Postmarketing Safety Surveillance of Generic Drug Products – An Update

Howard Chazin, MD MBA
Director, Clinical Safety Surveillance Staff
Office of Generic Drugs
CDER | U.S. FDA

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Learning Objectives

- Explain why generic drugs might require postmarketing safety surveillance
- Discuss unexpected quality issues with generic drugs
- Explain the concept of complex generic drug products under the Generic Drug User Fee Amendments
- Utilize examples to illustrate potential safety concerns, with a focus on proactive approaches for generic drugs

Section 505(j) of the Federal Food, Drug, and Cosmetic Act

An abbreviated new drug application (ANDA) applicant relies on FDA's finding that **a previously approved drug product** (the reference listed drug or RLD**), is safe and effective**.

An ANDA must have the same:

- Active ingredient(s)
- Conditions of use
- Route of administration
- Dosage form (tablet=tablet, capsule=capsule, etc.)
- Strength
- Labeling (with some permissible differences)
- Bioequivalence*
- No new studies are necessary to establish safety or effectiveness

* Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Allowable Differences in Generic Drugs

- Shape
- Release mechanisms
- Packaging
- Excipients/inactive ingredients depending on product type – with more restrictions for injectables, ophthalmic, and otic products
- Expiration time
- Container closure systems
- Labeling (certain permissible differences)

Generic Drugs are Safe and Effective!

- Most generic drug products do not have postmarketing safety or efficacy concerns.
- Of the hundreds of generic drugs approved and marketed every year, only a **very small number** of generic drugs products have postmarketing safety issues or concerns.

Generic Drug Postmarketing Pharmacovigilance

- **Focusing on past experience with quality issues** and developing new approaches to address complex generic drug-device combination products.
- **Utilizing drug marketing data** to consider evaluating a potential safety signal.
- **Proactive pharmacovigilance screening** of generic drug uptake over time and data mining MedWatch reports to detect early signals of potential safety concerns.
- **Working collaboratively with our postmarketing surveillance colleagues** in the Office of Compliance, the Office of Pharmaceutical Quality, and the Office of Surveillance and Epidemiology.

