Challenges in Generic Drug Safety and Surveillance – Opportunities for Research

Howard D. Chazin, MD, MBA, Director
CDER Office of Generic Drugs
Clinical Safety Surveillance Staff (CSSS)
Generic Drug Research Public Workshop
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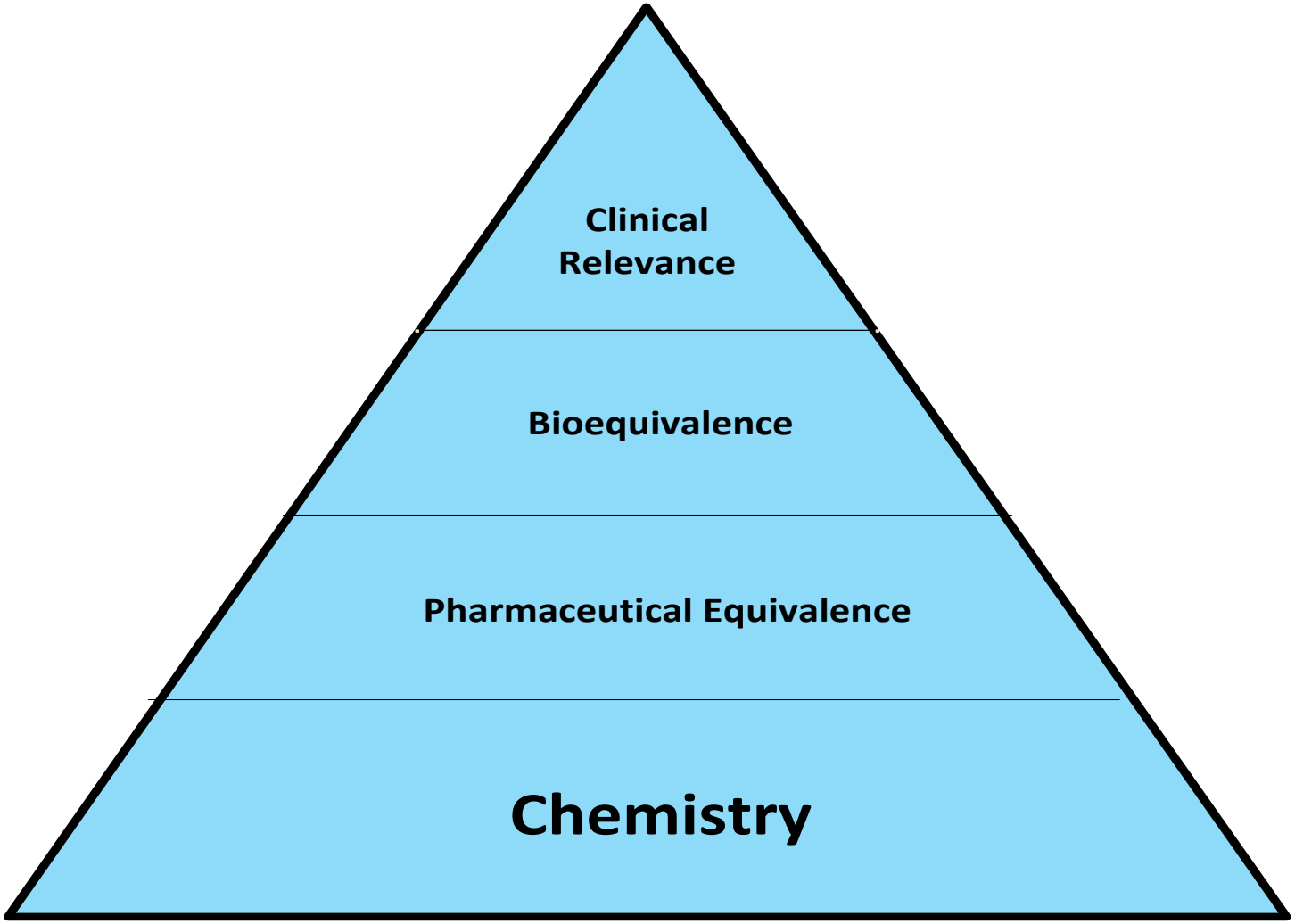
Outline

1. Generic Drug Approval Process
2. The Clinical Safety Surveillance Staff
3. CSSS research resources (FAERS, IQVIA, Sentinel)
4. Clinical significance of observed differences between brand and generic
5. Example perceived Orally Disintegrating Tablet drug inferiority

