Complaints and Investigations Compounding Incidents

Office of Compounding Quality and Compliance

Division of Compounding I

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Objectives

- Our roles
- Documents we receive related to incidents/complaints concerning outsourcing facilities (OF) and their compounded products.
- Case examples
  - Ophthalmic Injection
  - IV Drug Product
  - Syringe Drug Product
  - Ophthalmic Solution
  - Sterile Drug Product

Our Roles

- Help protect patients from poor quality compounded drugs that may pose a significant risk to public health.
- Develop compliance and enforcement strategies, guidances, and policies.
- Review FDA and state inspection reports
- Take actions that are patient focused and risk based to help protect patients from poor quality compounded drugs.

Compounding Incidents Program

- Involved in the weekly incident coordination group (ICG) meetings
- OCQC DCI provides consults within the incidents group to review adverse events and complaints
- Review and evaluate information obtained by the incidents team related to MedWatch reports/state inspectional reports/NABP reports/investigations, etc.
- Focused on adulteration related to insanitary conditions, product quality, and CGMPs
- Review and evaluate documents submitted by outsourcing facilities related to adverse events
- Provide recommendations of actions to take related to an incident
- Involved with sample collection and testing of drug products

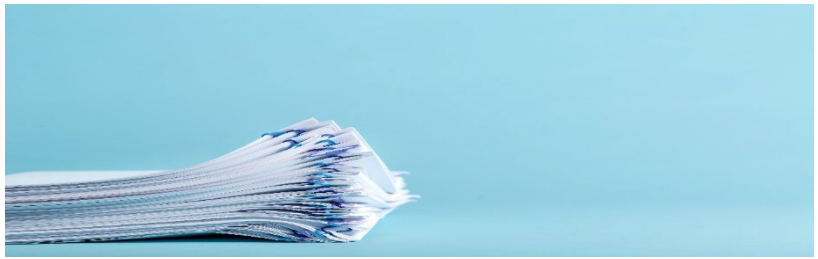
What Kinds of Information We Have Received For Review

Types of information received on incidents

- Patient information
- Description of the incident (complaints and adverse events, e.g., harm related to the medication)
- Date and time of when the incident occurred
- Drugs involved, including the manufacturer, lot number, and expiration date

Documents That We Have Received For Review (1 of 2)

- Batch records of all lots associated with the adverse event received from the outsourcing facility
  - Deviations associated with the batch record



Documents That We Have Received For Review (2 of 2)

- Preliminary investigation reports from OFs have contained:
  - Description of the events, contact information and correspondence between the firm and patient/customer
  - Includes assessment of the batch record review, release testing, environmental, and personnel monitoring
  - Complaints and adverse events trend analysis

Documents That Have Been Received From OFs For Review

- Final investigation reports
  - Testing of retains or returned products
  - Test result reports
  - Root cause analysis
  - Clinical assessment or health hazard evaluations
  - Corrective and preventative actions (CAPA)
  - Conclusions
  - Quality review

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Examples of Inadequate Investigations Performed by OFs

Disclaimer:

The background information and facts pertaining to the case examples exhibited in the following slides are for information and training purposes only. This is not a reproduction of actual cases reported to the FDA, but certain aspects of each case presented herein were previously received by FDA. All identifying information has been changed to protect confidentiality. Any resemblance to actual incidents, complaints, or adverse events, is entirely coincidental.

CASE EXAMPLE #1 (OPHTHALMIC INJECTION) (1 of 3)

ADE Reported

- MedWatch Report: 18 patients (two clinics) report inflammation and a gritty feeling of the eye after receiving an Antibiotic Ophthalmic Injection

OF Response:

- OF contacts clinics to get information on adverse event and requests return of the drug product; return of drug product is not possible due to it all being used by clinics.
- OF distributed 1,000 vials to date and has 500 vials in stock plus retains
- OF begins investigation, major elements include:
    - Batch record review, deviations non-conformances, visual inspection records
    - Release testing
    - Retain/reserve sample exam (visual inspection only)
- OF concludes root cause is not a manufacturing or drug quality issue

