one commentator (174), the opportunity to seek and acquire approval of orphan status of a drug may provide the following benefits. The opportunity encourages manufacturers to seek out orphan indications for drugs that could otherwise be tested in more general populations (this benefits patients). It provides public subsidies for the development of products (this benefits companies). Also, it may lead to the approval of drugs then widely used off-label without supporting data (this benefits patients, because of the supporting data).

Please note that the Code of Federal Regulations allows Sponsors to submit a request for orphan drug status, even if the disease is not a rare disease. Requests for diseases that are not rare will be accepted by the FDA if the Sponsor has information that it is not likely that any company will be developing drugs for that nonrare disease. The relevant law is in 21 CFR §316.20(b)(8)(ii), and is reproduced in footnote (175).

c. Examples of Drugs That Have Been Granted Orphan Drug Status

FDA has granted orphan drug status to various drugs to be used for the indications described in the following list. Documents written by FDA reviewers in the approval of all drugs, including orphan drugs, can be found on the FDA's website using the procedure in footnote (176). The following list identifies the indication, as well as the location (on FDA's website) of the FDA's Approval Letter and other documents that supported the FDA's decision to approve the drug:

- *Ibrutinib* for mantle cell lymphoma (MCL). Documents available on the FDA's website at November 2013.
- *Imatinib* for chronic myeloid leukemia, a disease characterized by a chromosomal location called, Philadelphia chromosome. Documents available on the FDA's website at January 2013.
- *Obinutuzumab* for chronic lymphocytic leukemia (CLL). Documents available on the FDA's website at November 2013.
- *Afatinib* for nonsmall-cell lung cancer where tumors have a deletion in exon 19 of the gene encoding epidermal growth factor receptor or a mutation in exon 21 that involves change of a leucine residue to an arginine residue (L858R). Documents available on the FDA's website at July 2013.
- *Velaglucerase alpha* for type 1 Gaucher disease. Documents available on the FDA's website at November 2013.
- *Glycerol phenylbutyrate* for urea cycle disorders. Documents available on the FDA's website at January 2013.
- *Cysteamine bitartrate* for nephropathic cystinosis. Documents available on the FDA's website at April 2013.
- *Riociguat* for pulmonary arterial hypertension. Documents available on the FDA's website at October 2013.

[174]Kesselheim AS. Using market exclusivity incentives to promote pharmaceutical innovation. New Engl. J. Med. 2010;363:1855–62.

[175]For a drug intended for diseases or conditions affecting 200,000 or more people, or for a vaccine, diagnostic drug, or preventive drug to be administered to 200,000 or more persons per year in the United States, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States as specified in §316.21(c).

[176]On the FDA website, click on DRUG tab, click on Search Drug Approvals by Month Using Drugs@FDA, then choose the month and year, then choose the drug, and finally click on Approval History, Letters, Reviews, and related documents. As a result of this process, you will gain access to the Approval Letter, Medical Review, Pharmacological Review, Statistical Review, and other documents that were prepared by FDA employees.