Postmarket Surveillance of Generic Drugs: Opportunities for GDUFA Research

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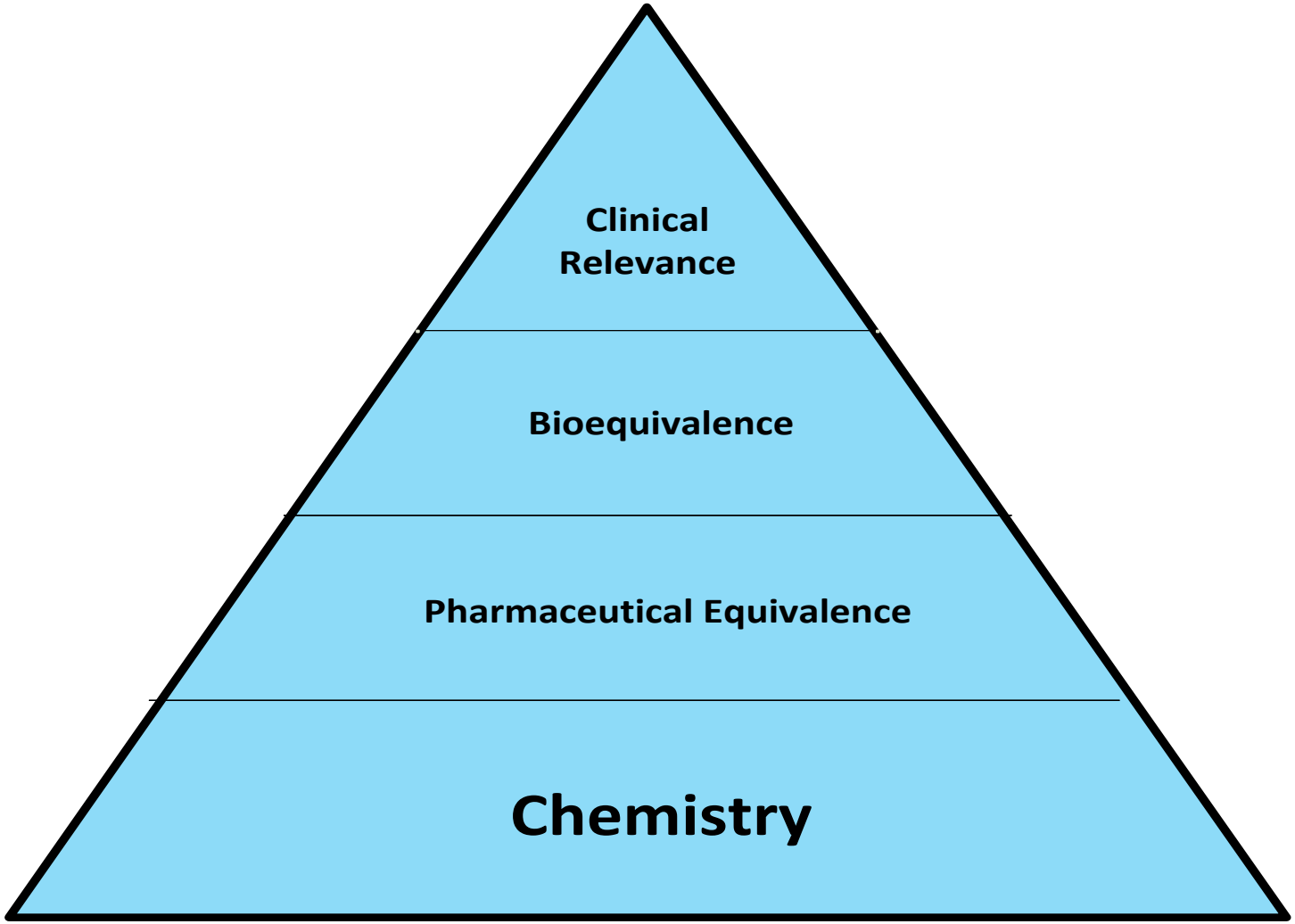
Outline

1. Generic drug identity and allowable differences
2. Excipients/impurity ongoing safety issue
3. Postmarket safety surveillance data resources
4. Examples of past research on safety: efforts/results
5. Preparing for the future
6. Engage with our breakout session this afternoon!