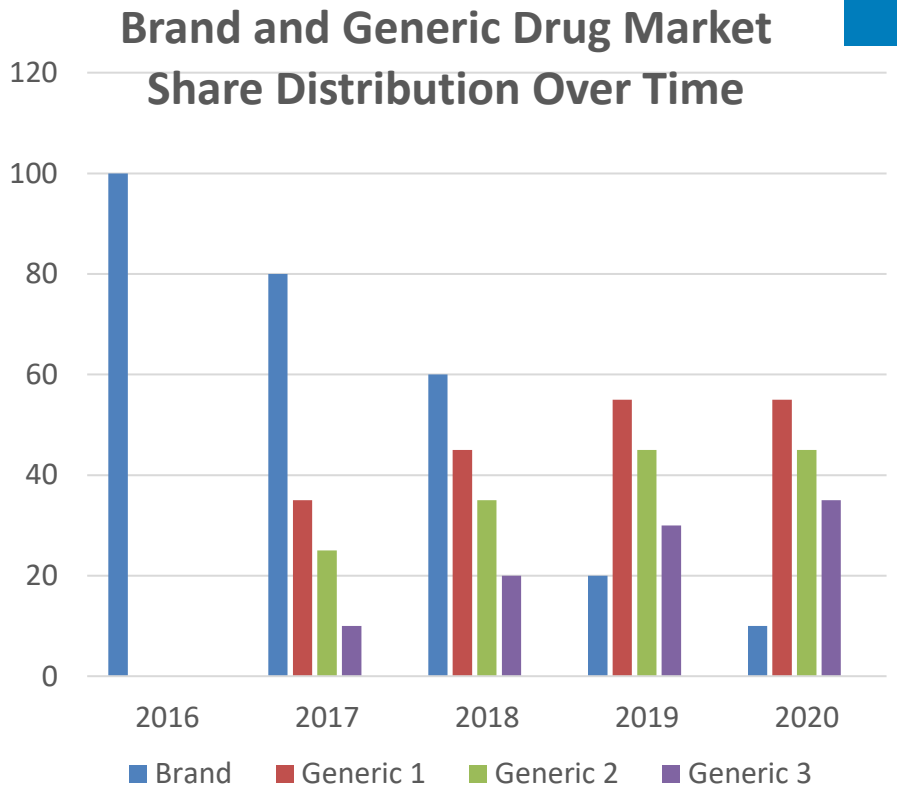
Past Experience with Quality Issues

- 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
- Container/closure issues
- Eyedrop safety seals falling off
- Large size tablet/capsule
- Extended-release products not lasting through the day
- Injector malfunctions/needle breaks

Drug Marketing Data

As a generic drugs are introduced, the brand loses market share and within a few years, generic drugs predominate the market.

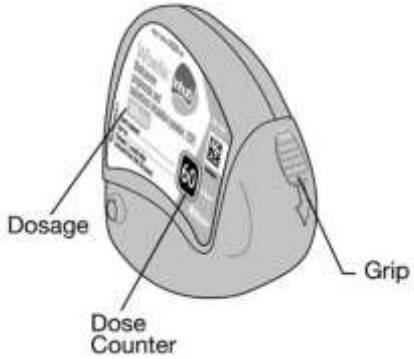
Market share data can be used as an **informal denominator** to screen for generic drug safety concerns.

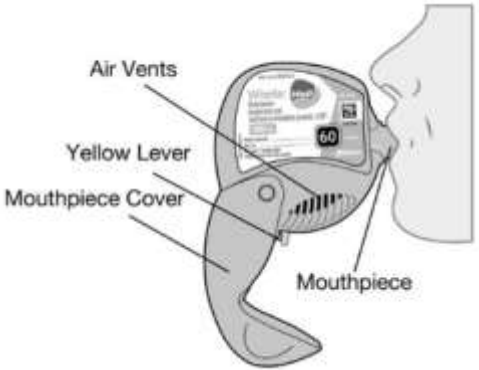


Proactive Pharmacovigilance Screening

Brand - Advair Diskus (Glaxo SmithKline) approved in 2003

Generic - Wixela Inhub (Mylan) approved in January 2019





Proactive Pharmacovigilance Screening

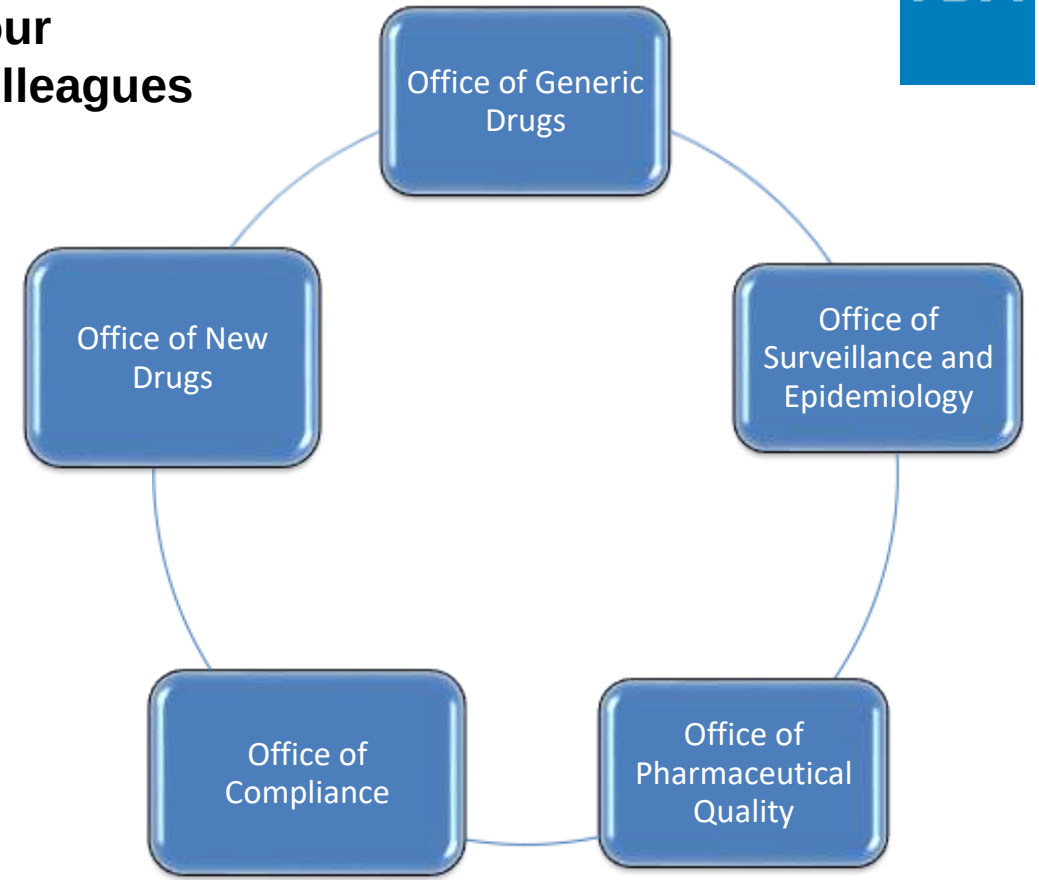
- **Proactive pharmacovigilance screening** was initiated to address any concerns regarding the different look and orientation of this first generic product compared to the brand.

