data. In other words, even if the patient was found not to be suffering from the infection that was required by the Clinical Study Protocol, the safety data will still be valid. The FDA requires (92):

> that safety be reported for all patients who received the drug, irrespective of whether a pathogen was identified or not. For purposes of efficacy, the population of interest varies by indication. While for some, the primary analysis is only in patients who had identified micro-organisms, for others it may be patients with a well-defined clinical entity, even if culture results are not positive.

To summarize, investigators may be inclined to analyze efficacy data by ITT analysis, modified ITT analysis, or PP analysis, and may decide to analyze safety data by ITT analysis, modified ITT analysis, or by PP analysis. These decisions are influenced by the following factors.

First, FDA requires all safety data, that is, data from the ITT population, not just from the PP population. Hence, while an investigator may analyze efficacy by way of PP analysis (thereby excluding study subjects who missed a few doses), missing a drug-taking schedule will not influence the validity of the existing safety data.

Safety data on any drug may be obtained within an hour of administering the drug. If a patient vomits or has a change in blood pressure within an hour or so of receiving the drug, the investigator can easily capture these adverse events. In contrast, efficacy can usually not be determined within an hour of receiving the drug, in particular, for diseases such as cancer and infections. In this way, safety data may have a different character than efficacy data.

If a study subject drops out of the study at a time point that is, for example, 1 week into a 2-year clinical study, any person would be able to understand that any safety data acquired in that 2-week period will be valuable. In contrast, any person can understand that efficacy data, acquired on the patient who drops out 2 weeks into the study, could be of questionable use.

e. Anticipated Versus Unanticipated Adverse Events

Investigators may need to distinguish between anticipated AEs and unanticipated AEs. This distinction informs the investigator whether or not any given AE needs to be reported to outside reviewers, such as the Data Monitoring Committee (DMC) or IRB. According to FDA's Guidance for Industry, unanticipated AEs are classified as follows (93):

- Unanticipated AEs include AEs that are uncommon and that are typically associated with drugs. A single occurrence of a serious, unexpected event that is uncommon but that is strongly associated with drug exposure, may include angiodema, agranulocytosis, hepatic injury, or Stevens–Johnson syndrome (SJS). SJS is a severe rash that occurs in response to various types of drug (94).
- Unanticipated AEs include AEs that are uncommon and not typically associated with drugs. A single occurrence, or more

[92]Drug Information RL, Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration. E-mail of October 15, 2010 from FDA.

[93]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for clinical investigators, sponsors, and IRBs. Adverse event reporting to IRBs—improving human subject protection; January 2009.

[94]Iannini P, Mandell L, Felmingham J, Patou G, Tillotson GS. Adverse cutaneous reactions and drugs: a focus on antimicrobials. J. Chemother. 2006;18:127–39.