Postmarketing Surveillance in the Office of Generic Drugs

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Postmarketing Surveillance in OGD

- Initiated in early 2010
- Requested by the CDER Director
- Part of the CDER Safety First Initiative
- Addresses generic skepticism
- Analyzes reports for potential safety issues
- Serves the function of the Therapeutic Inequivalence Action Coordinating Committee

Safety and Quality Reports

- Reports submitted directly to FDA and entered into DQRS
  - Adverse events (AEs)
  - Lack of effect
  - Perceived inequivalence
  - Quality concerns
- Reviewed by medical officers, chemists, and other scientists
- Field Alert Reports (FARs) reviewed by chemists
- Involves collaboration with OC, OND, OSE, and others

Limitations of Spontaneous Reporting

- Spontaneous reports are just the “tip of the iceberg”
- Most problems are not reported
  - Lack of awareness of MedWatch program
  - Lack of motivation to report problems
  - Attitudes about generic drugs in general
- Many reports do not identify a specific generic product
- Stimulated reporting

Review of Individual Reports

- Reports are tracked and archived in a database created by OGD specifically for these postmarket reports
- Evaluation for a Safety/Quality/Inequivalence Signal
  - Nature and severity of the reported problem
  - Number of other reports for the same ANDA product
  - Number of similar reports for the RLD and other generics
  - Trend in number of reports over time
  - Labeled treatment indication, dosage recommendations, and expected adverse events

Additional Details to Consider

- Compare ANDA and RLD
  - formulations
  - PK profiles
  - CMC considerations
  - delivery systems
  - physical characteristics
- Market Sales/Distribution Data
- Scientific/Medical literature research
- Quality issues related to the product and/or manufacturer
- Recent changes in manufacture of product

Summary of DQRS MedWatch Reports

1141 Reports in first 18 months (Subset of AERS MedWatch)

- 218 related to Adverse Events
- 534 related to Unexpected Therapeutic Effect
- 368 related to Quality Concerns
- 21 related to Labeling Issues

Unexpected Therapeutic Effect

- 346 DQRS reports of different effect when switching from RLD to generic or from one generic to another
- 186 reports of ineffective or decreased response (no mention of switching between products)
- 2 reports of increased response
- 28 reports of suspected therapeutic inequivalence with **authorized generics** (the RLD product marketed as a generic under the same NDA)

Quality Issues

- 73 -Packaging (57 wrong quantity)
- 25 -Container/Closure
- 25- Device Issues
- 10 -Different drugs found in the same container
- 53 -Lack of adhesion (30 reports for the same product)
- 41 -Contamination
- 39 -Bad odor
- 11 -Bad taste
- 29 -Abnormal solubility
- 25 -Poor Friability
- 15 -Unusual color or discoloration
- 5 -Lack of coating
- 4 -Large size tablet/capsule
- 30 -Miscellaneous (related to formulation or general quality)

Field Alert Reports (FARs)

- In 2010, we received approximately 650 FARs
- For 2011 thus far, we have received approx. 440
- We average 50-54 FAR reports per month
- FARs are sent from the field offices to OC to OGD
- Evaluated primarily by OGD chemists and managed in collaboration with OC
- CDER Quality Council working to further enhance our collaborative process in addressing FARs

Actions to Resolve Quality Issues

- OGD collaborates with OC and the field offices to address quality and manufacturing issues in FARS
- As a result, sponsors have taken actions to resolve the issues:
  - Changes to formulation
  - Changes to container/closure system
  - Reduction in expiration dating
  - Corrections to labeling errors

Lack of Adhesion with a Transdermal Product

- Recently approved transdermal product
- 30 reports of inadequate adhesion
- Many reports associated with lack of efficacy
- FDA investigation revealed manufacturing problems related to the adhesive layer of the patches
- In response, the sponsor voluntarily initiated a market withdrawal of the product

Dropper Issues with an Ophthalmic Solution Product

- Multiple MedWatch reports of eye burning/irritation, large and uncontrollable droplet size, and running out of the product too soon
- FDA lab tests showed that this product had a larger drop size than other generics and the RLD
- At OGD's request, the sponsor revised their container/closure system to resolve the issue

Serious Safety Issue Related to Generic Formulation

- Orally disintegrating tablet (ODT) product
  - labeled uses include potential for 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 RLD
- A Drug Safety Communication was posted on FDA Website
- The sponsor voluntarily withdrew the product from the market

Future and Ongoing Efforts

- Correlate formulation differences or quality issues with reports related to therapeutic performance of generic products
- Establish guidelines to help the generic industry avoid issues related to product quality, formulation, and/or physical characteristics that might contribute to different therapeutic results
- Pending guidance on tablet size limits

Advice to Industry

- Ensure consistent quality of products lot-to-lot, unit-to-unit, and throughout their shelf-life
- Anticipate and avoid product differences that may impact patient tolerance and ability to use the product as intended
  - Tablet size, coating, odor, taste
  - Excipients, container/closure function, color schemes, delivery mechanisms, devices, etc.
- Attend and participate in public meetings regarding safety or other issues relevant to generics as well as brand products
- Actively work to promote acceptance of generic drugs