Foundation for Identity of Generic Drugs



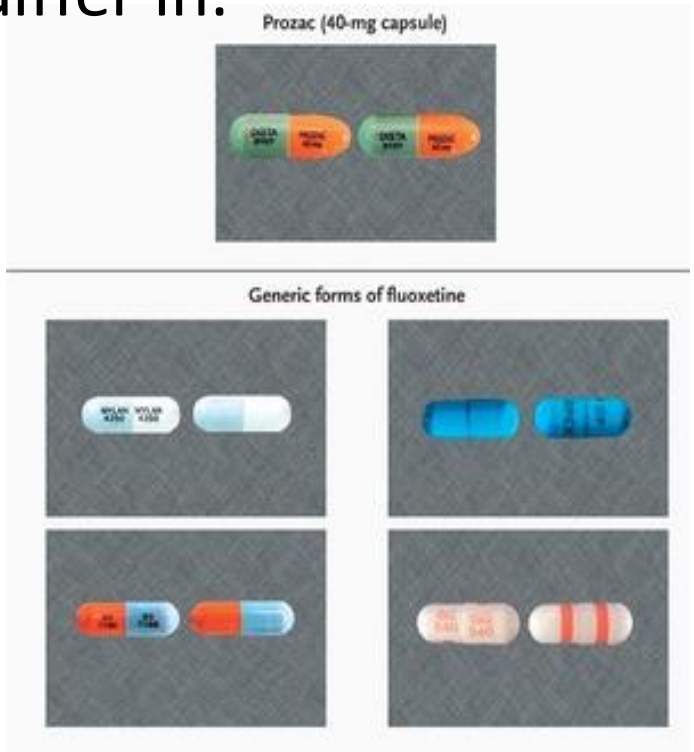
Generic Drugs – some basics

- Generic drugs are presumed to be **safe and effective** if they are pharmaceutically equivalent (PE) and have demonstrated bioequivalence (BE) in a statistically supportable manner to their "brand name" or reference listed drug (RLD).
- This is the basis for generic drug regulations and the ability of a generic drug to be **substitutable** for the brand name drug and are considered **therapeutic equivalents.**
- While generic drugs are required to be the same as the RLD in many aspects, generic drugs are generally **not required to be identical** to their RLDs.

Allowable Differences

Generic drugs can sometimes differ in:

- Shape
- Scoring configuration
- Release mechanisms
- Packaging
- **Excipients/impurities**
- Expiration time
- Container closure systems



Guidance for Industry: Determining Whether to Submit an ANDA or a 505(b)(2) Application (May 2019)
Picture reproduced from Greene JA and Kesselheim AS Why do the same drugs look different? Pills trade dress and public health. NEJM 2011;365:83-89.

www.fda.gov

Excipients

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

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

Impurities may be unanticipated substances in the active pharmaceutical ingredient, an inactive ingredient or as a result of stability of a finished drug product over time.

Nitrosamine Impurities – Brand and Generic Drug Products

- In June 2018, certain angiotensin II receptor blocker (ARB) drugs, commonly used to treat heart failure and high blood pressure were found to contain nitrosamines, which resulted in numerous recalls and ARB drug shortages worldwide.
- Nitrosamines are carcinogenic impurities that are byproducts of drug manufacturing or stability of finished drug products over time, and perhaps from other unanticipated sources.
- FDA requested a recall of ranitidine products on 4/1/2020 due to high levels of a nitrosamine under certain storage conditions.

https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market

Nitrosamine Impurities – Brand and Generic Drug Products

- This postmarket cross-CDER collaborative safety and surveillance work on nitrosamines has resulted in the development of:
  - Acceptable daily intake limits
  - Laboratory Testing methods
  - Interactions with global regulatory partners
  - Changes in drug manufacturing and development of risk assessments
  - Public communications
  - Other recommendations to address these impurities in other drug products.

https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications

Postmarket Safety Data Resources

- **FDA Adverse Event Reporting System**
- Field Alert Reports
- **IQVIA: Market Share**
- **Sentinel**
- Laboratory Testing
- Inspections
- **Generic Drug User Fee Amendments (GDUFA) Research**
- Real World Evidence

