reactions (131). The issue of these allergic reactions was detected and raised, while the trial was in-progress, by the Data Safety Monitoring Board (DSMB). Thus, the facts underlying this particular *Clinical Hold* provide an insight regarding one of the subjects of this textbook, namely, the DSMB.

In a *Clinical Hold* against a drug for *hepatitis B virus*, FDA required the company to cut the dose in half, and requested additional information on study subjects that had received elevated doses (132).

Upon receipt of an FDA *Clinical Hold Letter*, the Sponsor can respond by preparing an amendment to the IND that addresses the issues set forth in the Letter. An FDA reviewer then evaluates the amendment, and determines whether the Sponsor's response is satisfactory (133).

c. FDA's Decision-Making Process in Imposing a Clinical Hold

This is from FDA's *Medical Review* of *dinutiximab*, for treating neuroblastoma. The information is from BLA 125516 on Mar. 2015 of the FDA's website. FDA had imposed a *Partial Clinical Hold*, during the course of the clinical trial. The FDA reviewer wrote that the "IND placed on partial hold to prevent treatment of patients … where two patients received an overdose of IL-2."

About a half year later, the FDA imposed another *Partial Clinical Hold*, and the FDA reviewer wrote that the:

> IND placed on partial hold to prevent enrollment of new patients … [d]eficiencies included inadequate dose modification rules for IL-2 … lack of on-site training of principal investigator, and lack of criteria for screening clinical sites for their ability to administer toxic biologic therapies … [a]dditionally, pre-printed orders … appeared to be the cause of the IL-2 overdose.

Several years later, the clinical trial under the same IND was again placed on a *Partial Clinical Hold*, because of allergic reactions to the study drug. The *Medical Review* also documented the fact, that for each partial hold, it was the case that "FDA removed partial hold."

To conclude, in the clinical trial on dinutiximab, the *Partial Clinical Holds* mainly concerned adverse events to one of the drugs administered in the study. However, the available information suggests that essentially any aspect of the clinical trial, such as training of personnel, can result in a *Clinical Hold*.

XIX. EXEMPLARY ACCOUNT OF FDA TIMELINE, AFTER SUBMISSION OF NDA OR BLA

Archdeacon et al. (134) provides an exemplary account of communications and activities occurring following submission of an NDA or BLA. This particular example was with a BLA, and the drug under review was for the indication of preventing organ rejection. The following account demonstrates how various concepts, introduced at earlier points in this textbook, fit into the context of the FDA-approval process. These concepts include:

- Advisory Committee;
- Risk Evaluation and Mitigation Strategy (REMS);

[131]Press release Regado Biosciences announces clinical hold of REGULATE-PCI trial following voluntary halt of trial by Regado; July 9, 2014.

[132]Calia M. FDA informs Arrowhead of partial clinical hold for hepatitis B drug. Wall Street J.; July 12, 2015. Dow Jones & Co., Inc.

[133]Poole K. The Sponsor's guide to regulatory submissions for an investigational new drug. biological resources branch, DCTD, NCI-Frederick. SAIC-Frederick, Inc; March 2005 (104 pp.).

[134]Archdeacon P, et al. Summary of the US FDA approval of Belatacept. Am. J. Transpl. 2012;12:554–62.