CASE EXAMPLE #1 (OPHTHALMIC INJECTION) (2 of 3)

The patients are reporting inflammation and a gritty feeling in the eye

Investigation Deficiencies:

- Visual inspection of retains is not sufficient to rule out a potential product quality root cause
- The investigation should evaluate all relevant drug quality attributes

CASE EXAMPLE #1 (OPHTHALMIC INJECTION) (3 OF 3)

Investigation Deficiencies:

- The patients are reporting inflammation and a gritty feeling in the eye
- Visual inspection of retains is not sufficient to rule out a potential product quality root cause
  - Possible product quality root causes:
    - Precipitate
    - Subvisible particles (drug components or foreign matter)
    - Sterility
    - Chemistry related issue (pH, osmolality and osmolarity, impurities)
- Testing of retains and/or product on hand is necessary in order to rule out a product quality issue

CASE EXAMPLE #2 (IV DRUG PRODUCT) (1 OF 2)

ADE Reported

- MedWatch Report: 1 patient reports dizziness, fainting, sweating and vomiting after receiving a premix proprietary IV bag infusion. Patient requires hospitalization but recovers after discontinuing IV treatment.

OF Response:

- OF contacts clinic and patient to obtain more information and request return of the drug product, if possible; return of drug product is not possible due to it all being used.
- OF distributed 40 IV bags to date and has 10 bags in stock
- OF begins investigation, major elements include:
  - Batch record review
  - Release testing
  - Retain/reserve sample testing
- OF finds that the retains meet all release specifications and concludes that since there is only one reported ADE the likely root cause is a possible medical error or patient reaction.

CASE EXAMPLE #2 (IV DRUG PRODUCT) (2 OF 2)

- Investigation Deficiencies:
  - The patient had a severe adverse event requiring hospitalization
    - The OF did a thorough record review of the batch production records, and all activities performed by the OF
    - However, what about raw materials? The proprietary IV bag contained an active ingredient that is also dietary supplement and there is a potential for the source of the API to be manufactured under food quality standards and thus be food grade and not appropriate for parenteral use.
  - The OF did not extend their investigation into raw materials used to compound the IV product. The bulk CoAs and labeling need to be investigated along with possibly testing the bulk raw material as part of a thorough investigation.

CASE EXAMPLE #3 (SYRINGE DRUG PRODUCT) (1 of 2)

Complaint

FDA receives complaint through a field office: 46 units of “Wonder Gel” were observed to be discolored

OF Response:

- OF refunds all clients that were involved and does not request return of the product since the clients’ provided pictures of the discoloration
- OF begins investigation, major elements include:
  - Batch record review
  - Release testing
  - Retain/reserve examination
  - Labeling (notes labeling states do not use if product is discolored)
- OF concludes that it is likely that improper storage after distribution is the root cause.

CASE EXAMPLE #3 (SYRINGE DRUG PRODUCT) (2 of 2)

- Investigation Deficiencies:
  - The product is known to be light sensitive
    - The OF reviewed all production records, retains, and testing and found no anomalies
    - However, since the product is extremely light sensitive the OF's investigation should include investigating the adequacy of light protective packaging and/or stability studies.
- The OF did not extend their investigation into packaging (spectral transmission studies, USP <671>) and the whether stability studies included light exposure in the marketed packaging through photostability testing.

CASE EXAMPLE #4 (OPHTHALMIC SOLUTION) (1 OF 2)

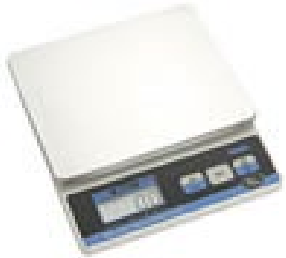
ADE Reported To OF

OF reports ADE to FDA after receipt

- Patient reports eye pain, light sensitivity, and dilated pupils for over 12 hours after receiving Ophthalmic Solution
- Product/lot is expired by the time the ADE is known to the 503B
- OF begins investigation, major elements include:
  - Batch record review
  - Release testing
  - Retain/reserve examination (visual inspection only)
  - Formulation
- OF concludes that since the product is expired analytical testing won't be conclusive and a root cause cannot be determined but the OF thinks that over-administration of the eye drops is the root cause.

