Quality Related to Tracked Safety Issues (TSI) – An Ophthalmic Case Study

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OUTLINE

• Management of Safety Issues within OPQ by Tracked Safety Issues (TSIs)

• Example of recent TSI affecting multiple ANDA Ophthalmic products

• Recommendations for Industry

• Summary
DRUG SAFETY OVERSIGHT WITHIN OPQ

• The Safety First Initiative, launched in 2008, provided CDER with greater leverage to identify, assess and act upon drug safety issues in the postmarket period.

• TSIs were created to establish a formal system for tracking significant safety issues.

• The TSI process brings together experts across FDA Centers and Divisions to provide multi-disciplinary perspectives on postmarketing safety issues.

• CDER’s Office of Pharmaceutical Quality (OPQ) has adapted the TSI review process to manage patient safety issues related to Drug Product quality risks.
HOW IS OPQ INFORMED OF SAFETY ISSUES

Patient Safety Issues related to Drug Product Quality risks

- National voluntary reporting programs for medication error reporting
- FDA MedWatch
- FDA Adverse Event Reporting System (FAERS)
- FDA Drug Labeling Review Divisions
- FDA Drug Product Quality Review Divisions in CDER/OPQ
- FDA Surveillance and Medication Error Prevention Divisions
- FDA Field Investigations

www.fda.gov
BACKGROUND TO OPHTHALMIC CASE RELATED TO EYE DROP BOTTLE PACKAGING DESIGN

• In recent years many prescription ophthalmic drug product manufacturers have begun using simple eye drop bottle designs with tamper-evident plastic seals which are generally more cost effective than plastic shrink wrap seals.

• The plastic tamper-evident seal (i.e. ring, collar, band) breaks away from the cap upon first opening of the bottle. The break away seal is a security feature of the packaging to prevent adulteration of the drug product since the seal cannot be easily reattached once broken.

• Non-retaining or loose tamper-evident seals which remain at the base of the bottle neck predispose patients to injury because the plastic seal may fall off into patients’ eyes when the bottles are tilted or inverted to apply eye drops.

• FDA has received adverse event reports (6 known FAERS cases in 2013-2014) of eye injury and the likelihood of injury due to the plastic seal falling from the bottle neck into patients’ eyes when using a prescription ophthalmic drug product solution.

• FDA has also received at least 3 similar cases affecting an Over-The-Counter (OTC) drug product in 2016.
Assembly of TSI team comprised of FDA Medical Officers, Quality reviewers, Policy advisors, Compliance officers, Labeling reviewers, Microbiology reviewers, and Surveillance staff across FDA/CDER.

Opened a Standard TSI with a 1 year review clock from December 2015 to November 2016.

TSI was led by OPQ/OLDP.

TSI team worked to (1) warn patients and public, and (2) make recommendation to enhance patient safety, and (3) identify all affected Drug Product and recommend changes for the eye drop bottle packaging design.
PATIENT SAFETY CONSIDERATIONS RELATED TO EYE DROP BOTTLE DESIGN

• Labeling changes are not considered an adequate mitigation strategy

• The issue with loose bottle tamper-evident seals selectively impacted generic drug products (i.e. no innovator products utilize this packaging design)

• Patient acceptability issues (e.g. switching between different supplier products; senior patients)

• The packaging design represents a design flaw that predisposes patients to injury.
FDA SAFETY ALERT

FDA warns consumers about potential risks of using eye drops packaged in bottles with loose safety seals

[06/15/16] The U.S. Food and Drug Administration (FDA) is warning the public about eye drop bottles that have loose plastic safety seals or tamper-evident rings below the bottle cap that may fall onto the eye when the product is used.

The plastic safety seal or tamper-evident ring, also known as a collar, or band, should stay connected to the bottle neck. However, some eye drop bottles are losing the safety seals or rings when consumers tilt or squeeze the bottle to place eye drops into their eyes. A loose safety seal or ring presents a safety risk as it may cause eye injuries.

Consumers and health care providers who have these products should not attempt to remove the ring or seal because there is a potential to contaminate the tip of the dropper.

FDA is in the process of identifying all relevant products and will require a change in the packaging design. FDA strongly recommends when using tamper-evident rings, the bottle-cap design include a positive retention mechanism similar to those on disposable plastic beverage bottles to prevent the rings from coming off while using the product.

