c. Omalizumab for Asthma

The study drug was *omalizumab*, a recombinant antibody. The information is from the FDA's review of BLA 103976, which can be found on December 2011 of the FDA's website. The study design required a run-in period, where all subjects were administered a dose of inhaled corticosteroid, a small molecule known as beclomethasone. The dose of the inhaled corticosteroid was kept the same during the run-in period "to achieve a level of symptoms and PEFR [peak expiratory flow rate] 'acceptable' to the subject and investigator."

Further information on the goal of the run-in period is evident from the FDA reviewer's comments on the consequences, where any given subject failed to comply with the drug dosing that must be taken during the run-in period. The consequence is confusion as to the efficacy of the study drug (omalizumab). In the words of the FDA reviewer:

> Violations of run-in periods were the most common protocol violation. . .[a] too brief run-in period could potentially have introduced uncertainty in the corticosteroid dosing at the start of the steroid stabilization period. The most problematic outcome of this would be to introduce variability in efficacy measures, but the effect would likely be equal since the violation was equally distributed between treatment arms and was in the same direction (too short a period for both arms).

To conclude, the goal of the run-in period was to ensure that all study subjects had the same ability to breathe, as determined by peak expiratory flow rate, prior to randomizing to the study drug or placebo control. The study drug and placebo control were both administered intravenously.

III. CONCLUDING REMARKS

The simplest type of run-in period is one where a placebo is taken during this period, and only persons found to comply are actually enrolled in the trial. In a review, Senn (55) provided additional remarks on placebo run-in periods:

> Many trials. . .are preceded by a *placebo run in*, in which all patients are given placebo. The practice is common within the pharmaceutical industry and recommended by standard texts as a means of weeding out noncompliers before randomisation, eliminating placebo responders, ensuring that patients are stable, washing out previous treatment, or simply to provide a period for baseline measurement.

The list of Senn (56) discloses an unusual reason for a placebo run-in period, namely, eliminating *placebo responders*. This particular rationale might be desired in clinical trials on antidepressants, but it would be irrelevant to clinical trials in oncology or infections.

Run-in periods that are a step greater in complexity are those that screen potential subjects who are relatively free from safety issues, and run-in periods that conduct a screen that confirms a diagnosis of the disease in question. Run-in periods can be used to exclude potential subjects who are found not to comply with the inclusion/exclusion criteria set forth by the Clinical Study Protocol. For example, the run-in period used by Boushey

[55]Senn S. Are placebo run ins justified? Br. Med. J. 1997;314:1191–3.

[56]Senn S. Are placebo run ins justified? Br. Med. J. 1997;314:1191–3.