Foundation for Identity of Generic Drugs



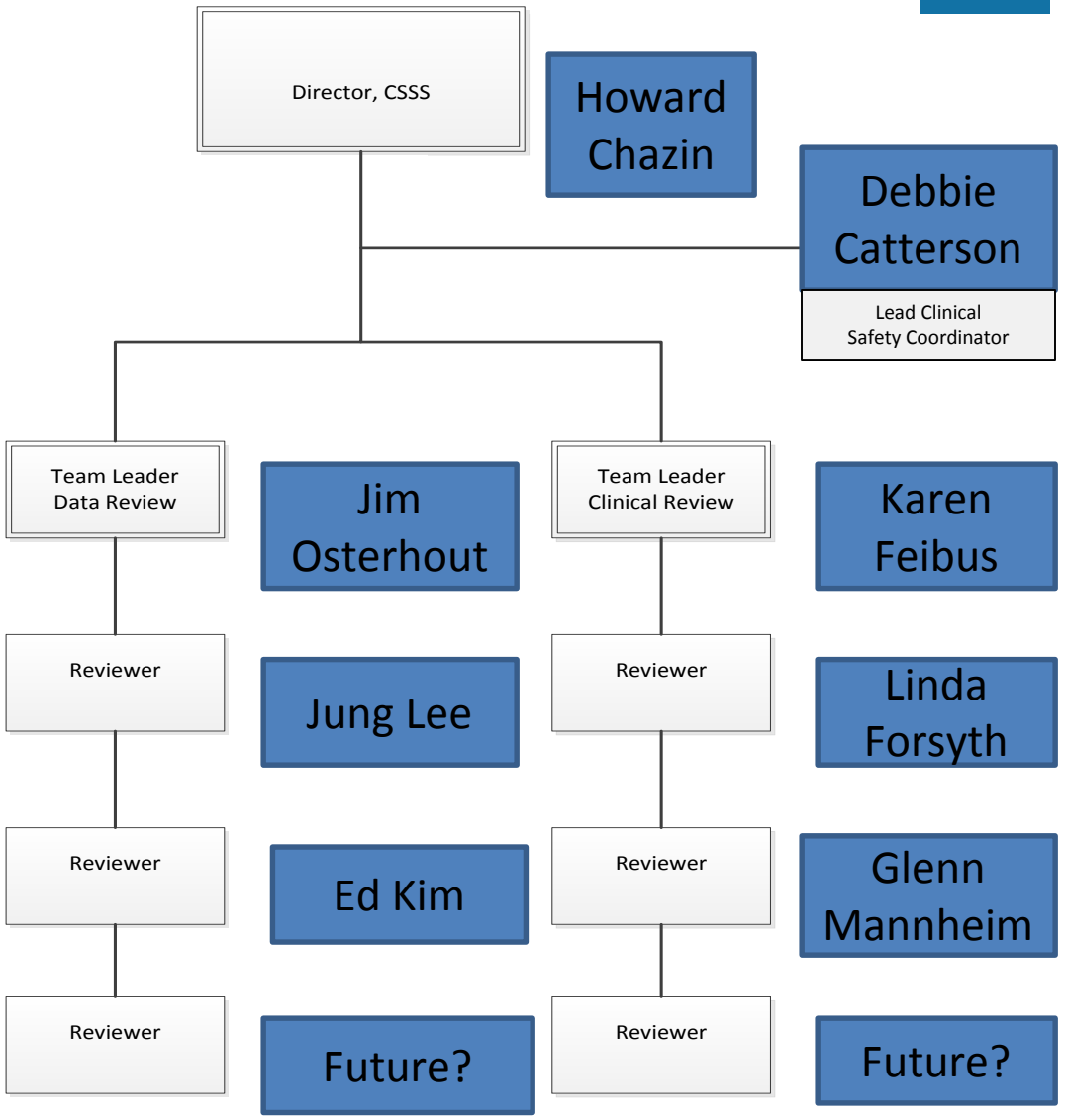
NDA vs. ANDA Requirements

Brand Name Drug NDA Requirements	Generic Drug ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal Studies 7. Clinical Studies 8. Bioavailability	6. Bioequivalence

Clinical Safety Surveillance Staff

Mission:

The CSSS serves as the OGD liaison to CDER's Office of Surveillance and Epidemiology (OSE) and other drug surveillance organizations within CDER to obtain and coordinate information to ensure the safety of generic drugs on the U.S. market.



The FDA Adverse Event Reporting System

Limitations as a data source:

- 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 generic formulation
- Safety signals are difficult to identify and verify due to concurrent medications and/or illnesses

IQVIA Drug Utilization Data

What can we learn from the distribution of market share among generics over time?