FDA has received reports of six adverse events associated with loose safety seals on eye drop bottles. Patients and consumers who are using prescription or over the counter eye drops and experience this issue or have concerns should contact their health care provider.

FDA encourages health care providers and consumers to report adverse events to FDA's MedWatch Adverse Event and Death Reporting program:

- Complete and submit the report online at www.fda.gov/medwatch/report.htm; or
- Download and complete the form, then submit it via fax at 1-800-FDA-0173.

FDA is continuing to investigate this issue and will provide more information when it is available.

Examples of eye drop bottles with loose safety seals or tamper-evident rings
QUARTERLY REPORT ON FDA FAERS WEBSITE

- FDA is directed to conduct screening of Adverse Event data in the FAERS database and to post quarterly information at

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/UCM082196
IDENTIFICATION OF AFFECTED ANDA DRUG PRODUCTS

- Issuing of INFORMATION REQUESTS to ANDA holders to:
  1. ask whether they use a packaging design with tamper-evident ring feature, and
  2. request eye drop bottle samples for review
- Conducted internal audits in FDA review Platforms to identify affected ANDAs
- Notified Quality reviewers and tracked the affected ANDAs in FDA review Platforms
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RESULTS
(1) 89 original ANDAs under review determined to require packaging design improvements

(2) 11 international suppliers of eye drop bottles (i.e. type III DMFs) identified as having poorly designed safety seals

(3) TSI Notification letters issued to 195 approved ANDAs with recommendations for changes to the container closure design(s) if loose safety seals are currently used as part of the packaging design
TSI RECOMMENDATIONS

• TSI unanimous recommendation is for drug applicants to make changes to the packaging design to either secure or remove the safety seal in order to mitigate risks to patients.

• When used, safety seals must be secured using a positive-retention mechanism similar to the beverage industry standards where the safety seals do not readily come off.

• FDA will monitor implementation of packaging design improvements during pre-market and post-marketing Quality review of ANDAs. At present, FDA has seen multiple examples of packaging design improvements. Three design improvements are as follows:

  (1) addition of snaps to bottle cap and adjustments to ratchet on bottle neck
  (2) addition of peel off tab on safety seal
  (3) replacement of safety seal with shrink wrap seal
TSI NOTIFICATION LETTER Quality Recommendations

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA ######

INFORMATION REQUEST – SAFETY ISSUE

APPLICANT NAME
Attention: CONTACT NAME
TITLE
ADDRESS

Applicants with marketed drug products are encouraged to submit supplements (as described below) within six months of receipt of this communication to implement a new or revised container closure design in their manufacturing process. An applicant may submit a lead ANDA supplement as a Prior Approval Supplement (PAS) for each packaging size (if multiple packaging size presentations exist) filled at each drug product manufacturing site. The applicant should provide drug product release data in the PAS with a commitment to place one production batch on the annual stability program and to submit the data in the Annual Report. Applicants who choose to make minor adjustments to the bottle ratchet and cap to secure the tamper-evident ring should submit container closure integrity testing and sterility validation or justification as to why such information is not required. Applicants with multiple approved ANDAs may submit subsequent ANDA supplements for the same proposed change as CBE-30 supplements referencing the lead PAS following its approval. These follow-on supplements generally will be reviewed as CBE-30 supplements if they provide for the same manufacturing process (e.g. filling and capping operations) and same type of container closure design to be used at the same manufacturing site(s) as the lead PAS. Each follow-on supplement should include drug product release data for one representative batch and a commitment to submit stability data in the relevant Annual Report.
SUMMARY

• The Office of Pharmaceutical Quality (OPQ) has a formal process for management of safety issues via TSIs.

• TSIs allow for a multi-disciplinary approach for the management of safety issues.

• OPQ is working to fine-tune the review process and develop an SOP for the management of quality TSIs.
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- CDER/Office of Communications

- CDER/Office of Pharmaceutical Quality
  - Office of Lifecycle Drug Products (OLDP)
  - Office of Program and Regulatory Operations (OPRO)
  - Office of Policy for Pharmaceutical Quality (OPPQ)
  - Office of Surveillance (OS)
Thank you!