

# The Physician Reviewer's Role in Premarket Safety Review of Generic Drugs

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# Learning Objectives

- Review the regulatory requirements for bioavailability/bioequivalence (BA/BE) study expedited safety reporting for generic drugs
- Describe the overall steps in premarket generic serious adverse event (SAE) safety review and the physician reviewer's role
- List the most common errors made with submission of SAE reports to FDA
- Provide general advice for more efficient and effective review process

# Clinical Safety Surveillance Staff (CSSS)



**Building a  
Coordinated  
Framework  
for  
Generic Drug  
Pharmacovigilance**

## Location in Organization:

- ▶ OGD Immediate Office

## Composed of:

- ▶ Clinical Team
- ▶ Data Team
- ▶ Drug Safety Coordinator



# CSSS (cont.)

- Oversee generic drug safety and surveillance
- Coordinate with other CDER offices on generic safety drug issues
- Investigate reports of adverse events or perceived therapeutic inequivalence of generic drugs
- Evaluate and act on potential emerging safety signals
- Inform CDER decision makers and external stakeholders

# Premarket Reporting Requirements for Generic Drugs



- 21 CFR 320.31(d)(3) describes sponsor SAE reporting requirements for IND-exempt BA/BE studies
- Report SAEs within 15 days
- Report fatal or life-threatening SAEs within 7 days
- Submit SAEs on [MedWatch](#) form
- SAE reports emailed to [OGD-PremarketSafetyReports@fda.hhs.gov](mailto:OGD-PremarketSafetyReports@fda.hhs.gov)

# Regulations

- Persons conducting the study MUST notify FDA and all participating investigators of ANY SAE observed during conduct of the study
- Follow-up SAE information received must be submitted no later than 15 days after receipt
- Expedited reporting requirements apply only to investigational new drug (IND)-exempt BA/BE studies conducted in the United States
- Guidance for Industry: [Safety Reporting Requirements for IND and BA/BE Studies](#)

# Physician **Reviewer's** Role

- Physician **will** review each SAE report
- Additional information **may be requested**
  - Upon request from FDA, the person conducting the study or contract research organization must submit any additional data or information within 15 days [320.31(d)(3)]
- Determine the safety of study conduct, study population, **any causal relationship, and risk analysis**

# Concerns Raised During Physician Review

- Subject selection and enrollment criteria
- Monitoring of subjects
- Lateness of reports
- Missing information in SAE reports
- Product-specific guidance (do we have the appropriate study population/study dose for the drug)

# Subject Monitoring

- Adequate subject protection in premarket BA/BE studies
- Physician or medically responsible person
  - Review results of all assessments performed on each subject during the study
  - Confirm subject continues to meet all inclusion/exclusion criteria
  - Medical care and follow-up

# Advice to Industry

Helpful to submit **MedWatch with:**

- Full protocol with inclusion/exclusion criteria
- Case report form
- Hospital records, discharge summary
- Unblinded study drug treatment for subject
- **Key study dates and events (screening, enrollment, drug dosing)**
- Timely submission

# Real Life Example of SAE Case Concern



- Long-acting central nervous system stimulant, indicated for the treatment of attention-deficit hyperactivity disorder
- 18-year-old female with negative medical history
- Screening ECG, marked sinus arrhythmia judged not clinically significant
- Single fasting dose administered, (baseline pulse 81 bpm, BP 118/83 mmHg), at 6, 8, 12 hours post-dose mild tachycardia (pulse 102-103) was observed and slight increase in BP at 12 hours (133/83)
- Subject found dead on Day 6 after dose

# Real Life Example (cont.)



- Toxicological studies were negative
- No clear cause of death on autopsy
- Did subject have an unknown cardiac structural or conduction abnormality?
- Concerns remain, internal discussion
- Careful screening when selecting subjects



# Challenge Question #1

**Within how many days of becoming aware of a fatal SAE must it be reported to the FDA:**

- A. 15 days
- B. 30 days
- C. 7 days
- D. 10 days



# Challenge Question #2

**Which of the following statements is NOT true?**

- A. Sponsors do not need to submit an SAE if it is unrelated in the opinion of the investigator.
- B. Sponsors must notify FDA of premarket SAEs conducted in BA/BE studies in the United States only.
- C. Sponsors conducting BA/BE studies outside the United States are not required to report premarket 7- and 15-day expedited reports to FDA.
- D. Follow-up information requests from FDA must be submitted within 15 days and sponsors must submit additional information as it becomes available.

# Summary

- Industry has the responsibility to submit SAEs in a timely manner according to the regulations
- Submit premarket SAEs with as many details as possible for FDA physician to review
- Protect subjects in generic drug studies by careful selection, adequate subject monitoring, and follow-up

# Resources

- [Title 21 Code of Federal Regulations 320.31](https://www.ecfr.gov)  
[Applicability of Requirements regarding an](https://www.ecfr.gov)  
[“Investigational New Drug Application”](https://www.ecfr.gov)  
[www.ecfr.gov](https://www.ecfr.gov)
- [Safety Reporting Requirements for INDs and BA/BE](https://www.fda.gov)  
[Studies: Guidance for Industry and Investigators.](https://www.fda.gov)  
[December 2012.](https://www.fda.gov) (U.S. FDA, Guidance Document,  
[www.fda.gov](https://www.fda.gov))

