# Premarket Review of Expedited Serious Adverse Event Reports from IND-Exempt BA/BE Studies

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# Learning Objectives

- Provide an overview of premarket safety reporting for serious adverse events (SAEs) occurring during investigational new drug (IND)-exempt bioavailability/ bioequivalence (BA/BE) studies conducted to support an abbreviated new drug application (ANDA)
- Review regulatory requirements for SAEs
- Aid in communicating good clinical practice during BA/BE studies that support ANDAs
- Provide general advice for a more efficient review process

# Reporting Requirements

- Safety reporting requirements for IND-exempt BA/BE studies are under 21 CFR 320.31(d)(3) *"The person conducting the study, including any contract research organization, must notify FDA and all participating investigators of any serious adverse event…observed during the conduct of the study…"*
- Applicants have an obligation to report **all** SAEs for BA/BE studies
- SAEs must be reported to FDA **regardless of causality or treatment arm**

# Reporting Time Frame

- All SAEs must be reported to FDA within:
  - **15** calendar days after becoming aware of its occurrence
  - **7** calendar days for **fatal or life-threatening** events



- SAE submissions should be timely

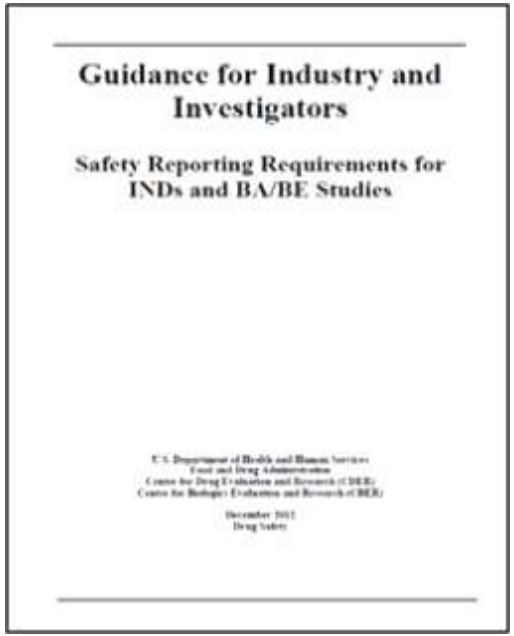
# Domestic vs. Foreign Study Reporting

- Expedited reporting requirements for IND-exempt BA/BE studies apply **only** to studies that are conducted in the **United States** (U.S.)

- SAE submissions for foreign BA/BE studies conducted at clinical sites outside the U.S. are voluntary
- However, adverse event information from both foreign and domestic studies must be included in the ANDA submission

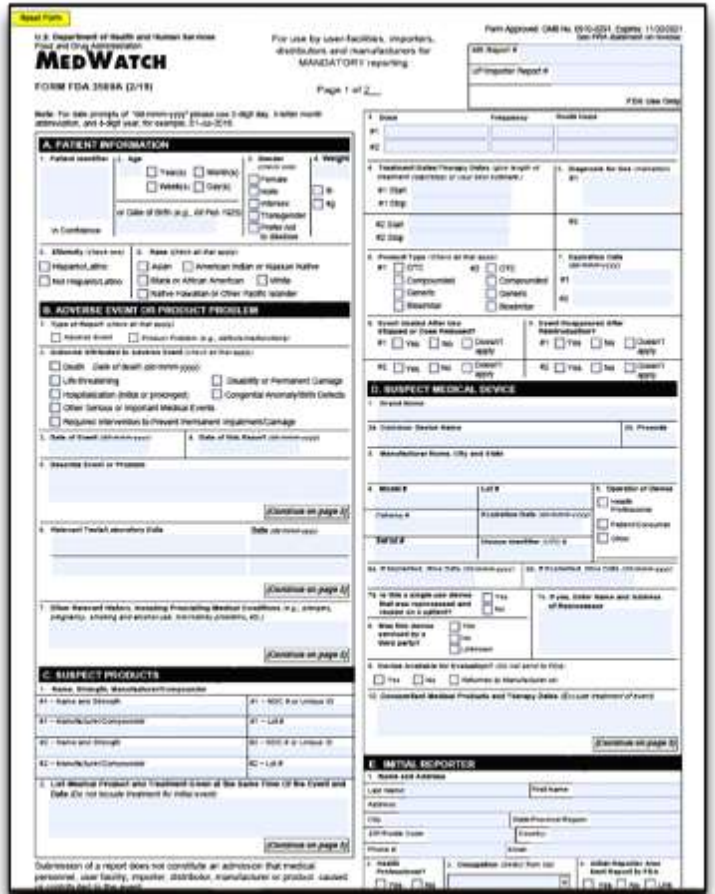
# Guidance

- Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies, December 2012



# SAE Submission

- Submit SAE using [MedWatch](#)
  FDA Form 3500A


MEDWATCH

FORM FDA 3500A (2/19)

