XVIII. CLINICAL HOLD

a. Introduction

A *Clinical Hold* is a notification issued by FDA to the Sponsor to delay a proposed clinical trial or to suspend an ongoing clinical trial. *Clinical Hold* has a basis in 21 CFR §312.42. Section 312.42 states, for example, that "[w]hen an ongoing study is placed on *Clinical Hold*, no new subjects may be recruited to the study … patients already in the study should be taken off therapy … unless specifically permitted by FDA in the interest of public safety."

Section 312.42 further discloses that the grounds for a Clinical Hold include FDA's assessment that human subjects are exposed to an unreasonable risk of injury, that the clinical investigators named in the IND are not qualified by reason of their training and experience to conduct the clinical trial, and that the Investigator's Brochure is misleading or erroneous. Where FDA imposed the clinical hold because of misconduct by the Sponsor, this misconduct can take various forms. Examples of misconduct include failure to report SAEs, enrollment of study subjects having conditions that put them at increased risk with exposure to the study drug, repeated failure to administer informed consent forms, and failure of the IRB to review and approve significant changes in the Clinical Study Protocol, and falsification of safety data (127).

This concerns the *Partial Clinical Hold*. According to FDA's Guidance for Industry, *Partial Clinical Hold* is "[a] delay or suspension of only part of the clinical work requested under the IND (eg, a specific protocol or part of a protocol is not allowed to proceed; however, other protocols or parts of the protocol are allowed to proceed under the IND)" (128).

b. Examples of a Clinical Hold

This provides an example of a *Clinical Hold*. A phase 3 clinical trial on an *inhaled drug* was suspended by the FDA, because of data showing that the drug was carcinogenic, as determined in a chronic study with rats. In the *Clinical Hold*, FDA requested additional information from the rat study (129). The press release stated that the company expected to provide all of the information to the FDA within a month.

FDA issued a *Clinical Hold* against a phase 2 clinical trial on fingolimod, a drug for multiple sclerosis, because of insufficient monitoring of adverse events. The clinical trial, which was under IND no. 70,139, was put on hold on June 29, 2005 because of insufficient monitoring of macular edema, pulmonary conditions, and pancreatitis. Shortly after the trial was put on *Clinical Hold*, the Sponsor requested an "End of Phase 2" meeting to discuss why the trial was put on hold. A year later the Sponsor was eventually able to convince FDA of sufficient monitoring, and FDA lifted the hold on May 19, 2006 (Medical Review dated August 26, 2010, NDA 22-527, FDA website).

In a *Clinical Hold* against a drug for *osteoarthritis*, FDA complained about an adverse event that took the form of a single occurrence of an infection in the injected knee joint of a study subject (130). In a *Clinical Hold* against an *anticoagulant drug*, FDA halted an ongoing phase 3 trial because of SAEs that were allergic

[127]U.S. Department of Health and Human Services. Food and Drug Administration Guidance for Industry and Clinical Investigators. The use of clinical holds following clinical investigator misconduct; September 2004 (8 pp.).

[128]U.S. Department of Health and Human Services. Food and Drug Administration Guidance for Industry. Submitting and Reviewing Complete Responses to Clinical Holds; April 1998 (3 pp.).

[129]Press release Insmed announces clinical hold on ARIKACE® Phase 3 clinical trials; August 1, 2011.

[130]Press release Flexion Therapeutics announced clinical hold of FX006 Phase 2b clinical trial in osteoarthritis of the knee; September 17, 2014.