placebo. In the FDA's Guidance for Industry for rheumatoid arthritis, what is recommended is that, "the availability of effective RA therapies and the shifting paradigm in the treatment of both early and established RA with a focus on early control of disease activity . . . have provided a rationale for limiting the exposure of patients to placebo" (67).

To conclude, the issue of whether a placebo is appropriate for a given clinical trial needs to be decided on a case-by-case basis, and not on a per se basis.

IX. FDA's DECISION-MAKING PROCESS IN EVALUATING THE PLACEBO ARM

a. Introduction

At the time that the FDA provides its Approval Letter, the FDA also publishes its *Medical Reviews*, *Pharmacology Reviews*, and other reviews of the Sponsor's NDA or BLA. These reviews provide an accurate picture of the FDA's decision-making process. Guidance for using or interpreting placebos is provided by the following *Medical Reviews*.

b. Everolimus for Astrocytoma

This concerns a clinical trial that had a placebo control arm. The study drug was *everolimus* for astrocytoma, a type of brain cancer. This information is from NDA 203985, available on November 2015 on FDA's website. The *Medical Review* provides some very insightful comments as to the acceptability of the placebo control group. The most interesting of the reasons for ethical acceptability is that the cancer is a slow-growing tumor, and that the trial design *permitted patients to crossover from placebo to the study drug*, at the first sign that the tumors were growing beyond a prespecified size. This prespecified size was established by way of the conventional meaning of the term "progression."

In the FDA reviewer's own words, the placebo was ethical for the following reasons:

- "The study protocol excluded enrollment of patients that required immediate surgical intervention."
- "Surgery was not considered an appropriate control arm in this population due to the potential for surgical morbidity."
- "There was no active pharmacologic comparator that had been shown benefit to patients . . . at the time this study was initiated."
- "SEGA [subependymal giant cell astrocytoma] are slow-growing tumors, and [the clinical trial] . . . permitted [placebo] patients to crossover at the first radiologic sign of progression."

c. Dasafinib for Chronic Myeloid Leukemia

This concerns a clinical trial on patients with chronic myeloid leukemia (CML). The following discloses the situation where there does not exist a suitable comparator drug, for use as an active-control, and where use of a *placebo would have been unethical*. When faced with this situation, the Sponsor may use a *single-arm study*, that is, a study design where there is no control arm. The information is from NDA 21986, from January 2015 of FDA's website. To view the detail of suitable comparator drugs, imatinib might be considered to be a suitable comparator, but all of the subjects enrolled in the dasafinib trial

[67]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Rheumatoid arthritis: developing drug products for treatment; May 2013 (11 pp.).