by laboratory tests for the serum levels of the enzyme, alanine aminotransferase (ALT). This enzyme was formerly known as glutamate pyruvate transaminase (SGPT).

The presentation of the ADR of flu-like symptoms declined with continued administration of the drug. In other words, the patient develops tolerance. This phenomenon of tolerance is called *tachyphylaxis*. The flu-like symptoms are fever, chills, headache, myalgia, nausea, and vomiting. Fatigue increases in intensity as therapy continues and it can be very debilitating. Levels of hepatic enzymes, as measured in serum samples, are assayed on a weekly basis in order to monitor drug-induced liver toxicity. Where liver toxicity presents, the physician may respond by lowering the dose, or delaying dosing, of the IFN-alpha2b. In the context of a clinical trial, this response is called *dose modification*.

c. Anticipating Adverse Events in the Design of Clinical Studies

Planning the study design includes planning which types of adverse events should be monitored. According to the ICH Guidelines (17):

> [a] hierarchy of organ systems can be developed according to their importance with respect to life-supporting functions. Vital organs or systems, the functions of which are acutely critical for life, such as the cardiovascular, respiratory and central nervous systems, are considered to be the most important ones to assess in safety pharmacology studies. Other organ systems, such as the renal or gastrointestinal system, the functions of which can be transiently disrupted by adverse pharmacodynamic effects without causing irreversible harm, are of less immediate investigative concern.

The ICH Guidelines specifically focus on adverse events involving the immune system, and where these adverse events reside in two categories, namely, where a study drug impairs the immune system, and where the study drug induces immune-system-mediated harm to various tissues of the body (18):

> Toxicity to the immune system encompasses a variety of adverse effects. These include suppression or enhancement of the immune response. Suppression of the immune response can lead to decreased host resistance to infectious agents or tumor cells. Enhancing the immune response can exaggerate autoimmune diseases or hypersensitivity. Drug or drug−-protein adducts might also be recognized as foreign and stimulate an anti-drug response. Subsequent exposures to the drug can lead to hypersensitivity (allergic) reactions.

d. Dose Modification as Part of the Clinical Study Protocol

The Clinical Study Protocol optionally includes instructions for dose modification. Dose modifications can include changing dose levels, delaying doses, changing the frequency of dosing, permanent discontinuation, and so on. Where dose modification is not appropriate, then the Clinical Study Protocol should state that dose modification is not allowed. An example of this prohibition appears, for example, in a Clinical Study Protocol for a cystic fibrosis drug. The Protocol reads "**Dose Modification for Toxicity.** No change in dosing of lumacaftor or ivacaftor is permitted" (19).

[17]ICH Harmonised Tripartite Guideline. Safety pharmacology studies for human pharmaceuticals S7A. Step 4 version; November 2000. 9 pp.

[18]ICH Harmonised Tripartite Guideline. Immunotoxicity studies for human pharmaceuticals S8. Step 4 version; September 2005. 14 pp.

[19]Clinical Study Protocol A Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects aged 12 years and older with cystic fibrosis, homozygous for the f508del-CFTR mutation vertex study number: VX12-809-103 Lumacaftor IND No: 79,521 Ivacaftor IND No: 74,633 EUDRACT No: 2012-003989-40.