U.S. FOOD & DRUG ADMINISTRATION

Complaints – Investigation and Review

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AGENDA

How To Proceed…Essential Parameters

- FDA consumer complaints
- FDA regulatory requirements
- FDA complaint handling essential parameters
- Complaints, adverse events and field alert report (FAR) requirements
- FDA's focus during investigations

Consumer Complaints

A consumer complaint is notification that a product in commercial distribution:

- May be in violation of the laws or regulations administered by the FDA
- May have caused an illness, injury, or death.
- Is alleged to have caused problems not covered by the above

Sources of Complaints

- Complaints may be received from
  - consumers
  - other government agencies
  - trade sources
  - or health care professionals
  - anonymous sources, etc

FDA's Minimum Regulatory Requirements

21 CFR §211.198

- Written procedures – SOP established & followed
  - -Review by a Quality Control Unit
  - -Evaluation of possible failure to meet specifications
- Determination of need for an investigation
  - -Whether complaint represents a serious and unexpected adverse drug experience that needs to be reported to FDA
- Conducting an investigation to determine root cause
- Corrective and Preventive Action

FDA's Minimum Regulatory Requirements

21 CFR § 211.198

- Complaint Files
  - Maintained at establishment or another facility
  - Readily available for inspection
- Must be kept for at least 1 year after product expiration or 1 year after complaint was received – whichever is longer

❑ Must Include where known

- Name and strength of product
- Lot number
- Complainant information
- Nature of complaint
- Reply to complainant

FDA's Minimum Regulatory Requirements

[211.198(b)(2)]:

Where an investigation is conducted

- The written records must include:

  - Findings of the investigation
  - Follow-up to the investigation

[211.198(b)(3)]:

Where an investigation is not conducted

- The written record shall include
  - The reason that an investigation was found not to be necessary
  - The name of the responsible person making such a determination

FDA's Minimum Regulatory Requirements

Firm must:

- Have a designated complaint unit / dedicated personnel
- Have detailed SOP regarding handling of complaints that prioritizes complaints that may be ADE reportable
- Ensure all relevant information is collected and kept in file
- Have a procedure to make sure all possible sources of complaints are reviewed
- Segregate and maintain separate complaint files designated as such and have personnel dedicated to maintain files

FDA's Minimum Regulatory Requirements

Complaint Handling SOP should address:

- Initial determination of complaint type
- Handling of complaints that represent potentially significant safety concerns
- Field alert report, product correction or ADE
- Notification to Quality Personnel/Committee
- Referral for Investigation
  - ➢ evaluation of retain samples
- Follow up with complainant
- Close out of complaint file

FDA's Minimum Regulatory Requirements

Product Recall SOP should address:

- Process for review and evaluation of priority complaints
- Responsibility for recall determination
- Medical assessment of potential patient risk
- Depth of recall
- FDA reporting
- Handling of recall
- Termination of recall
- Recall Effectiveness Checks

FDA's Minimum Regulatory Requirements

Firm must:

- Conduct training/retraining of personnel on an annual basis, to ensure compliance with requirement to report complaints
- Have a detailed, but easy to use, complaint intake form that includes all required information so follow-up reduced
- Review status of complaints/investigations on a routine basis to ensure timelines are met

Field Alert Reports (FAR)

- Mandatory Postmarketing reporting program
  - 21 CFR 314.81(b)(1)(i) and (ii) - NDA applications
  - 21 CFR 314.98(c) - ANDA applications
- Effective on May 23, 1985
  - **Intended to establish effective system for FDA's surveillance of marketed drug**

Required Reporting

21 CFR 314.81 (b) (1)(i)

- Any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article
- Bacterial Contamination
- Significant chemical, physical or other change
- Product deterioration
- Failure of one or more distributed batches of drug products to meet the specification established in the application

NDA/ANDA Field Alert Reports

Requirements:

- Report to local FDA District Office
- Within 3 working days of receipt of information
- Can be telephoned in / but must be followed up by written report
- Report/Mailing Cover Must Specify “NDA-Field Alert Report”
- Form FDA 3331 or 3331a (Automated)

Foreign NDA/ANDA Holders

- Required to submit certain information about distributed drug products to the jurisdictional FDA district offices
- US Office/Agent (21 CFR 314.50(a)(5)) is responsible for reporting to the FDA District Office where registered/located
- Report within 3 WORKING DAYS of receipt

NDA/ANDA Field Alert Reports

What should be included:

- Brief description of information received
- Brief description of any preliminary investigation
- Evaluation, if any, of possible corrective/preventative action
- Timetable for investigation/communicating additional information to FDA
- Contact person/contact information
- For FARs that affect more than one product, submit one FAR per NDA/ANDA
- Multiple lots of the same product may be submitted on one form.

