genotoxicity, carcinogenicity, and general safety (systemic and local safety)
  - Does not exceed levels in the RLD, only if supported by comparative analytical data: reviewed by OPQ
  - *Special case:* impurity is a known metabolite in animals/humans at levels higher than clinical exposure to impurity

Key Principles of Safety Review of Impurities in Generics

- The goal is to ensure safety profile of generic is comparable with RLD
- Evaluate potential toxicity profile for the impurity
  - Published literature
  - Information submitted by applicant: can include in silico, in vitro, or in vivo studies
- Context of use of the generic drug is critical when conducting safety assessment
  - Route of administration
  - Dose
  - Duration of use
  - Target patient population

Impurity Review Process

- Determination of mutagenic potential
  - Could the impurity cause a change in the DNA sequence?
  - Cumulative duration of exposure over lifetime determines the acceptable limit
- Determination of general toxicity
  - General toxicity (systemic and local) in animals
    - Effects on mortality, clinical signs, body weight, blood chemistry, organ pathology (i.e., organ weights, gross pathology, and histopathology)
  - Context of use of the drug determines the study design and relevant toxicity endpoints necessary for safety evaluation
- Conduct risk assessment to identify potential impurity-related adverse effects

Determination of Genotoxicity Potential:

- Context of use (duration of treatment) to determine threshold of toxicological concern (TTC) per ICH M7 guidance
  - TTC is a level below which there would be no appreciable risk to human health
  - Longer cumulative duration of use → lower TTC
- Approaches to characterizing genotoxicity are described in ICH M7 guidance
  - *In silico* prediction [(Q)SAR analysis]* using appropriate models
  - Ames bacterial reverse mutation test
  - Follow-up *in vitro* and *in vivo* studies
- Exception: drugs intended for advanced cancer indications are not subject to TTC limit in ICH M7 guidance

*(Q)SAR: Quantitative Structure-Activity Relationship

Determination of General Toxicity Potential:

- General toxicity is assessed when impurity exceeds qualification threshold (QT) per ICH Q3A or Q3B guidances
  - QT varies depending on maximum daily dose (MDD) of the drug
- Identify impurity level associated with toxicity in animals and compare with proposed clinical exposure when drug is taken at MDD
- General toxicity studies (context of use is key for study design):
  - Doses with sufficient margins as compared to clinical exposure
  - Duration of nonclinical study (e.g., 14, 28, 90 days, with recovery times)
  - Route of administration
  - Specific parameters (e.g., local toxicity)
  - Species: generally rodent studies

Determination of General Toxicity Potential:

- *In silico* predictions to assess general toxicity are not considered acceptable

- If an impurity is a known metabolite in animals/humans at levels higher than proposed clinical exposure to impurity, it is considered qualified

Example: Safety Evaluation of Impurity "X"

- In ANDA submission for an oral drug product of chronic use, the applicant proposed a control limit for impurity X in drug product
  - Clinical exposure to Impurity X exceeds QT (ICH Q3B) and TTC (ICH M7) of 1.5 mcg/day
  - Therefore, genotoxicity and general toxicity assessment is needed
- Applicant's justification: Only submitted *in silico* (Q)SAR analysis:
  - Genotoxicity concern adequately addressed
  - General toxicity of proposed clinical exposure not addressed (in silico prediction not accepted)
- Deficiency issued to lower specification to QT, or qualify safety of the proposed clinical exposure in oral repeat dose animal studies

Summary

OGD Pharmacology/Toxicology conducts safety assessment of impurities in generic drugs to ensure that the safety profile of the generic drug is comparable to that of its RLD

- Is based on FDA and internationally harmonized guidances
- Uses the same Pharmacology/Toxicology principles as the RLD
- Considers the maximum daily dose and duration of use to determine safety thresholds for genotoxicity and general safety
- Considers the context of use (route of administration, dose, duration of use, clinical indication, target patient population) when evaluating drug substance and drug product impurities for safety

Premarket and Postmarket Safety and Surveillance of Generic Drugs

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Premarket Safety and Surveillance of Generic Drugs

Clinical Evaluation of Serious Adverse Events

- Physician evaluates serious adverse event (SAE) reports from Bio-INDs and IND-exempt bioequivalence studies that support abbreviated new drug applications (ANDAs)

- **Serious Adverse Event (SAE)**
  - Death or life-threatening adverse event
  - Inpatient hospitalization
  - Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - Congenital anomaly/birth defect

- Sponsors are required to report to FDA all fatal or life-threatening SAEs within 7 days and all other SAEs within 15 days

SAE Clinical Evaluation

- Additional information such as autopsy reports, medical records, etc., can be requested from the Sponsor

- Clinical evaluation includes determination if there is a safety concern with:
  - Study drug(s) including dose or administration
  - Study procedures
  - Study population
  - Monitoring of study subjects

