Tip #1: Terms to know

- **Adverse Event (AE):** any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

- **Suspected Adverse Reaction:** any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

- **Adverse Reaction:** any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

- **Unexpected:** An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

- **Serious:** An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
  - Death
  - a life-threatening adverse event,
  - inpatient hospitalization or prolongation of existing hospitalization
  - a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
  - a congenital anomaly/birth defect.
  - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

- **Life-threatening:** An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
Tip #2: Your responsibilities as the Investigator
Most of the information about the safety of a drug prior to marketing comes from clinical trials. Therefore, adverse event reports from investigators are critically important, as they observe subjects’ responses to the drug. Except for study endpoints, the investigator must immediately report to the sponsor all serious adverse events, regardless of whether the investigator believes that they are drug related, including those events listed in the protocol as anticipated to occur in the study population independent of drug exposure or in the investigator brochure as predicted to occur with the drug. The FDA recognizes that it may take the investigator a short period of time (i.e., a day) to compile information about the event, but then expects the information to be immediately reported to the sponsor. Investigators are not required to determine whether an event is “unexpected”. This is a sponsor responsibility.

- Document all adverse events in your patient study subject records
- Determine and document if the adverse event or suspected adverse reaction meets any of the definitions of seriousness
- Determine and document your assessment about whether the adverse event may be caused by the investigational product, using either a rating scale, or yes/no response to a question such as:
  - “Was there a reasonable possibility that the drug caused the adverse event?”

- Determine if and who needs to be informed of the event based on your determinations above
  - Sponsor
  - IRB
  - others

Tip #3: Your additional responsibilities as the Sponsor and IND holder

- Make final determination if the adverse event is expected
- Make final determination whether there is a reasonable possibility that the drug caused the event.
- Make a final decision if and how quickly the event needs to be reported to the FDA

- The sponsor is required to review promptly all information relevant to the safety of the drug. During the course of drug development, adverse event information is generally reported to a sponsor by investigators conducting clinical trials; however, a sponsor may become aware of new safety information from a variety of sources, both domestic and foreign. Some examples of sources are listed as follows, but safety information from any other source would also need to be reviewed and evaluated by the sponsor.
  - Animal studies or in vitro studies
  - Clinical or epidemiological investigations
  - Reports in the scientific literature
  - Unpublished scientific papers
  - Information presented at scientific meetings
  - Reports from foreign regulatory authorities
  - Reports from commercial marketing experience
  - Safety information presented at a professional meeting
  - Foreign spontaneous reports

- The sponsor’s review should include examining data from all sources and deciding whether the information meets the criteria for expedited reporting to the FDA and all participating investigators, as well as evaluating all
accumulating data at regular intervals to update safety information and to identify new safety signals. Some types of information should be sought by the sponsor as part of its continuous pharmacovigilance on the safety of the drug. For example, the sponsor should conduct literature searches regularly with a frequency appropriate to the drug or study design to seek safety information and report that information if necessary.

- For IND safety reporting, the FDA recognizes that a sponsor or sponsor-investigator may not have access to the complete safety data maintained by a commercial sponsor, but sponsors and sponsor-investigators are required to evaluate all safety information that is available to them to determine whether the information qualifies for reporting. For example, sponsors and sponsor-investigators should examine reports in the scientific literature and perform literature searches to actively seek new safety information about the drug under investigation. To protect human subjects, the Agency recommends that entities that provide drug to or receive drug from other entities share safety information with each other.

- For IND safety reporting in general, sponsors should have a predefined safety monitoring plan that includes processes and procedures for the review, evaluation, and management of safety information. For reporting events in the aggregate, sponsors should perform an aggregate analysis of specific events both for individual studies and across all studies, including across INDs of the drug, to determine whether they meet the criteria for expedited reporting.

Tip #4: If your IND studies the effect of a marketed drug

- A sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND must submit IND safety reports for suspected adverse reactions that are observed in the study.

Tip #5: What events to report to the FDA and participating investigators, and how

- As sponsor you must report to the FDA any event that meets all three of the definitions:
  o Suspected adverse reaction
  o Serious
  o Unexpected
- The report must be done in the form of an IND safety report

Tip #6: How quickly to submit the IND Safety Report to the FDA and all participating investigators

**INITIAL REPORT**

- No later than 15 calendar days after the sponsor determines that the suspected adverse reaction or other information qualifies for reporting.

- Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and, therefore, must be reported more rapidly to FDA. The requirement for reporting any unexpected fatal or life-threatening suspected adverse reaction to FDA is no later than 7 calendar days after the sponsor’s initial receipt of the information. If the safety report submitted within 7 calendar days is complete, an additional submission within 15 days from day zero is not required.

- The day of initial receipt for cases that are interpretable as single cases and the day the sponsor determines that multiple cases qualify for expedited reporting are considered day zero.

- If FDA requests any additional data or information, the sponsor must submit it to FDA as soon as possible, but no later than 15 calendar days after receiving the request.
Sponsors should have a predefined safety monitoring plan that includes processes and procedures for the review of safety information, including the frequency of review. FDA expects that events that are interpretable as single cases (i.e., uncommon and known to be strongly associated with drug exposure) should be reported to FDA within 15 days from initial receipt. For events that require more than one occurrence to assess causality and events evaluated in the aggregate, the time clock starts when the sponsor determines that the events qualify for expedited reporting. This means that, for example, incomplete cases should be immediately followed up for additional information so that a determination can be made about whether the event is reportable as an IND safety report.

