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PRODUCT COMPLAINTS AND ADVERSE EVENTS

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ABSTRACT

Product complaints and reports of adverse events are unwelcome events at any company, especially if a product recall must be considered. However, these must be handled promptly and with all due diligence to prevent authentic drug-related events from negatively impacting the health and well-being of patients. This article provides an overview of the receipt, investigation and categorization of product complaints. An example of a product complaint triggered by a serious adverse event is also described. Please note that the example serious adverse event and product complaint is described in a high-level manner to protect confidentiality of the patient, hospital and company involved.

INTRODUCTION

FDA requires pharmaceutical companies to have an effective, documented system for the handling of product complaints (PCs). 21 CFR 211.198 Complaint Files specifies:

- Written procedures regarding the handling of all oral or written PCs;
- Review of all PCs by the Quality Control Unit;
- Documented criteria to assess the need for an investigation;
- Reporting serious and unexpected adverse drug experiences to FDA;
- Maintenance of PC records including retention windows.

PCs may be linked to an Adverse Events (AEs) which may be serious (Serious Adverse Event; SAE) which are described below:

PRODUCT COMPLAINTS

For a commercial pharmaceutical product, a PC reflects customer dissatisfaction with a drug. The reporter could be a physician, nurse, pharmacy staff member, user or patient. The PC is any written, electronic, or oral communication that describes a perceived deficiency in the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug product. Information that should be collected for PCs include the following:

- Relevant Dates: Event date, purchase date, etc.
- Product Information: name, lot number, expiration date
- Event Description: How was the product used or administered? Missed dose?
- A verbatim copy of any customer verbal descriptions

Additional dates that are important to include in PCs are:

- Aware Date: when did someone at the company learn about the event.
- Open Date: Date the complaint was opened.

Companies should start investigating PCs as soon as they become aware of the event.

ADVERSE EVENT

As defined by FDA, an adverse event is a drug reaction also known as a side effect, and is any undesirable experience associated with the use of a medicine in a patient. Adverse events can range from mild to severe. Serious adverse events are those that can cause disability, are life-threatening, result in hospitalization or death, or are birth defects.

ASSESSMENT

The assessment of a PC/AE should be performed by a multi-disciplinary team including, but not limited to, representatives from Quality, Regulatory, Manufacturing, and Supply Chain. Companies should also have designated contacts at all contract manufacturers, packagers, and distributors to support PC investigations. Companies should maintain positive and collaborative relationships with their contractors to support the determination of root causes, as needed. The need to include external partners in the assessment is because the exact root cause may be beyond the reach of the company itself. Especially for drugs that require additional preparation steps prior to administration or use, companies want to support positive relationships between sales and medical science liaisons with prescribers and providers for the same reason, that they may be able to provide insight to investigations.

The team must consider if there is a likelihood that further use of the product could harm other patients. If yes, a product recall should be initiated. Companies should be prepared to act promptly in the event a recall is required, or if a voluntary recall is elected. The scope of the recall may be batch specific, though certain product quality issues may trigger the recall of multiple batches of the product.

RECEIPT AND CATEGORIZATION OF PRODUCT COMPLAINTS

All PCs should be evaluated with urgency as there could be an associated AE or SAE or the need for a potential market action such as a recall. PCs could arise for several different reasons and each complaint will have a certain degree of severity and likelihood of occurrence. The severity links to a particular recall class defined by FDA. This is summarized in Table 1.

PC Severity	Severity Description	Examples	FDA Recall Class [1]
Critical	Safety and efficacy of the product are called into question. Patients are at risk of experiencing a critical side effect or adverse reaction which may be life-threatening, leading to irreversible morbidity or mortality.	- Incorrect label - Potential for under- or over-dosing, especially critical for Narrow Therapeutic Index drug products - Sterility failure or foreign material observed in a parenteral drug product	Class I: a situation in which there is a reasonable probability that the use or exposure to a violative product will cause serious adverse health consequences or death
Major	Safety and efficacy of the product are called into question, but the risk is not considered life-threatening.	- Broken, malformed, or discolored tablets or capsules - Foreign residue in oral drug product container - Leaking containers for liquid drug products - Illegible or missing printed information	Class II: a situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.
Minor	Questions or concerns regarding the product are not related to safety or efficacy and not considered life-threatening.	- Improper quantity(s) received at warehouse or pharmacy sites - Dented secondary or tertiary packaging	Class III: a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences

Table 1: PC Severity, Description and Recall Class

[1] Refer to Health hazard evaluation and recall classification for the several factors FDA considers during evaluation of the health hazard presented by a product being recalled or considered for recall.

Per 21 CFR 211.198 Complaint Files: "The written record shall include the following information, where known: the name and strength of the drug product, lot number, name of complainant, nature of complaint, and reply to complainant." A company may have to act on incomplete information, emphasizing the importance of reserve samples and comprehensive tracking of all PCs.