- Limitations of Clinical Evaluation of SAEs
  - Difficult to reach conclusions or identify patterns when receiving SAEs one at a time
  - Federal regulations require that Sponsors submit SAEs only for IND exempt bioequivalence studies conducted in the United States

Investigational New Drug Applications (Bio-INDs)

- Per Federal Regulations, certain bioequivalence study protocols for ANDAs are required to be submitted to FDA via Bio-IND to ensure that the proposed study **does not** expose the subjects to unreasonable and significant risk of illness or injury

- Bioequivalence study protocols must be submitted to FDA for review are those drug products that are:
    1) Radioactively labeled
    2) Cytotoxic
    3) Greater than the maximum single or total daily dose specified in the labeling

Bio-IND Review

- Bio-IND is reviewed by experts in clinical safety, pharmaceutical quality, and bioequivalence
- Focus on reviewing the study protocol, informed consent documents, qualification of Investigators, drug product, drug substance, and manufacturing
- Study can be placed on "Clinical Hold" according to the Code of Federal Regulations (21 CFR 312.42)
  - Subjects **may not** be given the investigational drug when a proposed study is placed on clinical hold
- Non-hold comments may also be provided to the Sponsor to improve patient safety and the study protocol

Product-Specific Guidance (PSG)

- Represent FDA's current thinking on a particular topic
- Contain FDA's recommendations to Sponsors about:
  - Studies to be performed
  - Study population
  - Inclusion/Exclusion Criteria
  - Study safety monitoring (example: need for electrocardiogram, etc.)
  - Laboratory value monitoring
- As of August 2022, over 2,030 Product-Specific Guidances are available at: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

Product-Specific Guidance (PSG) Example

Draft Guidance on Encorafenib

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Encorafenib

Dosage Form; Route: Capsule; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 75 mg
   Subjects: Healthy adult males
   Additional comments: Elderly subjects and subjects with history of oral herpes or shingles, or with risk factors for prolonged QTc interval and Torsades de Pointes should be excluded from the study. Subjects should be appropriately monitored for electrocardiogram changes during the study.

Postmarket Safety and Surveillance of Generic Drugs

Health Hazard Evaluations

- Clinical risk assessments of marketed drug product defects that are usually limited to a batch or lot of product
- Often related to impurities (identified or unidentified), other tests that are not within specifications, or other defective products
- Evaluation determines “Likelihood of Adverse Event Occurring” and “Degree of Adverse Event Occurring”
- Assists CDER’s Office of Compliance decision on recall classification and strategy

OGD Clinical Safety and Surveillance Committee

- Multidisciplinary group of physicians, chemists, and scientists from Office of Generic Drugs (OGD), Office of Pharmaceutical Quality, and other CDER Super offices

- Discuss and decide on Newly Identified Safety Signals and other safety issues related to approved generic drug products

- Results of DCSS pharmacovigilance activity report presented and evaluated by committee
  - Exploratory proactive data analysis (including drug marketing data) helps OGD detect generic drug complaints or medication use errors

Proactive Postmarketing Surveillance

- Identify emerging safety issues through:
  - Published literature reviews
  - Direct contacts from patients or health care professionals to FDA
  - Information shared by pharmacies and drug safety-focused organizations
  - Data analytic tools and technologies

MedWatch

MedWatch is FDA's medical product safety reporting program for health professionals, patients, and consumers to report:

- Unexpected side effects or adverse events
- Product quality problems
- Product use/medication errors that can be prevented
- Therapeutic failures

FDA Adverse Event Reporting System

- FDA Adverse Event Reporting System (FAERS) is a database that contains:
  - Adverse event reports
  - Medication error reports
  - Product quality complaints
- Reports are from healthcare professionals, patients, and manufacturers
  - Manufacturers are required to send reports from patient and healthcare professionals to FDA
- FAERS Public Dashboard
  - User-friendly
  - Several limitations to raw data

Potential Regulatory Actions

- If new or unanticipated safety risks are detected after approval of a generic drug, OGD investigates the potential safety issue and regulatory actions may include:
  - Enforcement actions (example: voluntary product recalls)
  - Updating a product's patient and doctor information (example: change in labeling, Dear Healthcare Provider Letter)
  - Communicating new safety information to the public through Drug Safety Alerts or Drug Safety Communications
  - Lowering a therapeutic equivalence rating in the Orange Book
  - Removing a drug from the market

Lansoprazole Orally Disintegrating Tablet

- Lansoprazole, a proton pump inhibitor, is indicated for the treatment of gastric and duodenal ulcers, gastroesophageal reflux disease, erosive esophagitis, and Zollinger-Ellison Syndrome
- Lansoprazole is available as an orally disintegrating tablet (ODT) - labeling included the potential for administration through nasogastric tubes
- The generic Lansoprazole ODT product was reported to clog feeding tubes requiring surgical replacement in some patients
- FDA laboratory investigation showed different product performance compared to the Reference Listed Drug (brand product)
- Applicant voluntarily withdrew the product from the market
- ODT products indicated for use with a feeding tube are required to be tested for this functionality