A. PATIENT INFORMATION

B. ADVERSE EVENT OR PRODUCT PROBLEM

C. SUSPECT PRODUCTS

D. SUSPECT MEDICAL DEVICE

E. INITIAL REPORTER

# SAE Submission


- Emailed to OGD-PremarketSafetyReports@fda.hhs.gov
- Stay tuned for new electronic reporting options in the future!

# SAE MedWatch 3500A Form

- Include screening and enrollment dates
- Study drug therapy dates
- Concomitant medications
- Medical history
- Unblinding
- Provide as much information as possible

# SAE Submission: Suggestions for Improvement

- Include full study protocol with every initial SAE submission
- SAE reporting should be within the required timeframes and not delayed
- Include all available information, such as:
  - Case report form
  - Hospital records
  - Discharge summary
- Provide death certificate and autopsy report if available

# SAE Evaluation

- Clinical study protocol
  - Inclusion and exclusion criteria
  - Study population
- Conduct of the study
- Any causal relationship with study drug
- Risk analysis

# SAE Review

- Clinical Team reviews each SAE individually
- FDA may occasionally request additional data for review in the form of an Information Request (IR)
- Applicant responses to IRs and any relevant additional follow-up information obtained must be submitted to FDA within 15 days [as per 21 CFR 320.31(d)(3)]

# SAE Root Causes

- Poor subject selection
  - Inadequate screening of subjects
  - Selecting subjects with comorbidities
- Lack of adherence to inclusion and exclusion criteria
- Lack of, or reduced subject monitoring during or after study

# Clinical Study Monitoring

- Adequate screening and monitoring of subjects during the study
- Appropriately qualified medical staff
- Results of all clinical assessments performed (e.g., BP, EKG, lab work) should be reviewed
- Confirm that subjects continue to meet inclusion/exclusion criteria
- Subjects should receive follow-up

# Summary

- Applicants must submit an SAE observed during conduct of the study regardless of whether the event is considered drug-related (test or reference) in the opinion of the investigator
- Applicants conducting studies in the U.S. are required to submit all SAEs according to regulations within 7 or 15 days after becoming aware of its occurrence
- Applicants conducting BA/BE studies outside the U.S. are not required to report premarket SAEs within 7 and 15 days. However, all adverse event information from both foreign and domestic studies must be included in the ANDA submission

# Summary (cont.)

- SAE submissions should include the study protocol and as much information as possible
- Follow-up information that becomes available, and any requests from FDA for additional information, must be submitted as soon as possible, but in no case later than 15 calendar days after receiving the request
- Select subjects carefully and protect study subjects with adequate monitoring and follow-up

# Resources

- Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies, December 2012 (www.fda.gov/media/79394/download)
- Title 21 Code of Federal Regulations 320.31 Applicability of Requirements regarding an "Investigational New Drug Application" (www.ecfr.gov)
- Final Rule, Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans (75 FR 59935) published September 29, 2010
- Check https://www.fda.gov/regulatory-information/search-fda-guidance-documents website for the latest guidances

# Challenge Question #1

**Within how many days of becoming aware of a <u>fatal</u> SAE during a BA/BE study 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. If an investigator considers an SAE to be unrelated to the study drug, then the applicant does not need to submit the SAE to FDA within 7 or 15 days

B. Applicants must notify the FDA of premarket SAEs in BA/BE studies in the U.S. only, and must report ALL adverse events, including SAEs, when the ANDA is submitted

C. Applicants conducting BA/BE studies outside the U.S. do not need 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 applicants must submit additional information as it becomes available

# Acknowledgements

Clinical Safety Surveillance Staff

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# Thank You!

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