Surveillance Processes of Generic Drugs

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Potential Safety Signal

- Contacts from the public directly to FDA
- MedWatch reports submitted to FDA
- Identified in CDER's Office of Generic Drugs (OGD) and Office of Surveillance and Epidemiology (OSE) databases
- Sponsor reports
- Scientific Literature
- OGD definition of a potential signal may be different from that of OSE
  - Generic drug complaints (inequivalence) differ from rare adverse events related to the active pharmaceutical ingredient

Scope of Generic Surveillance

- Generic surveillance does NOT focus on complaints related to the active ingredient
- Generic surveillance DOES involve:
  - Therapeutic inequivalence
  - Problems with quality - odor, taste, rapid oral disintegration
  - Problems with packaging - dropper, cap
  - Novel or more prevalent AEs as compared to the reference listed drug (RLD) product
- These problems may be related to allowed differences between the RLD and the generic

Databases

- Drug Quality Reporting System (DQRS)
- FDA Adverse Event Reporting System (FAERS)
- Marketplace Data - IMS, Symphony

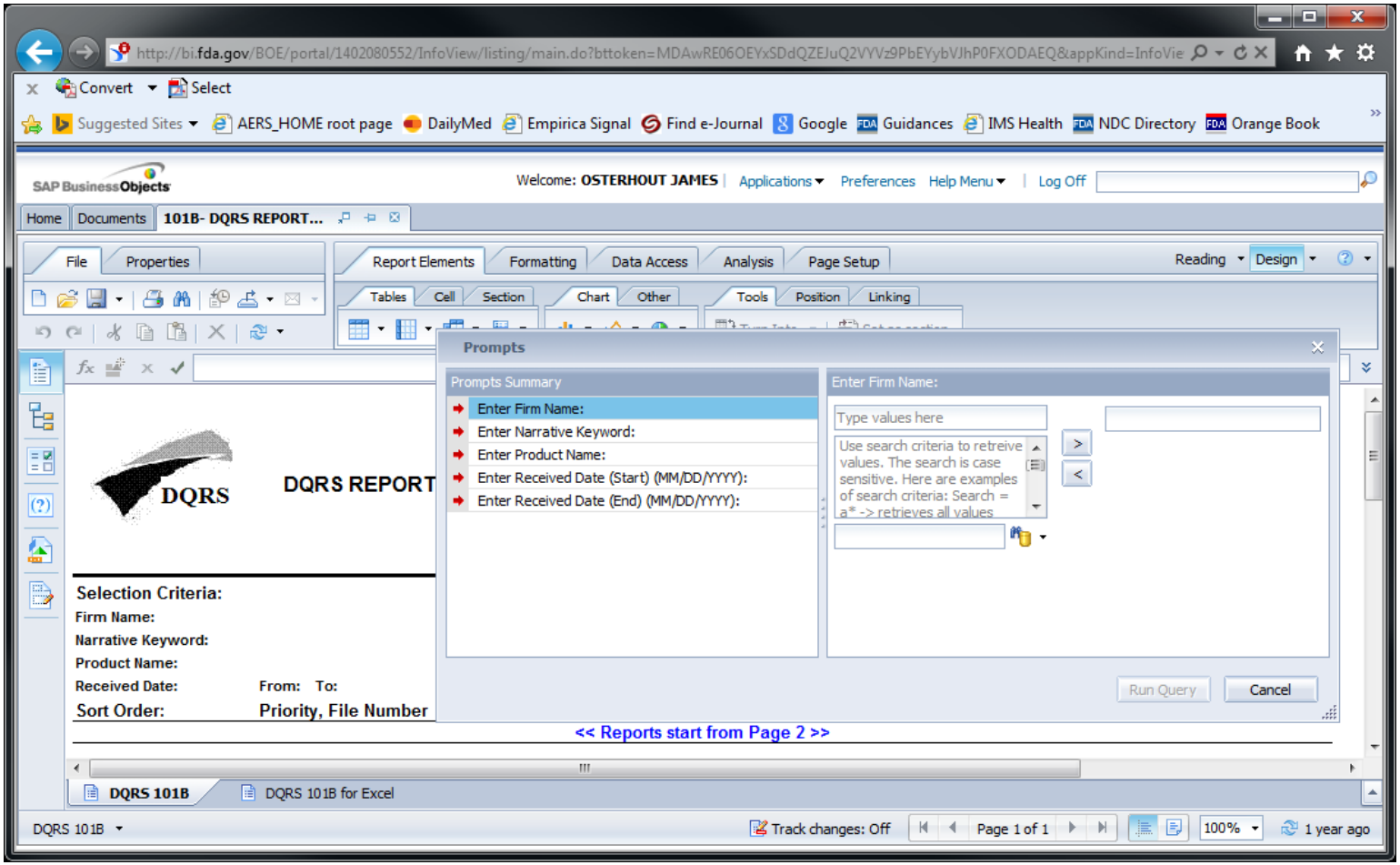
  – Limitations of Spontaneous Reporting
    - Many reports do not identify a specific generic product
    - Many complaints for generics are misattributed to the RLD product