CASE EXAMPLE #4 (OPHTHALMIC SOLUTION)

- Investigation Deficiencies:
  - Since the patient reported an extended period of pupil dilation, super potency is a potential cause.
    - The OF reviewed all production records and found the measured amounts of atropine in the batch record to be accurate.
    - However, the amounts of atropine API added to the batch were recorded by one person and there was no scale print-out or second person verification of the measured amount.
- The OF did not extend their investigation into controls in place for measuring and weighing APIs. Moreover, the 503B could have tested the expired retains on an investigational basis. If super potency was found in the expired retains then it is likely the measured amount recorded in the batch record is not accurate.



CASE EXAMPLE #5 (INTRAMUSCULAR INJECTION) (1 of 2)

ADE Reported to OF

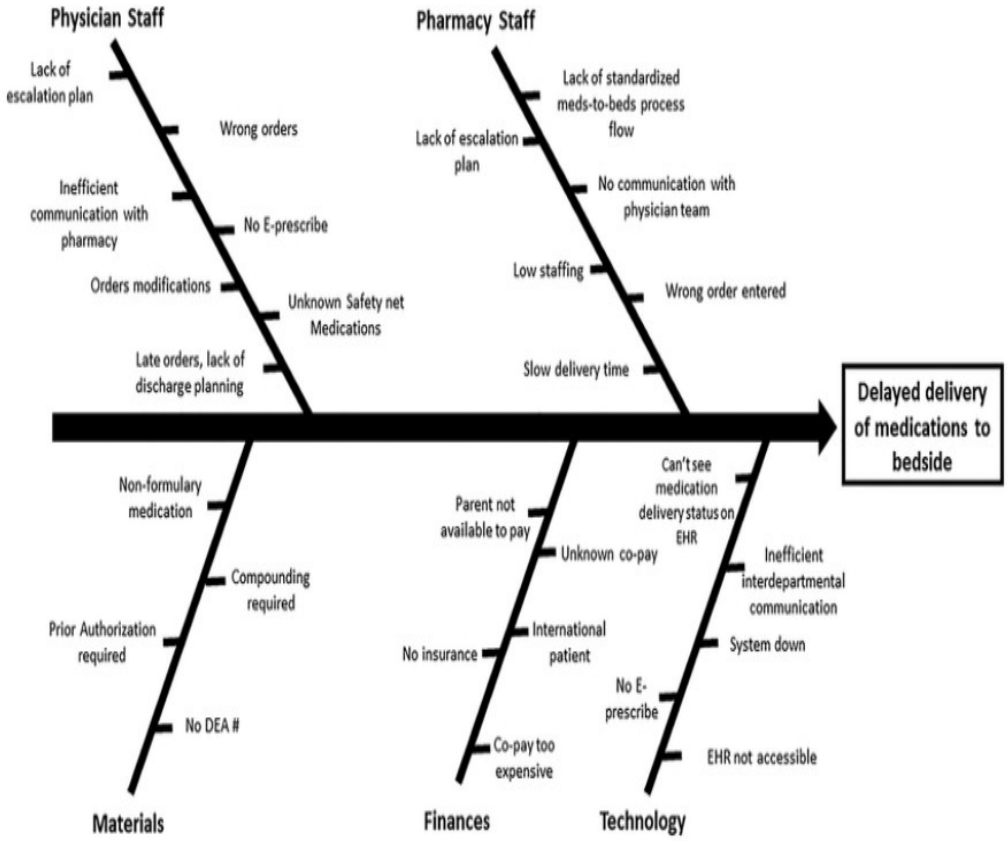
OF reports ADE to FDA after receipt

- Physician reports cellulitis in 8 patients after administration of “Mega Energy Injection (IM)”
- OF contacts physician to obtain more information and request return of the drug product, if possible; return of drug product is not possible due to it all being used.
- OF distributed 20 vials to two clinics and has 15 vials in stock
- OF begins investigation, major elements include:
  - Batch record review
  - Release testing
  - Formulation
  - OF conducts only potency and pH testing on the retains due to a loss of some retains during transfer from production to storage