Copaxone/Glatiramer Acetate Injection

- Glatiramer acetate injection is used in the treatment of relapsing forms of multiple sclerosis
- Currently three FDA-approved glatiramer acetate injection drug products on the market - all available in a single-dose prefilled syringe with an attached needle for subcutaneous administration
- FDA's Center for Devices and Radiologic Health approved three general use auto-injector devices as 510(k)s - marketed independently by drug companies on their respective websites

Copaxone/Glatiramer Acetate Injection

- FDA received mediation error reports related to the use of an optional autoinjector that was not compatible with the patient's specific glatiramer acetate prefilled syringe drug product
- Concern that the available optional autoinjector devices were not cross-compatible with all approved glatiramer acetate prefilled syringes was causing the medical errors such as bent needles and incomplete or missed doses
- FDA requested that drug product manufacturers update their labeling to instruct users to confirm that the optional autoinjector is compatible before using it to assist with injection of glatiramer acetate
- CDER Drug Safety Alert was published on August 18, 2022

FDA alerts patients, caregivers, and health care providers of cross-compatibility issues with autoinjector devices that are optional for use with glatiramer acetate injection

[8/18/2022] FDA is alerting patients, caregivers, and health care professionals that autoinjector devices that are optional for use with glatiramer acetate injection may not be compatible for use across FDA-approved glatiramer acetate injection drug products. FDA has received reports that using an autoinjector that is not compatible with the patient's specific glatiramer acetate injection drug product has resulted in missed and partial doses.

Glatiramer acetate injection is used in the treatment of relapsing forms of multiple sclerosis. There are currently three FDA-approved glatiramer acetate injection drug products on the market—all available in a single-dose prefilled syringe with an attached needle for subcutaneous administration. Patients may inject glatiramer acetate using only the syringe or by inserting the syringe into an autoinjector. The autoinjectors are reusable, designed to facilitate injections in patients with limited dexterity, and are available by prescription separately.

The table below lists the three FDA-approved glatiramer acetate injection drug products and its compatible autoinjector device that is optional for use.

Drug Product Name	Drug Manufacturer	Compatible Autoinjector Device
Copaxone (glatiramer acetate injection)	Teva Pharmaceuticals	*autoject 2 for glass syringe*
Glatopa (glatiramer acetate injection)	Sandoz	Glatopa*ject*
Glatiramer Acetate injection	Viatris/Mylan	*Whisper*JECT

FDA has requested that drug product manufacturers update their labeling to instruct users to confirm the autoinjector is compatible before using it to inject glatiramer acetate. Users can confirm compatibility by speaking with their health care professional or visiting the drug manufacturer's patient information website. Users should also confirm the autoinjector is compatible each time they receive a new prescription for a glatiramer acetate injection drug product.

FDA encourages health care professionals and patients to report adverse events or quality problems experienced using glatiramer acetate injection products to FDA's MedWatch Adverse Event Reporting program. Complete and submit the report online at www.fda.gov/medwatch/report.htm (/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program); or download and complete the form, then submit it via fax at 1-800-FDA-0178.

Summary

- Premarket and postmarket safety and surveillance of generic drugs includes a variety of tools and methods and involves a cross-disciplinary approach

- Premarket and postmarket safety and surveillance of generic drugs helps to ensure generic drugs are as safe and effective as Reference Listed Drugs

Review

- Recognize how clinical studies and other assessments are used to evaluate the bioequivalence and safety of new generic drug products
- Identify scenarios and approaches when OGD Pharmacology/Toxicology assesses the safety of excipients in generic drug products
- Describe the sources of drug impurities and how OGD Pharmacology/Toxicology assesses their safety in generic drug products and drug master files
- Review the methods used by FDA to monitor the safety and effectiveness of generic drugs in the pre-market and post-market settings

Conclusion

- Generic drugs must meet high standards for comparative safety, efficacy, and quality during review and post-approval

- Generic Drug Program at FDA helps to ensure safe and effective generic drugs are available for the American public

References

- Guidance for Industry Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients (2005) https://www.fda.gov/media/72260/download
- Guidance for Industry ANDAs: Impurities in Drug Products https://www.fda.gov/files/drugs/published/ANDAs--Impurities-in-Drug-Products.pdf
- FDA Adverse Event Reporting System (FAERS) https://www.fda.gov/drugs/drug-approvals-and-databases/fda-adverse-event-reporting-system-faers
- MedWatch: The FDA Safety Information and Adverse Event Reporting Program https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program
- Product-Specific Guidances for Generic Drug Development https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm
- Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry https://www.fda.gov/files/drugs/published/Comparative-Analyses-and-Related-Comparative-Use-Human-Factors-Studies-for-a-Drug-Device-Combination-Product-Submitted-in-an-ANDA--Draft-Guidance-for-Industry.pdf