

Emerging Trends in Postmarketing Safety Surveillance for Generic Drugs

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Learning Objectives



- Explain the importance of generic drug surveillance
- List examples of potential quality issues for generic drug products
- Illustrate, with real-life examples, some quality issues that have been evaluated by the Office of Generic Drugs
- Identify emerging trends in generic drug surveillance



Why do we need postmarketing surveillance for generic drugs?

- Generic drugs are evaluated to ensure they are therapeutically equivalent to brand name drugs
- On occasion, issues may arise from allowable differences between the brand and generic drugs
- Drug products are getting more complex and have unique quality/reliability issues

Allowable Differences

Generic drugs can sometimes differ in:

- Shape
- Scoring configuration
- Release mechanisms
- Packaging
- Excipients/inactive ingredients
- 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.

Examples of Some Generic Drug 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
- Injector malfunctions/needle breaks



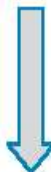
Potential Safety Issues



CSSS Safety and Surveillance Committee Meeting



**CSSS Lead Clinical
Safety Coordinator**



Forwards
Potential
Safety
Issues



**CSSS Safety and Surveillance
Committee Meeting**

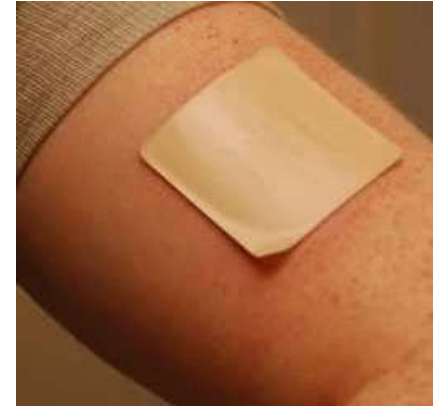
- Multidisciplinary group of physicians, chemists, and scientists from Office of Generic Drugs (OGD), Office of Pharmaceutical Quality, and other CDER offices as needed
- Results of CSSS pharmacovigilance activity report presented and evaluated by group
- Discusses and triages emerging safety issues forwarded by CSSS
- Decides on investigation/path forward

Real Life Examples of Safety Issues Identified and Resolved by CSSS



Lack of Adhesion with a Transdermal Product

- Generic transdermal system indicated to treat hypertension
- 30 reports of inadequate adhesion soon after approval
- Many reports associated with lack of efficacy
- FDA 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



Real Life Examples (cont.)

Serious Safety Issue Related to Generic Formulation

- Lansoprazole Orally Disintegrating Tablet (ODT)
 - labeled uses include administration through feeding tubes
- Generic 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
- An FDA Drug Safety Alert was posted:
<http://web.archive.org/web/20131010042431/http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm251575.htm>
- Applicant voluntarily withdrew the product from the market
- ODT products indicated for use with a feeding tube are now tested for this functionality, using a protocol developed in OGD



Real Life Examples (cont.)



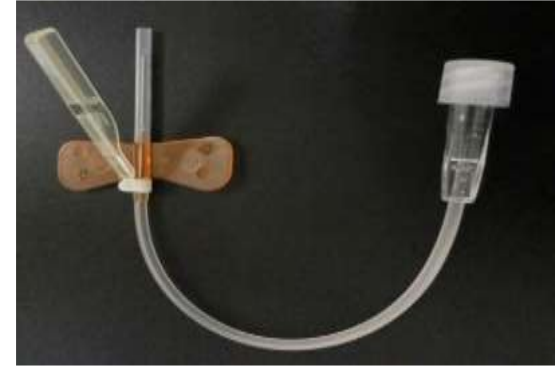
Dropper Issues with an Ophthalmic Solution Product



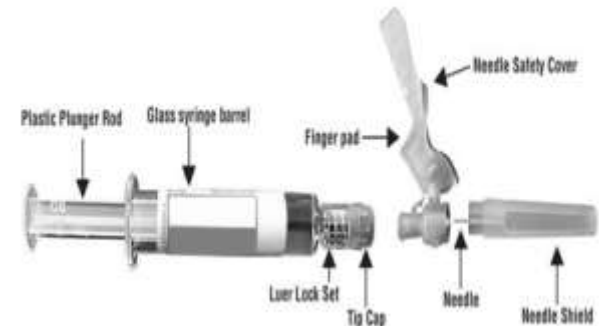
- Generic ophthalmic solution indicated to treat elevated intraocular pressure
- Multiple MedWatch reports of eye burning/irritation, large drop size, and running out of product too soon
- FDA lab tested the product, which showed a larger drop size than the brand or other generics
- At OGD's request, the applicant revised their container/closure system to resolve the issue

Complex Generic Drug Combination Products

- More complex products can have different quality/reliability issues:
 - Patches that fall off or were too large
 - Prefilled syringe kit can have a different needle presentation
- What happens if the device constituent causes the safety problem in a combination product?
 - Collaborative efforts between Center for Drug Evaluation and Research (CDER) and Center for Devices and Radiological Health (CDRH)



Winged needle



Straight needle

Unintended Consequences

- Prefilled syringes containing drug product are approved as NDAs or ANDAs
- General use **auto-injector devices** are approved separately as 510(k)s
- Companies may sometimes promote the use of the auto-injector with the prefilled syringe to the target patient population
- Consequence:
The brand and generic drug products and their auto-injectors may not be interchangeable and may cause use errors

Example: Glatiramer Acetate Injection Auto-Injector Devices



- Brand (Teva, approved in 1996) prefilled syringe for multiple sclerosis
- Generics: Sandoz (approved in 2015) and Mylan (approved in 2017)
- CDRH approved three general use auto-injector devices as 510(k)s; they are marketed independently by each manufacturer
- Medical errors related to bent needles and injector failures have been reported

Emerging Trends in Generic Surveillance: Using Proactive Approaches



- Instead of reacting to potential safety issues, the trend is to be more proactive especially with complex products
- CSSS is looking at generic drugs and assessing proactively whether any allowable differences may be problematic
- Proactively thinking about these products starts internal conversations that help engage staff, support research, and develop public communications



Advice to Industry



- Ensure consistent quality of products lot-to-lot, unit-to-unit, and throughout their shelf-life
- Anticipate and avoid allowable product differences that may impact patient perception and ability to use the product as intended, for example:
 - Tablet size, coating, odor, taste
 - Excipients, container/closure function, color schemes, delivery mechanisms, devices, etc.
- Attend public meetings regarding safety relevant to generic products
- Actively work to promote confidence in generic drugs

Challenge Question #1

Which one of these is an allowable difference between the generic and the brand product?

- A. Shape
- B. Container/closure system
- C. Inactive ingredients
- D. Packaging
- E. All of the above

Challenge Question #2



Which of the following statements about the CSSS Safety and Surveillance Committee is NOT true?

- A. Results of CSSS pharmacovigilance activity report presented and evaluated by group
- B. Only includes members from the Office of Generic Drugs
- C. Decides on investigations/path forward
- D. Discusses and triages emerging safety surveillance issues forwarded by CSSS

Questions?

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