- As a generic drugs are introduced to the market, the RLD slowly decreases market share and generic drugs predominate the market.
- Market share data can be used as an informal denominator to screen for safety concerns for particular generic drugs.
  - 10 complaints per month for 3 months related to a product that has 10% of the market.
  - 10 complaints per month for 3 months related to a product that has 50% of the market.

FDA Sentinel Initiative

- A complimentary 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 redispensed brand or another generic
  - Patients who are receiving brand instead of generic

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

Patient perceptions of generic drug inferiority

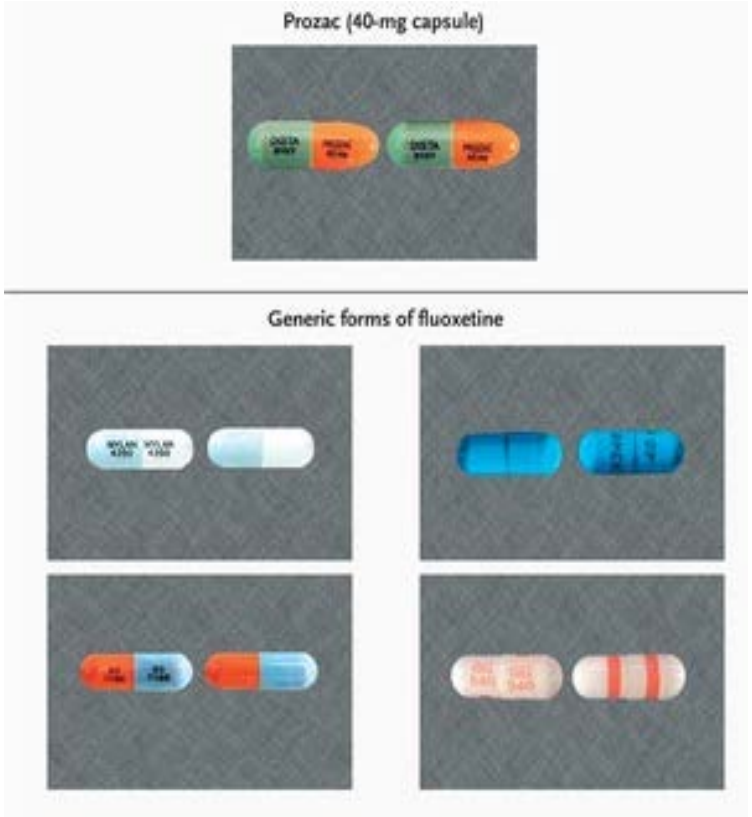
- Why are there allowable differences in generic drugs?

- How can these differences lead to changes in patient perceptions?

CSSS research need is to determine when these observed differences are acceptable and when they are a concern.

Allowable Differences

Generic drugs can sometimes differ in:



- Shape
- Scoring configuration
- Release mechanisms
- Packaging
- Excipients
- Expiration time
- Labeling (within certain limits)

Quality Issues and Complaints

- 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
- Device issues
- Dropper issues with ophthalmologic products
- Large size tablet/capsule

Olanzapine Orally Disintegrating Tablets (ODT)

- In March 2018, CDER's Office of Surveillance and Epidemiology received complaints on the listserv of the College of Psychiatric and Neurologic Pharmacists related to generic olanzapine ODT not dissolving adequately.
- Olanzapine is an antipsychotic medication.
- ODT formulations are helpful as no water is necessary to swallow and this aids in medication compliance.