FOLLOWUP INFORMATION

- If any information necessary to evaluate the suspected adverse reaction is missing or unknown, the sponsor should actively seek such information from the source of the report. Any relevant additional information that the sponsor obtains that pertains to a previously submitted IND safety report must be submitted as a Followup IND Safety Report without delay, as soon as the information is available, but should be submitted no later than 15 calendar days after the sponsor receives the information. The sponsor should maintain records of its efforts to obtain additional information.
- If the sponsor obtains other information that is not relevant to evaluating the suspected adverse reaction, records of such information should be maintained by the sponsor and, if applicable, submitted in an information amendment or in an IND annual report.

Tip #7: IND Safety Report Identification

- Each IND Safety Report must prominently identify its contents. The label must be one of the following:
  - “IND safety report” for 15-day reports
  - “Followup IND safety report” for followup information
  - “7-day IND safety report” for unexpected fatal or life threatening adverse reaction reports
- The type of report should be checked in box G7 on the FDA Form 3500A. The report can also be identified in box B5 and/or on a cover letter submitted with the FDA Form 3500A.

Tip #8: IND Safety Report Format

INDIVIDUAL CASES

- For reports of individual cases, a sponsor would ordinarily use FDA Form 3500A. FDA will accept foreign suspected adverse reaction reports on a CIOMS I Form instead of FDA Form 3500A. These forms should be completed with all available information, including a brief narrative describing the suspected adverse reaction and any other relevant information. If applicable, the narrative must also include identification of similar reports and an analysis of the significance of the suspected adverse reaction.

AGGREGATE REPORTS

- An IND safety report based on data in the aggregate must be in a narrative format. Sponsors should use judgment in deciding what to include in the narrative report. The report should include a description of the suspected adverse reaction, along with all relevant information, such as summary information about symptoms, concomitant medications, demographics, comorbid conditions, past history, pertinent laboratory test results, timing of events (onset and duration), and duration of treatment. Data from previously submitted individual case IND safety reports should be included, if applicable. Finally, the narrative report should describe the characteristics and results of the analysis, including a description of the databases, how the conclusion was reached, who reviewed the analysis, any planned changes in monitoring or to study documents (e.g., informed consent, investigator brochure), and any planned further analyses.
• To evaluate the aggregated data in narrative format, FDA and participating investigators need the information on the individual cases that are summarized in the report. Therefore, at the same time that the narrative format IND safety report is submitted, the individual cases that were analyzed should also be submitted (e.g., a completed FDA Form 3500A for each case). If some individual cases were previously submitted as IND safety reports, they should be resubmitted and clearly identified as duplicates. Before submission, each individual case report should generally be unblinded. If a sponsor has concerns that unblinding will compromise the integrity of the study, the sponsor should discuss this in advance with the review division.

• The sponsor should determine an appropriate approach for reporting subsequent occurrences of the same event to FDA and all participating investigators, and the sponsor should include a description of this approach in the initial expedited narrative IND safety report. For example, each subsequent occurrence of an infrequent event with immediate health implications or an event that is uncommon in a specific study population (e.g., stroke in young adults) should be reported in an expedited report. For an event that is known to occur independent of drug exposure in the study population, the sponsor may specifically describe an approach for reporting to FDA and all participating investigators (e.g., an updated aggregate narrative once a certain number of additional cases are identified or after a specified period of time, as appropriate).

Tip #9: Where and How to Submit
• The report must be transmitted to the CDER or CBER review division that has responsibility for review of the IND.
• IND safety reports should be submitted to all of the sponsor’s INDs under which the drug is being administered.
• The sponsor should reference all INDs to which the IND safety report is being submitted in the subject line of the cover letter. If applicable, the sponsor should also identify (e.g., with use of an underline) the specific IND under which the suspected adverse reaction occurred (e.g., “Suspected adverse reaction occurred under IND XXXX1, reference to INDs XXXX2, XXXX3”).

Tip #10: For how long to send IND Safety Letters to participating investigators
• The purpose of sending IND safety reports to participating investigators is to provide them with information they need to protect their patients participating in clinical trials. Once they are no longer enrolling or monitoring patients, this information is no longer necessary. Cutoff dates for sending IND safety reports to investigators may be described in the protocol. If no cutoff dates are specified, once a site has been officially closed out, the sponsor usually does not need to continue sending IND safety reports to that site, and an investigator does not need to receive or review them. If the sponsor continues to send IND safety reports to the investigator and the investigator does not wish to continue receiving them, the investigator should contact the sponsor and request that the sponsor stop sending them.

Tip #10: Where else do I need to report new adverse information?
• In your next IND Annual Progress Report to the FDA
• “Summary Information” section
• “Understanding of Drug’s Action” sub-section
  o Summary of any new adverse information (since the last progress report) that may affect the risk analysis; this includes preclinical data, animal studies, foreign data, clinical studies, etc.
  o Reprints of any articles published from data collected from this study
  o New risk analysis, if necessary, based on new information and on study progress
Tip #12: For more information, go to:

Guidance for Industry and Investigators. Safety Reporting Requirements for INDS and BA/BE Studies.  

Guidance for Industry and Investigators. Safety Reporting Requirements for INDS and BA/BE Studies - Small Entity Compliance Guide  

IND Application Reporting: Annual Reports  

Form FDA3500A:  
http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

• If you have additional questions or would like assistance, please call the Clinical Research Support Center at (303) 724-1111 or email clinicalresearchsupportcenter@ucdenver.edu