Evaluation of Complaints

Adverse Event?

- Serious? Unexpected?
- Reportable Adverse Event?

Need to file an NDA field alert?

- Failure to meet specifications –chemical, physical?
- Mislabeling?

Need for a recall?

When to Report FAR to FDA

- FAR not required
  - If root cause determined and found to not be related to drug product quality within 3 working days
    - e.g. Analytical lab error
- FAR required
  - Further investigation required
  - Root cause not determined
  - Corrective action initiated
    - i.e. Formulation revision, labeling change

Three Working Days

- Starts when the applicant becomes aware of the reported problem
  - Complaint
  - Internal testing
- DOES NOT begin the day the applicant confirms or invalidates a problem

When to Report Recalls to FDA

Recalls:

- Most are voluntary actions
- FDA has limited authority to order recalls for drugs
- For devices, FDA has authority to order recalls (21 C.F.R. §810)
- No legal requirement to notify FDA of voluntary recall of drugs
- In most cases, market withdrawals being an exception –advising FDA of a recall is advisable
- Do not need to await FDA input to commence recall
- FDA will categorize level of recall –I, II or III –after recall notice submitted

When to Report Recalls to FDA

- When in doubt – report
- There is little downside to reporting

FDA's Expectations During Investigations

- Are complaint procedures in place? Are they followed?
  - Do they include oral complaints?
- Is there a formally designated unit to review complaints?
- Are there formally designated complaint files?
- Are complaints evaluated for need to report as an ADE?
- Were complaints reviewed to determine if an investigation was necessary?
- Were efforts to obtain information from complainants performed/documented?

FDA's Expectations During Investigations

- If no investigation was conducted, was the rationale for not conducting an investigation documented?
- Does the complaint file include all records relating to the investigation of the complaint?
  - Was a root cause identified?
  - Were the complaint investigations concluded?
- Were complaints reviewed in a timely manner?
- Was need for corrective action evaluated?
- Was trend analysis conducted?

FDA's Expectations During Investigations

NDA/ANDA Field Alerts

- Were complaints evaluated for the need to file a Field Alert report?
- Were Field Alert reports filed on a timely basis?
- Did your Company keep FDA informed as to the investigation into the complaint that led to the Field Alert report and was the investigation/action adequate?
- Was Management made aware of Field Alerts?
- Were Field Alerts closed?

Warning Letter

- **Your firm failed to establish and follow adequate written procedures describing the handling of all written and oral complaints regarding a drug product, including provisions for review by the quality control unit of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a determination as to the need for an investigation in accordance with 21 CFR 211.192 (21 CFR 211.198**).

- From January 2012 to August 2016, your firm received numerous (approximately 1,500) consumer complaints related to leaking, empty, and under-filled sterile (b)(4) solution (b)(4)% bottles. Your firm's investigation indicates this persistent critical quality defect is due to a filling machine issue in which the (b)(4) is improperly placed into the bottle (b)(4). Because of this recurring malfunction, operators frequently perform aseptic interventions at the insertion station when they detect stuck (b)(4) defects. These defects are not easily detected, and the line has produced finished, capped units with non-integral container-closures. In addition, in some cases, (b)(4) cracks do not immediately occur in finished units, but instead develop days later. Specifically, your investigation states, "…it is evident that a wrong placement of the (b)(4) on the bottle on the filling machines must be resulting in a damaged or cracked (b)(4) which does not occur immediately and occurs on standing for a few days." Because of the location and delayed timing of these defects, they are not readily detectable by final manual or automated inspections

References

- Compliance Program Guidance Manual. Drug Quality Reporting System (DQRS) (MedWatch Reports); NDA Field Alert Reports (FARs) https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM282847.pdf
- Jenny Qin. (2012). NDA Field Alert Reporting system
- US FDA Inspections Operation Manual. Chapter 7. (2018) https://www.fda.gov/iceci/inspections/iom/default.htm
- Peter Reichertz. (2016). Update on FDA guidance and regulations for the complaint handling process and on FDA Field Alert Reports

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