ODT Guidance for Industry 2008

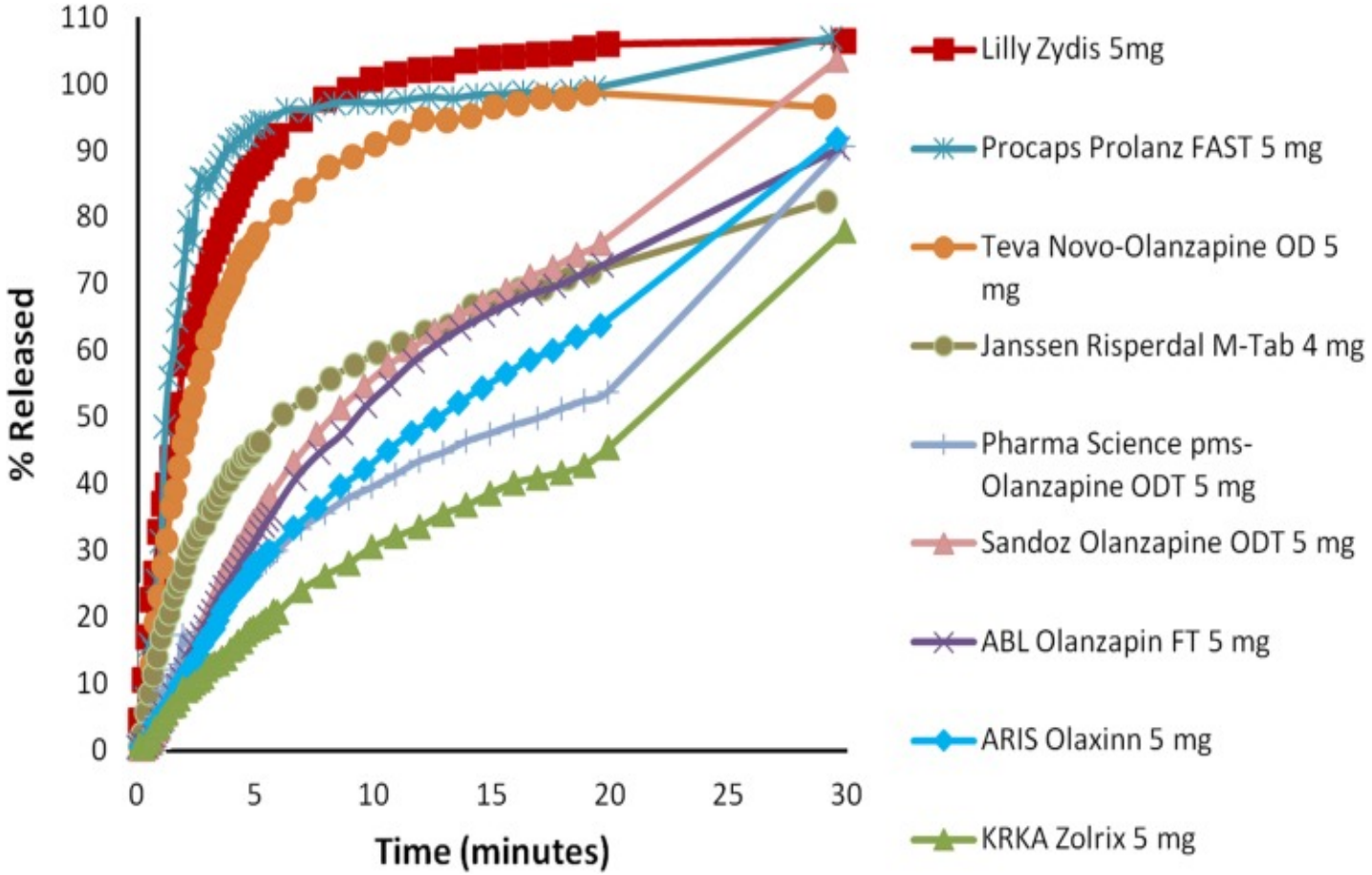
- A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue
- An in-vitro disintegration time of approximately **30 seconds or less,** when based on the United States Pharmacopeia disintegration test method or alternative

Olanzapine ODT disintegration times

- NDA- 21086 Eli Lilly
  - Formulation - Lypholized/freeze dried formed in a blister cavity (patented)
  - Disintegrates almost immediately

- U.S. approved ANDAs –
  - Formulation - Soft compression tablet with disintegrants
  - Disintegration time between 15 and 30 seconds.

Olanzapine in vitro dissolution differences



Note: Not all of these products are U.S. approved generic olanzapine products. This graphic represents differences in dissolution times related to different ODT formulations compared to the RLD (Lilly Zydis)

Hobbs, D. et al (2013) An In Vitro Analysis of Disintegration Times of Different Formulations of Olanzapine Orodispersible Tablet: A Preliminary Report. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3879822/

Perceptions and Future Research

- Allowable differences in ODT products (disintegration time up to 30 seconds) makes physicians, nursing staff and other healthcare providers believe that generic olanzapine ODT tablets are not dissolving
- Generic product is **perceived** as inferior to brand
- Generic product is effective and safe meeting all criteria for approval
- **Research on perceptions when patients switch from RLD to generic is valuable**
- Challenging as subtle perceptions are not easy to quantify

Therapeutic Areas of Substitution Concern

FDA has looked at the following drugs in patient substitution studies to address patient concerns:

- Antiepileptic drugs
- Immunosuppressant drugs
- Bupropion (antidepressant)
- Methylphenidate (stimulant)

What other drugs are prone to patient concerns related to substitution?


THANK
YOU