Drug Quality Reporting System

- A subset of MedWatch reports that contain complaints related to quality or inequivalence are entered into DQRS.
- These reports may also contain adverse events (AEs) and thus the same reports would also be in FAERS.
- Largely spontaneous reports - enriched in cases of product inequivalence and quality problems
- Approximately 600 MedWatch reports per month
- Searchable for multiple fields with dynamic reporting

101B DQRS Report

- Main report used is the 101B that was designed by OGD staff to accommodate the periodic surveillance reports



DQRS

- Search results are exported into Excel for sorting and analysis for any potential signals
- The report output contains manufacturer and lot if available, defect and a full narrative from the reporter.
- A custom SAS program written by CSSS is used to analyze the complaints and identify and potential signals.
- Individual narratives are reviewed to identify any single report that may need further review by a medical officer.

Marketing Data

- Two sources of marketing (distribution) data are used
  - IMS Smart
    - National Sales Perspective (NSP)
    - National Prescription Audit (NPA)
  - Symphony
- Drug distribution data is considered when investigating a potential signal in an attempt to compare multiple generic manufacturers by calculating a relative rate.

Retrospective and Prospective Generic Surveillance 1

- Retrospective - Monthly Surveillance Report
  - Short-term emerging signals
  - Safety Evaluator reviews 1 month of DQRS complaints to identify any single report warranting further scrutiny by safety team
  - Reports sorted by manufacturer/product to identify clusters for a single manufacturer indicating a possible emerging problem
  - Any problems or potential signals identified are forwarded for discussion at the Monthly CSSS Committee Meeting.

Retrospective and Prospective Generic Surveillance 2

- Prospective – “Newly Approved” Generic Watch List
  - Anticipates future Signals
  - Each surveillance period, the Safety Evaluator reviews the list and searches for complaints on new generics
  - DQRS complaints in initial weeks of marketing are documented
  - New generics that meet signal criteria are added to the New Generic Watch List and monitored over time.
    - Weber Effect?

Detailed Review of Individual Potential Safety Issues 1

- Safety Evaluator performs an in-depth evaluation for a safety, quality, or inequivalence signal:
- Search of FDA databases: DQRS (quality) and FAERS (AEs):
  - Additional observations related to the problem
  - Background rate of same observations for RLD
- Review of ANDA and RLD Information
- Market Share Determination-IMS Sales Data
- Scientific / Medical literature research

Detailed Review of Individual Potential Safety Issues 2

- Components & Composition, Release Mechanism, Excipients
- CMC changes, recent manufacturing changes
- Review of BE data for possible areas of concern
- Relevant FARs (Field Alert Reports) for the product

Real Life Example: Metoprolol ER Tablet

- CDER received a letter in December 2012 from prominent cardiologist
- Described episodes of therapeutic failure for generic products from several manufacturers
- Occurred when patient switched from RLD or Authorized Generic (AG) to generic product
- Samples of the RLD and generic product were obtained and tested by the FDA Office of Testing and Research
- Differences in the reporting of adverse events between the RLD and the generics was assessed by CDER (OGD, OSE)
- A Tracked Safety Issue was opened by OGD and a safety investigation team was formed
- TSI Result - Based on the review of available data the FDA safety investigation team determined all products should remain acceptable for substitution to the RLD (AB)

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Real Life Example: Clonidine Patch

- Clonidine Transdermal System (0.1, 0.2 or 0.3 mg per day)
  - Indicated in the treatment of hypertension
- OGD identified 89 reports for this new to market generic product, largely involving lack of adhesion and efficacy
- MedWatch report narratives complained of the large size of the generic patch as compared to the RLD
  - For 0.3 mg/day: generic = 32.4 cm^2 and RLD = 10.5 cm^2
- FDA inspected generic company in December 2009 and serious problems were identified in the manufacture of the clonidine patches
- A warning letter was issued to generic on May 21, 2010.
- Subsequently, generic company voluntarily removed the product from the market

Acknowledgements

- Clinical Safety & Surveillance Staff
  - Howard Chazin, MD : Director
  - Linda Forsyth, MD : Medical Officer
  - Debbie Catterson, RPh : Safety Coordinator
  - Jung Lee, MS : Safety Officer