- As Wixela Inhub gained market share, the OGD CSSS monitored the FDA Adverse Event Reporting System (FAERS) and the Drug Quality Reporting System monthly throughout 2019 and 2020.

- **No quality or safety signals were detected!**

Working collaboratively with our postmarketing surveillance colleagues across CDER

Communicating to the public through research initiatives or directly to consumers may help mitigate safety risks of brand and generic drugs.



Complex Generic Drug Products Under the Generic Drug User Fee Amendments

- Complex active ingredients or formulations
- Complex routes of delivery such as locally acting drugs in dermatological products and complex ophthalmological products
- Complex dosage forms (transdermals or extended release injectables)
- Complex drug-device combination products such as auto injectors and metered dose inhalers
- Other products where complexity or uncertainty concerning the approval pathway or possible alternative development approaches would benefit from early scientific engagement

Complex Generic Drug-Device Combination Products

Complex drug-device combination products may raise unique potential safety concerns related to:

- **Drug delivery**
- Differences in **device constituents**
- **Unexpected quality issues** that may require immediate action!

Complex Product Safety Postmarketing Examples…

- When prefilled syringes containing a product are approved as NDAs or ANDAs and general use autoinjector devices are approved as a 510(k)s, there may be postmarketing messaging by application holders of these components to be used together by the target patient population.

- Potential safety issues can arise when a first generic drug product is introduced into a market.

Example: Copaxone auto-injector devices

- Brand (Teva, approved in 1996) and generics - Sandoz (approved in 2015) and Mylan approved in 2017) for copaxone (a drug for multiple sclerosis) were prefilled syringes.

- CDRH approved three general use auto-injector devices as 510(k)s and these are marketed independently by each manufacturer on their websites.

- **Medical errors related to bent needles and injector failures** have been reported in FAERS since the generics were approved.

Brand - Teva - Proair HFA - albuterol sulfate inhaler approved in 2004

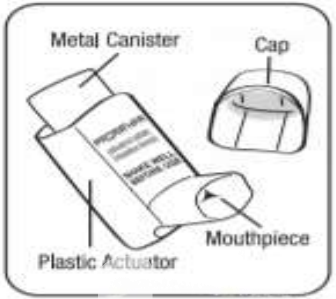


Figure A

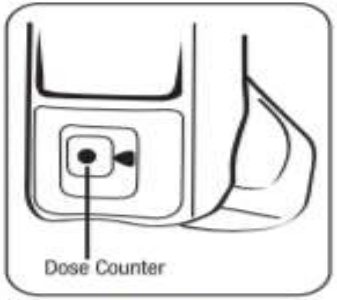
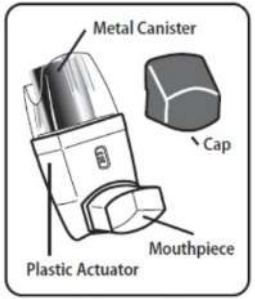


