

NDA Field Alert Process – An industry perspective

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Post Market Surveillance: NDA Field Alert Reports

NDA Field Alert Reporting Requirement CFR 314.81

- (1) Any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article and/or
- (2) Bacteriological contamination,
- (3) Significant chemical, physical, or other change or deterioration, or
- (4) Failure of one or more distributed batches of the drug product to meet the specification established for it in the application.

FDA Compliance Policy Guide 7356.021

- The 3 working days begins when the applicant becomes aware of a reported problem through either a complaint or internal testing. It does not begin the day the applicant confirms or invalidates a problem. FARs may be reported via telephone or other means of rapid communication with prompt written follow-up.
- FARs, in contrast to the "postmarketing reporting of adverse drug experiences" covered by 21 CFR § 314.80, contains a variety of drug quality issues and are of interest to both field and CDER offices.

Purpose of the NDA Field Alert

- The purpose of the New Drug Application (NDA) Field Alert Program is to **quickly** identify drug products that pose potential safety threats. All drug manufacturers with approved NDAs and ANDAs are required to submit Field Alert Reports to the FDA if they find any **significant** problems with an approved drug within three days of identification.
- <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm082083.htm>

What does “Significant” mean?

- “Significant chemical, physical, or other change or deterioration”
- Definition of Significant:
 - Having or expressing a meaning; meaningful
 - Having or expressing a covert meaning; suggestive
 - Having or likely to have a major effect; important
 - Fairly large in amount or quantity
- Significant as the adjective modifies what portion of the phrase?

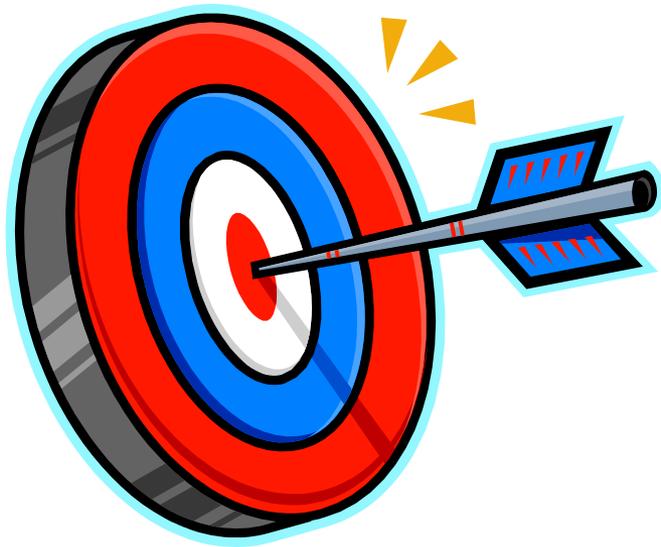
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3 DAYS



- What's Clear
 - The 3 working days begins when the applicant **becomes aware** of a reported problem through either a **complaint or internal testing**. It does not begin the day the applicant confirms or invalidates a problem.



- PharmPro reported on their website newsletter (August 2011) that failure to file Field Alerts was the number 9 most frequent observation cited in Warning Letters
- <http://www.pharmpro.com/blogs/2011/08-The-Top-Ten-Warning-Letter-Observations-about-the-Pharmaceutical-Quality-Unit/>

Regulatory Landscape

- Firm V 2009
 - Complaints on 2 to 3 tablets thicker than the rest of the tablets received May 2008; Field Alert submitted November 2008.
 - The firm responded it was due to significant delays in reporting between the "discovery of the concern by the Firm's personnel and it being reported to senior management to facilitate an investigation of the incident." They attributed delays to the fact that training on this procedure was limited to its users.
- Firm W January 15, 2010 Warning Letter
 - "You did not submit the FAR until September 18, 2009, after again noting an adverse, continuing trend of numerous complaints over the course of a several month period."
- Firm X January 2011
 - Deficiencies for failure to file field alerts for identified trends that signal a FAR
- Firm Y December 2011 WL
 - you did not submit FARs within three days regarding trends of complaints for **(b)(4)** Injectable that could signal chemical, physical, or other changes or deterioration in the distributed batches of that product. For example, from January to June 2011, you received 33 complaints for crystallization/cloudy solution of this product.
- Firm Z January 2012
 - Did not file FARs for reserve inspection results

Firm “Z” failure to file Field Alert Reports for reserve sample and complaint investigations

Reserve sample inspection identified 3 lots in which major defects were observed and did not submit a FAR within 3 days of identification of the defect.

According to the firm’s SOPs these defects may include vials with defects such as foreign matter, particulate matter and vials with defective glass.

Firm did not submit a FAR when the firm confirmed the presence of particulate matter in reserve samples after receiving a complaint of particulate matter

FDA stated that when a firm must submit a FAR within 3 working days of becoming aware of a significant problem (particulates or foreign material in reserve samples, defective glass complainant samples containing particulates)

Expectations of Industry of Field Alert Reporting

- **Confirmed vs. Unconfirmed:**
 - Field alert reports are required to be submitted for confirmed and unconfirmed investigations (complaints) meeting the definition of the regulation within three working days of becoming aware of the problem.
- **Individual complaints:**
 - Individual Complaints: a significant single individual complaint
 - Awareness begins at the time the complaint handling process has captured and reasonably verified all available complaint information and a field alert reporting assessment is requested
- **Complaint trends :**
 - Required clear defining of trends warranting further investigation
 - Define awareness date of complaint trends
- **Further Investigation / Corrective Action:**
 - Any incident involving a distributed product requiring further investigation or corrective action as a result of the incident
- **API Manufacturing:**
 - Impact of OOS stability investigations on finished product lots using this API

Regulatory Expectations

- There is a noticeable shift and focus on FARs
- Early Warning System
 - The NDA Field Alert process is considered as an early warning system so that potential significant problems brought to the Agency's attention to prevent potential safety hazards from drug products already in distribution.
- Expectations
 - FARs linked to trending or responding to new defects
 - A logical approach and response to significant events
 - Meaningful complaint trending
 - An abundance of caution

Next Steps for the Industry

- Solidify Internal Practices
 - Abundance of Caution: Increase awareness individual complaints and trends could be potential FAR events.
- Ensure procedures call out FAR events properly:
 - High Impact Events (e.g. bacterial contamination, significant change or deterioration, or failures of product specification that give rise to potential safety issues)
 - Complaint Trends (need to evaluate trending practices and criteria)
 - Specific Individual Complaints (e.g. extraneous matter, new defects that reflect change)
 - Ensure documentation of significance and/or impact

Signal Detection



“Surveys in Joplin, Missouri, discovered that's what happened before a tornado struck the city and killed more than 150 people in June of last year; residents ignored the sirens until they sounded a second time and by then, it was too late to make it to safe shelter.”

"It's like anything you get used to," says Steve Spiegler, a visitor attending the Arnold Sports and Fitness Expo. "Y'know, you're living close to the train track, you hear the trains and if you're new to the area, you'll hear the train all the time. But, eventually, it becomes part of your life. You don't really hear it."



**THANK YOU FOR YOUR ATTENTION
ANY QUESTIONS?**