where the ITT population includes many subjects not having the infection.

This example is from a clinical trial on antibiotic (*azithromycin*) eye drops versus placebo eye drops. The information is from the *Medical Review* and *Statistical Review* of NDA 050810, at April 2007 of the FDA's website. In a section of the *Medical Review* entitled, "Intent to Treat (i.e., not necessarily culture positive," the FDA reviewer stated that, "[t]he Intent-to-Treat population included patients who were suspected to have bacterial conjunctivitis but did not meet the criteria needed to confirm bacterial conjunctivitis" (108).

The *ITT group* had 683 subjects, the *modified ITT group* had 283 subjects, and the *PP group* had 279 subjects.

The FDA reviewer provided a definition of the modified ITT group, which was, "all randomized subjects who received at least one drop of the study medication, had baseline cultures indicating pathogenic bacterial levels." The PP group was defined as, "all randomized subjects who received at least one drop of the study medication, had baseline cultures indicating pathogenic bacterial levels and had at least one post-first-dose efficacy measurement."

FDA granted approval to the study drug, and stated that results from the ITT group were not necessary, writing, "[a]lthough not necessary to support approval, AzaSite [study drug] was superior to its vehicle [control] in the Intent-to-Treat population."

Thus, in contrast to clinical trials on chronic conditions, such as cancer, chronic viral infections, and autoimmune disorders, it is the case that for some bacterial infections, enrollment and randomization must take place before it is time to confirm the suspected identity of the bacterium. In this situation, mITT and PP analysis are preferred as the primary basis for FDA approval.

c. FDA's Decision-Making Process in Evaluating Efficacy Data Based on the ITT Population Versus the Modified ITT Population

This concerns *ceftolozane* plus *tazobactam* for urinary tract infections. The information is from the *Statistical Review* of NDA 206829 at December 2014 of the FDA's website.

The FDA reviewer complained that the modified ITT population might be stratified in a way that was not consistent with that of the ITT population, that is, the population of subjects as originally randomized. The reviewer cautions that any analysis based on the modified ITT population might give misleading results, writing that, "[f]or example, although the initial randomization of ITT subjects ... was stratified by study site, some imbalances in the MITT population were observed for the region variable."

The reviewer further cautioned that this could lead to confounding results, but proceeded and compared analyses using both ITT and modified ITT analysis, adding that, "[a]lthough this can lead to potential confounding in the primary analysis, findings from Reviewer sensitivity analyses which adjusted for major risk factors (eg, stratification factors) showed findings which were similar to those of the primary analysis."

The Sponsor's main analysis was not on the ITT population, but on a subset of this group, called the "modified microbiological intention-to-treat (mMITT) population." The Sponsor defined two subsets of the ITT population, and these were the MTT population, which was all randomized subjects who received any amount of study drug, and the mMITT population, which was all randomized subjects who received any amount of study drug and had a microbiologically confirmed infection from

[108]Page 17 of 38-page pdf file containing the Medical Review, of NDA 050810 (April 2007 of FDA website).