CASE EXAMPLE #5 (INTRAMUSCULAR INJECTION) (2 of 2)

- Investigation Deficiencies:
  - The patients are presenting with cellulitis (bacterial skin infection) near the injection site:
    - The OF reviewed all production records and found that release testing for sterility passed.
    - Due to a low number of retains the OF concluded there were not enough vials for sterility testing to be conclusive.
    - However, the OF had vials on-hand which are under their control and stored under similar conditions (temperature, humidity, etc.) as the retains. The OF failed to extend their investigation to the inventory of the lot on-hand to include a visual exam of all vials and sterility testing of a necessary random subset.

Root Cause Analysis Tools



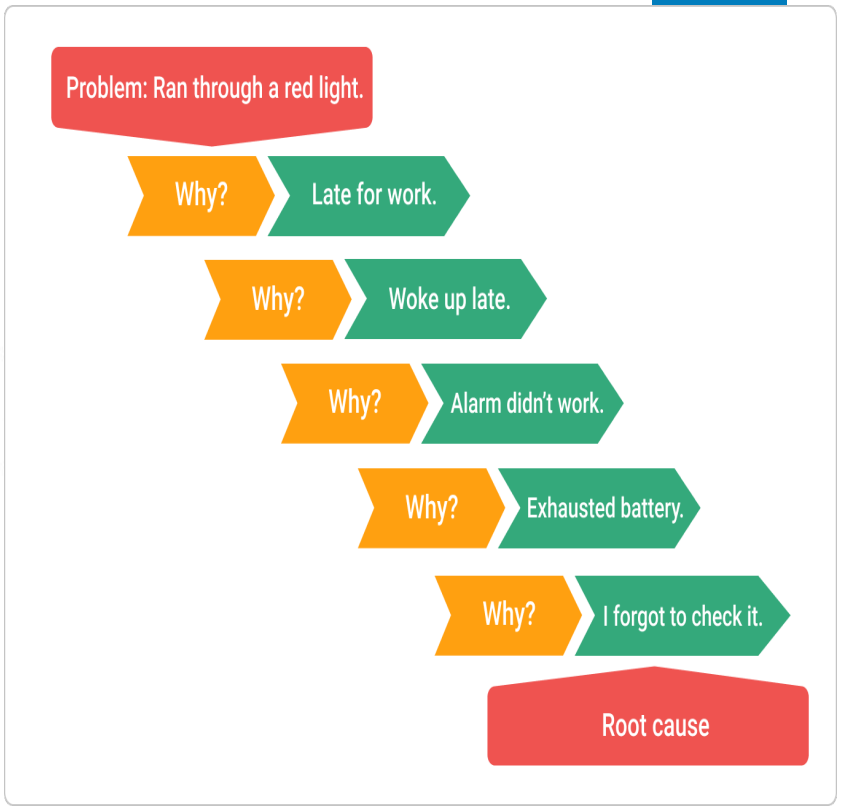


image references: researchgate.com; kanbanize.com

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Example of Adequate Investigations

Case Example #6 (Potency) (1 of 7)

- Lack of effect of an IV bag solution
  - A OF reported a patient with septic shock was being transitioned on an IV infusion.
  - A patient did not respond to new therapy and a new bag was given and the patient responded. The original bag was sent for testing, which revealed that there was no active ingredient in the bag.