Figure B

Generic - Perrigo/Catalent albuterol sulfate first generic - approved on February 24, 2020



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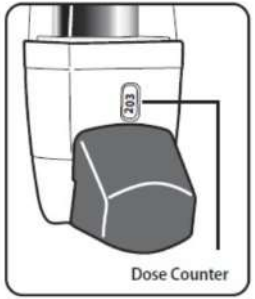

Figure B

Timeline of Unexpected Clogged Inhaler Safety Signal

- February 24, 2020 – Perrigo/Catalent ANDA approval
- From April through August 2020, FDA received complaints of **clogging of the generic inhalers**, even after washing under water and following labeling instructions. MedWatch forms indicated “inhaler malfunction” or “inhaler clogged”
- CDER’s Office of Compliance, Office of Pharmaceutical Quality, and the Office of Generic Drugs postmarketing surveillance teams worked together sharing data on the potential safety signal
- Perrigo/Catalent stopped producing and distributing the inhalers on August 21, 2020 and were investigating the malfunction.

Perrigo/Catalent Albuterol Inhaler Voluntary Recall

Perrigo Voluntarily Recalls Albuterol Sulfate Inhalation Aerosol; Reaffirms 2020 Guidance

Perrigo

NEWS PROVIDED BY
Perrigo Company plc →
Sep 17, 2020, 07:29 ET

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DUBLIN, Sept. 17, 2020 /PRNewswire/ -- Perrigo Company plc (NYSE: TASE: PRGO) today announced a voluntary U.S. nationwide recall of albuterol sulfate inhalation aerosol to the retail level after previously halting production and distribution. These actions are being taken out of an abundance of caution as a result of complaints that some units may not dispense due to clogging. Perrigo's generic albuterol sulfate inhalation aerosol was developed in partnership with and manufactured by Catalent Pharma Solutions.

Increasing Outreach to Generic Drug Stakeholders

- Increase use of broad or focused drug safety alerts and communications when necessary
- Engage with the generic drug industry, provider, and pharmacy stakeholder groups
- Obtain feedback from patients and providers
- Educate the public about the value of generic drugs through online postings, articles, webinars, podcasts
- Collaborate with our international partners across the globe

Summary

- **Generic drugs are as safe and effective as brand drugs**
- **Allowable differences on rare occasions** may lead to unexpected or unanticipated quality or safety issues
- **Complex generic drug-device combination products** raise unique potential safety concerns due to **drug delivery**, differences in **device constituents** or **unexpected quality issues** that may require immediate action
- Anticipating concerns related to **increasing generic drug market share** helps to focus generic drug pharmacovigilance efforts
- **Internal conversations across CDER** help engage staff, support research, and develop public communications
- **Outreach to generic drug stakeholders** is key to refining OGD's ongoing safety surveillance processes and procedures

Challenge Question #1

True or False:

New clinical trials are necessary before a new generic drug is approved.

Challenge Question #2

True or False

After the introduction of several generic drugs to the marketplace, the market share of brand drug increases.

Helpful Resources

General Article on Generic Drug Pharmacovigilance

Chazin HD, Peters JR, Catterson DM, et al. Drug Information Association Pharmacovigilance and Risk Management Strategies 2017: Overview of the Generic Drug Program and Surveillance. Therapeutic Innovation & Regulatory Science. 2019;53(2):249-253. https://rdcu.be/cg40m

Podcast – Challenges in Generic Drug Safety & Surveillance

https://diapublications.podbean.com/e/challenges-in-generic-drug-safety-surveillance

Center for Drug Evaluation and Research Drug Safety Priorities 2020

https://www.fda.gov/media/145716/download

Thank You!

Howard D. Chazin, MD MBA

Director, Clinical Safety Surveillance Staff

Office of Generic Drugs

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howard.chazin@fda.hhs.gov


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