the per protocol group. However, in this situation, the FDA will still require safety 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 (83):

> *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.*

e. Summary

The investigator may be inclined to analyze efficacy data by ITT analysis, modified ITT analysis, or per protocol analysis, and may decide to analyze safety data by ITT analysis, modified ITT analysis, or by per protocol 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 per protocol population. Hence, while an investigator may analyze efficacy way of per protocol analysis (thereby excluding study subjects who missed a few doses), missing drug-taking schedule will not necessarily 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 can 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.

f. Classification of adverse events as anticipated versus unanticipated

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 Institutional Review Board (IRB). According to the FDA's Guidance for Industry, unanticipated AEs are classified as follows (84).

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

[84] 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).