often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population, for example, tendon rupture or progressive multifocal leukoencephalopathy (PML). PML is caused by a virus called John Cunningham virus (JC virus), and is associated with a drug used for multiple sclerosis (natalizumab).

- Unanticipated AEs include AEs that are not uncommon, but that occur in the study at a greater rate than usual, for example, at a rate above the baseline rate.
- Unanticipated AEs also include any safety findings, including findings based on animal data or epidemiological data, that would cause the Sponsor to modify the investigator's brochure, Clinical Study Protocol, or consent form. (The term adverse event is not used in the context of animal studies. Instead, the term "toxicity" is used for animal data.)

In the context of preapproval reporting, the Office of Human Research Protections (OHRP) has stated that an unexpected (or unanticipated) adverse event includes any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is not consistent with either, "the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in ... the protocol-related documents, such as the **IRB-approved research protocol**, any applicable **investigator brochure**, and the current IRB-approved **informed consent document**" (95).

The fact that the Investigator's Brochure can be used to distinguish between an adverse event that is anticipated and unanticipated, is revealed by one of FDA's Warning Letters. The Warning Letter states that (96,97), "We disagree that a hospitalization for somatic transformation was an anticipated event, because this type of reaction was not described in the **Investigator's Brochure**."

Please note that according to the OHRP, the term "unanticipated" encompasses "unexpected," as is evident from the following excerpt. Also, please note that the term "unanticipated" encompasses other adverse events, in addition to those that are "unexpected." The excerpt reads (98):

> What are *unanticipated problems*? ... OHRP considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets all of the following criteria: unexpected (in terms of nature, severity, or frequency).

The classification of ADRs into anticipated versus unanticipated was based on a scheme

[95]Office for Human Research Protections (OHRP) Department of Health and Human Services (HHS). Guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events; January 15, 2007.

[96]Warning Letter to Emord and Associates, P.C. (the letter has no Warning Letter No.) (March 16, 2007) from Mary Malarkey, Office of Compliance and Biologics Quality, CBER, U.S. Food and Drug Administration. The letter sent to Emord and Associates is an attachment to Warning Letter No. CBER-07-06 (February 1, 2007), as available on FDA's website.

[97]Warning Letter No. CBER-07-06 (February 1, 2007) from Mary A. Malarkey, Office of Compliance and Biologics Quality, CDER, U.S. Food and Drug Administration.

[98]Office for Human Research Protections (OHRP) Department of Health and Human Services (HHS). Guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events, January 15, 2007.