> *Example: A PC for a surgical drug product was received by a company with relatively complete information: the suspected drug product, lot number, name of complainant, and nature of complaint were known. A hospital claimed that the drug did not work as intended, causing a significant adverse event leading to the patient's death. The drug product required dilution prior to infusion and the infusion solution administered to the patient was collected and stored by the hospital.*
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> *All available information was documented in the company quality documentation management system. Per the documented communication plan, all required team members were notified and information communication to FDA. The PC was categorized as Critical by the company and an urgent-priority investigation was initiated. The company reported the AE to MedWatch, FDA's Safety Information and Adverse Event Reporting Program, issued a Field Alert Report, and considered the need for a Class I recall based on the event reported by the hospital.*

INVESTIGATION

Analysis of PCs should include historical review of all relevant product documents and laboratory testing of any available samples. The combination of retrospective and future sample analysis is needed to fully inform the PC process. In the historical review, the following should be considered:

- Other complaints regarding this drug product or the specific batch
- Outcomes of other PC investigations including Corrective Action or Preventative Action (CAPA)
- Batch records and batch release documents reviewed, with an eye for anything unusual or non-standard
- Review any deviations associated with the batch or, more broadly, within the manufacturing equipment or suite(s)

Laboratory analysis should, of course, include any samples associated with the product complaint itself, if available. The impact of storage conditions, time, intentional (such as dilution) or inadvertent (such as evaporation) manipulation should all be considered when evaluating samples. Sample preparation, recovery, and any other preparation steps by quality control laboratory technicians should be documented in detail. In addition to working and reference standards, reserve samples from the specific lot should be procured for comparison, as the PC sample(s) may not represent the actual manufactured material released previously by the company quality unit.

> *Example: After the company was notified of the PC and learned the infusion solution was retained by the hospital, the company immediately alerted their GMP laboratory to the sample shipment and to analyze the PC sample by the validated HPLC method as soon as possible. Transfer of the PC sample to the laboratory was expedited at every step, including the use of custom-critical shipping. Shipment of reserve samples from the specific batch to the analytical laboratory was also expedited. There were at least daily phone calls between the company and the laboratory until results were obtained and the analytical report delivered to the company.*
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> *Analysis of the reserve product confirmed data comparable to that generated at release: identity by HPLC retention time, potency and impurity profile by HPLC, as well as pH, osmolality and withdrawable volume.*

Analysis of the PC sample from the infusion bag confirmed the absence of the intended product in the sample: no signal recorded at the main peak retention time and no known impurities observed. The only unusual feature in the HPLC chromatograph was an unusually wide peak collocated with the solvent front.

The historical review of company data did not yield any PC associated with this batch of drug product.

OUTCOME

With the retrospective data reviewed and new analytical data in hand, the root cause of the product complaint should be identified.

As specified in 21 CFR 211.198, when an investigation is conducted, "the written record shall include the findings of the investigation and follow up." Alternatively, if an investigation is not conducted, "the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination." When written complaint records are not maintained in a file designated for drug product complaints, this can be cited as an inspectional observation on FDA Form 483, if not maintained properly.

Example: The analysis of the PC sample established the absence of the intended drug. Concurrent analysis of a sample from the same batch established that the product had not degraded; the drug as manufactured was confirmed to be acceptable, approximately 18 months after the company quality unit originally released the batch for distribution (36 month shelf life). The drug product itself was not identified as the root cause.

The hospital pharmacy prepared the drug for infusion and all hospital records confirmed the proper receipt, storage, and preparation of the drug. There were no concerns of a fraudulent product due to matching lot numbers, proper trade dress, and other drug supply chain security elements. The company resolved their internal investigation and concluded no product recall was required.

What was the root cause though? During its investigation, the company learned that the hospital had an informal practice of allowing infusion solutions prepared for one patient to be transferred to another patient if the infusion solution was not used. In this case, a missing label led to the assumption of the infusion bag contents. Very unfortunately, the second patient did not receive the needed drug and died. This SAE is due to an example of "User Error" rather than a fault of the drug.

The patient's family sued the hospital to ensure this informal practice was formally prohibited by the hospital. An independent Analytical Chemistry expert was able to explain the patient never received the intended drug. To the family's satisfaction, this drove a major revision to the hospital policy which documented and provided training that transferring of solutions was not permitted.

ABOUT THE AUTHORS

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Kimberly Wallbank is the Managing Owner and Principal Consultant for Quality Systems Services, LLC. With more than 25 years of industry experience, she has diverse experience and expertise in assisting pharmaceutical, biotechnology and medical device companies achieve compliance with FDA, EMEA, ISO and other recognized standards. Kimberly collaborates with companies to establish, maintain, and improve their quality systems so they can provide world

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