Case Example #6 (Potency) (2 of 7)

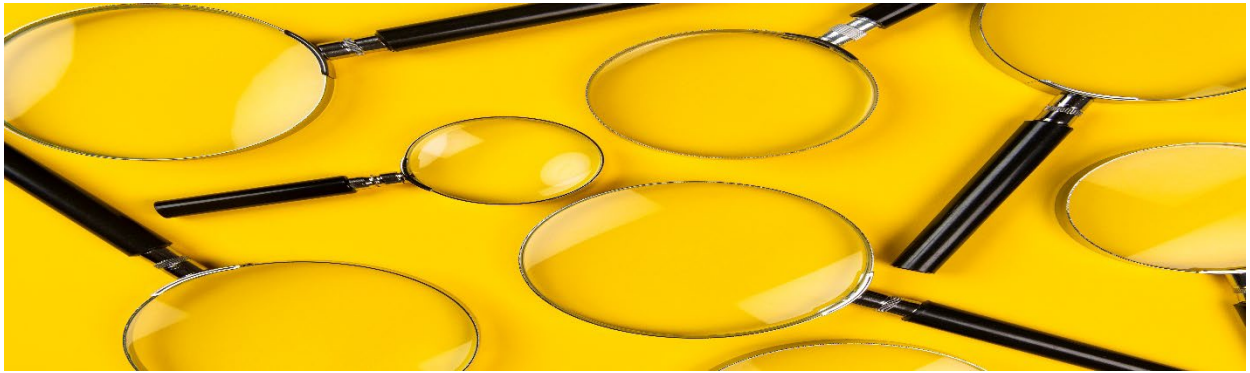
- The OF firm provided batch records, investigation report and CAPA.
  - The firm performed an investigation involving process review that included, but was not limited to the following:
    - Raw material review
    - Batch records of bulk formulations specifically, including weigh tape
    - Testing of retention sample
    - Analytical Testing
    - Other complaints

Case Example #6 (Potency) (3 of 7)

- Additional documents provided by the firm in support of the investigation and CAPA:
  - Weigh tape
  - Retention sample record
  - Material work order
  - Compounding reconciliation
  - Dosing weight verification record
  - Awareness communication and training of staff on the procedure updates
  - Root cause analysis

Case Example #6 (Potency) (4 of 7)

- Root cause analysis report
  - Synopsis
    - Overview of the complaint



Case Example #6 (Potency) (5 of 7)

- **Ishikawa method (5Ms)**
  - Material
    - All materials reviewed were identified within expiration
    - Confirmation of bulk formulation assay within normal limits and review of other lots compounded from bulk meeting all QC test requirements for release
    - Not a contributing factor
  - Machine
    - Review of equipment/cleanroom/laminar flow bench.
    - Review of validation of filling equipment and calibration
    - Equipment not a contributing factor

Case Example #6 (Potency) (6 of 7)

- Method
  - Aseptic processing that includes the use of a cart to place acceptable compounded IV bags on the top shelf and mark defective/rejected bags on the bottom shelf.
  - After one operator compounds and weighs the bag, another operator removes the bag from the laminar flow bench and places on the top shelf of the cart.
  - All materials were reconciled, and equipment was verified, leading the possible exchange of one bag that was intended to be removed was inadvertently exchanged for one acceptable compounded unit during the process.
- Man
  - The two operators involved were reviewed for all required training and qualifications.
  - Both operators were interviewed and recorded on the possible mix up
  - Review of video footage was considered
- Medium (environment)
  - Review of aseptic complex, including laminar flow benches and HEPA filter inspections
  - Environment not considered a contributing factor

Case Example #6 (Potency) (7 of 7)

Conclusion

- Cause and corrective actions
  - Probable root cause was determined to be a defective IV bag being placed on the work cart where acceptable compounded units were to be placed. Typically, defective or unused IV bags would be placed on the bottom of the shelf. During the process, the uncompounded IV bag was inadvertently switched with an acceptable compounded IV bag. The results of their investigation found to be due to Method and Man.
  - Method in providing clear instructions and revisions in process handling of defective uncompounded IV bags
  - Man in handling and unintentionally exchanging of one uncompounded defect bag for an acceptable bag.
  - The returned suspect product did result in 0% potency.
  - An awareness communication was performed with all operators, process improvements including procedure updates in segregation methods and engineering solutions to support clear segregation of defective/rejected units from acceptable lots.

Questions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