FDA Adverse Event Reporting System

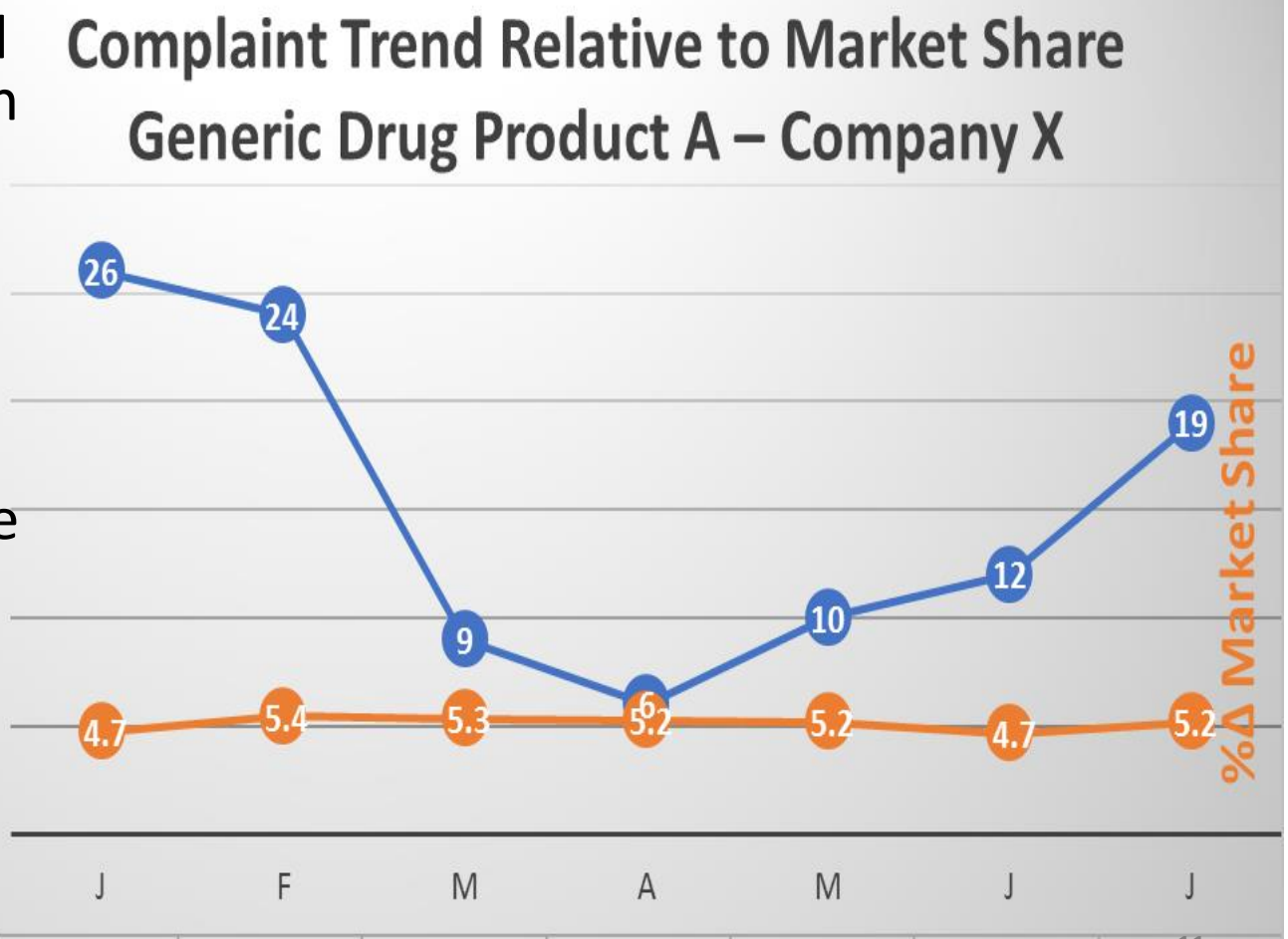
- Difficulty identifying brand versus generic; many reports related to generic products are misattributed to the brand
- Source of some reports can be unreliable
- Reports are often incomplete
- Safety issue may not be specific to a brand or generic drug product
- Safety signals are difficult to identify and verify due to concurrent medications and/or illnesses

Good at providing details in patient narratives that help us to understand qualitative issues at the patient use level.

IQVIA Drug Utilization Data – Research Question

Can market share data be used as an informal denominator to screen for potential safety concerns for generic drugs?

If a particular generic drug product has more complaints relative to its market share, this trend may signal a quality issue requiring more scientific investigation.



	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19
Company X Product Complaints	26	24	9	6	10	12	19
Market Share % Change (%Δ Baseline)	4.7	5.4	5.3	5.2	5.2	4.7	5.2

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FDA Sentinel Initiative

- A complementary tool to help address ongoing safety concerns coming from other sources
- Limited to retrospective data
- Research questions require specificity
- Data on switching helps to identify potentially problematic generic drugs
  - Patients who return their medications and are re-dispensed brand or another generic
  - Patients who are receiving brand instead of generic

Research Idea: Can we pair Sentinel data with IQVIA drug distribution data longitudinally to identify specific generic drug concerns related to market changes?

