The following concerns another potential source of confusion. The Code of Federal Regulations distinguishes between the term "expected" and "anticipated." To quote from 21 CFR 312.32(a), "Unexpected adverse drug experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure…[u]nexpected, 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." To repeat, "expected" is not synonymous with "anticipated."

b. Classification of adverse events as induced by disease versus induced by the study drug

The following teaches the distinction between AEs due to the disease and drug-induced AEs. This particular example is from the Council for International Organizations of Medical Sciences (CIOMS). The example provided by CIOMS concerns the AE of skin eruptions (55):

> *In diagnosing a cutaneous eruption that may be an adverse drug reaction it is important to decide whether the eruption is due to the disease, primarily due to the drug, or due possibly to an interaction between the disease and the drug. Cutaneous reactions frequently occur when patients are receiving a number of drugs, and thus etiological relationship may be difficult to assess. When patients take drugs for a febrile disorder [increased body temperature] that ultimately proves to be an infection, an eruption may be due to the underlying disorder or the prescribed drug.*

The following concerns AEs that are accidents, such as accidents occurring when using machinery. Where a subject enrolled in a clinical study is injured by an automobile accident, for example on the way to the clinic, this injury is classified as an AE (56,57,58,59,60,61,62). Although some publications may state that an injury from

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