etiologies." Abnormal liver transaminase levels, that is, as measured in the serum, are distinguished in that they are often the result of factors other than the study drug, such as hepatitis C virus and nonalcoholic steatohepatitis (56). An excerpt from a Clinical Study Protocol on a drug for hepatitis C virus establishes that the medical writer has the option of including instructions (in the Protocol) for reporting laboratory values. The excerpt reads (57), "laboratory abnormalities (e.g. clinical chemistry, hematology, urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable."

4. *Adverse Drug Reaction*

FDA's Guidance for Industry provides the following definition of ADRs (58):

> In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Regarding marketed medicinal products: A response to a drug that is noxious and unintended and that occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

5. *Unexpected Adverse Drug Reactions*

FDA's Guidance for Industry provides the following definition of unexpected drug reactions (59):

> An "unexpected adverse drug reaction" is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

This provides an example where a Clinical Study Protocol expressly stated that a given drug-related adverse event was expected. The narrative based expectedness on the mechanism of action. This is from a clinical trial on leukemia. The Protocol read (60):

> Treatment-related lymphocytosis, for the purposes of this protocol, is defined as an elevation in blood lymphocyte count of >50% compared to baseline that occurs in the setting of … improvement in at least one other disease-related parameter including lymph node size, spleen size, hematologic parameters (Hgb or platelet count), or disease-related symptoms. Given the **known mechanism of action** of BCR-inhibiting agents including ibrutinib,

[56]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Drug-induced liver injury: premarketing clinical evaluation; July 2009 (25 pp.).

[57]The Clinical Study Protocol was included as a supplement to, Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. New Engl. J. Med. 2013;368:1867–77.

[58]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. E6 good clinical practice:consolidated guidance; April 1996.

[59]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. E6 good clinical practice: consolidated guidance; April 1996.

[60]A randomized, multicenter, open-label, phase 3 study of the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. NCT01578707; Phase 3. ORIGINAL PROTOCOL PCYC-1112-CA.