age) on renal failure. Further regarding renal failure, the reviewer stated that the Sponsor should consider including a warning, on the package label, that the study drug might increase the risk for renal failure, even though approval was based only on a single-arm clinical trial.

5. Need to Explore Efficacy of Lower Doses for Patients

At the time of the Approval Letter, FDA also issued a *Clinical Pharmacology Review*. The information is from NDA 205552, from Nov. 2013 on the FDA's website.

FDA's review commented on the dosing level, and suggested that the Sponsor explore the efficacy of doses that were lower than that which had been approved by the Approval Letter. To this end, the reviewer stated that:

> [a]lthough the proposed dose ... [is] acceptable based on the limited effectiveness and safety data in the ... study population, the proposed doses are ... higher than the lowest dose that resulted in maximum BTK occupancy and maximum response. Therefore, the applicant should consider exploring lower doses in further development programs.

"BTK" refers to the target of the drug. The drug's target is an enzyme, *Bruton's Tyrosine Kinase* (BTK). In the review's comment, the term "occupancy" refers to the binding of the study drug to the enzyme, thus inhibiting the enzyme.

6. Issue of Toxicity of Excipient in Animal Tests

Further regarding concerns about toxicity of the drug formulation, the reviewer also commented on the excipient in the drug formulation. In comments about a dosing study in dogs, he remarked that "intolerance to the treatment of 100 mg/kg/day of ibrutinib ... may possibly be due to the intolerance to the vehicle which contained 28% (w/v)."

The following bulletpoints summarize the reviewer's comments:

- *Efficacy.* The FDA reviewer stated that the reviewer recommends approval, because the data showed that the drug was effective in humans.
- *Safety.* Regarding safety, the reviewer requested an entirely new clinical trial designed to examine certain adverse events, that is, relating to blood clotting disorders and renal failure. Also regarding safety, the reviewer commented on the possible toxicity of the excipient, as determined by data from animals, but refrained from making any recommendation.
- *Endpoint.* Regarding criteria for evaluating an efficacy endpoint, the reviewer requested information that correlated an older method (computed tomography) with a newer method (FDG-PET).
- *Dose.* Regarding the dose, which is a vital component of all package labels, the reviewer requested additional clinical studies addressing the efficacy of lower doses.

c. Autoimmune Diseases, As Exemplified by Multiple Sclerosis

This is from the *Medical Review* of *pegylated interferon-beta-1a*, a drug used for treating multiple sclerosis. The information is from BLA 125499, from Jan. 2014, on the FDA's website.

The reviewer recommended approval of the study drug, writing, "[t]his review recommends approval of ... 125 micrograms given subcutaneously every 2 weeks for the treatment of adults with relapsing forms of multiple sclerosis ... [t]he trial data supports that the benefits of peginterferon-beta-1a outweigh the risks."