The Importance of Critical Clinical Product Attributes in GDUFA Research

Two examples of quality issues that raised concerns for generic therapeutic equivalence:

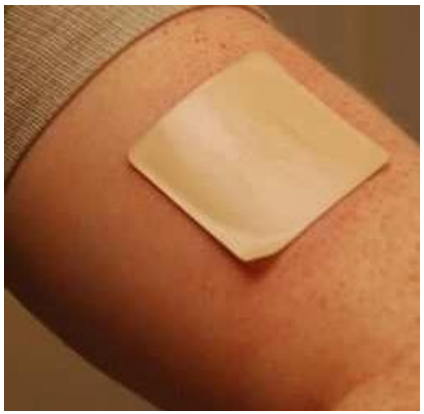
- Clonidine - Lack of adhesion of a transdermal product
- Lansoprazole - Formulation issue of an orally disintegrating tablet

These examples led to increased cross-center activities, including inspections and FDA laboratory testing that raised awareness of these types of attributes for future generic products under review.

Clonidine – Lack of Adhesion with a Transdermal Product

Generic clonidine transdermal system indicated to treat hypertension

- 30 reports of inadequate adhesion soon after approval
- Many reports associated with lack of efficacy
- FDA inspection/investigation revealed manufacturing problems related to the adhesive layer of the patches
- These findings were conveyed to the applicant and they voluntarily withdrew the product from the market



Lansoprazole Orally Disintegrating Tablet - Clogged Nasogastric Tubes

- 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 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.

Bupropion Hydrochloride ER – Reduced Efficacy

- FDA received reports of reduced efficacy for a 300 mg generic bupropion hydrochloride extended-release (ER) tablet.
- Office of Generic Drugs (OGD) asked the generic company to conduct a bioequivalence (BE) study on its 300 mg ER product and to include patients who had reported a lack of efficacy after switching from the RLD (Wellbutrin) to compare its bioequivalence to the RLD 300 mg ER product.
  - FDA funded and performed its own BE study comparing the generic drug and the RLD while the generic company's BE study was ongoing.
- The FDA's study confirmed the reports of decreased efficacy.
  - The 300 mg dose generic bupropion ER drug failed to release the drug into the bloodstream at the same rate and extent as the RLD's 300 mg ER product.
- The generic manufacturer took the 300 mg product off the market.

Bupropion – Recent FDA-funded Research on Therapeutic Equivalence

- Concerns for the efficacy of generic bupropion XL 300 in major depression and the ability to substitute a generic for the brand or one generic for another were the subject of recent FDA research.
- 70 adult patients were studied in a prospective, randomized, double blind crossover study of the brand with three generics.
  - There were no differences between any generic or brand, and all products met bioequivalence criteria for bupropion and its metabolites.
  - There were no differences in efficacy, safety, or patient perceptions of the brand and generic drug products.
- This research supports the therapeutic equivalence of generic bupropion and assures providers and the public that these generics are as safe and effective as the brand.

Kharasch, E et al., Bioequivalence and Therapeutic Equivalence of Generic and Brand Bupropion in Adults with Major Depression: A Randomized Clinical Trial. Clinical Pharmacology and Therapeutics. 105 (5), 1164-1174, 2019 (doi:10.1002/cpt.1309).

Generic Post-Mmarket Surveillance – Future Outlook

- Internal meetings and communications between FDA and industry are increasingly focused on anticipating possible generic drug safety issues before and during application review, rather than waiting for postmarket safety signals.

  This is especially true with complex generic drug/device issues. OGD's Office of Research and Standards leads this effort through controlled correspondence or pre-ANDA meetings.

- Proactive and future planning starts conversations that engage review and research staff, support GDUFA research, and attend to the entire generic drug lifecycle.
- Postmarket safety surveillance of generic drugs is just one of many efforts to ensure generic drugs are as safe and effective as brand drugs for the American Public.

Post-Mmarketing Safety Breakout Session Industry and FDA Experts

- **Samrat Sisodia, PhD, MBA**
  - Vice President Regulatory Affairs - North America
  - Glenmark Pharmaceuticals Inc.
- **Candis Edwards**
  - Senior Vice President, Regulatory Affairs
  - Amneal Pharmaceuticals
- **Jason Rodriguez, PhD**
  - Supervisory Chemist, Office of Testing and Research, Division of Pharmaceutical Analysis I
  - CDER Office of Pharmaceutical Quality
- **Raphael Brykman,**
  - Consumer Safety Officer, Office of Quality Surveillance, Division of Quality Data Science
  - CDER Office of Pharmaceutical Quality
- **Howard Chazin, MD MBA**
  - Director, Clinical Safety Surveillance Staff
  - CDER Office of Generic Drugs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