

A. 21 CFR 312.32(a)

Effective Prior to March 28, 2011	Effective March 28, 2011	Description of Significant Change(s)
N/A	Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.	New definition
<i>Associated with the use of the drug. There is a reasonable possibility that the experience may have been caused by the drug.</i>	Suspected adverse reaction means 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. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.	<ul style="list-style-type: none"> • Replaced definition of “associated with the use of the drug” with “suspected adverse reaction” • Defines reasonable possibility • Defines adverse reaction
<i>Life-threatening adverse drug experience. Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.</i>	<i>Life-threatening adverse event or life-threatening suspected adverse reaction. 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.</i>	Change in determination of whether an event is life-threatening from the investigator’s opinion to either the investigator’s or sponsor’s opinion (i.e., if either believes it is life-threatening, it must be considered life-threatening for reporting purposes).

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<p><i>Serious adverse drug experience: Any adverse drug experience occurring at any dose that results in Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience 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.</i></p>	<p><i>Serious adverse event or serious suspected adverse reaction. 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, or 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.</i></p>	<p>Determination of whether an event is serious is based on the opinion of either the investigator or sponsor (i.e., if either believes it is serious, it must be considered serious for reporting purposes).</p>
<p><u>Disability. A substantial disruption of a person’s ability to conduct normal life functions.</u></p>	<p>N/A</p>	<p>Definition of disability incorporated into definition of serious</p>

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<ul style="list-style-type: none"> • <i>Unexpected adverse drug experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which 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 only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents.</i> • <u>“Unexpected,” as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.</u> 	<ul style="list-style-type: none"> • <i>Unexpected adverse event or unexpected suspected adverse reaction. 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 great specificity) if the investigator brochure listed only cerebral vascular accidents.</i> • “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. 	<p>Minor edits for clarification.</p>