NATIONAL INSTITUTES OF HEALTH
OFFICE OF THE DIRECTOR

DETERMINATION IN THE CASE OF FABRAZYME® MANUFACTURED BY GENZYME CORPORATION

Introduction

Dr. C. Allen Black, Jr. submitted a request ("the Request") on behalf of his clients ("Requestors"), dated August 2, 2010, to Secretary Sebelius, Department of Health and Human Services ("HHS"), asking the Government to exercise its march-in rights under the Bayh Dole Act, 35 U.S. §§ 202-212 (the "Act"). The Request concerned certain patents owned by the Mount Sinai School of Medicine ("Mount Sinai") that are based on inventions funded by the National Institutes of Health ("NIH") and exclusively licensed by Mount Sinai to the Genzyme Corporation ("Genzyme"). Specifically, Requestors have asked HHS to grant an open license to United States Patent Nos. 5,356,804 ("the '804 patent") and 5,580,757 ("the '757 patent") to permit the manufacture of Fabrazyme® (agalsidase beta), a form of alpha-galactosidase A, to treat Fabry Disease.[1] Fabrazyme® is in critically short supply due to Genzyme's manufacturing difficulties which are currently being monitored by and are under a Consent Decree with the U.S. Food and Drug Administration ("FDA"). The Requestors also seek an open license to the cell line producing Fabrazyme® and any technical know-how developed in conjunction with producing Fabrazyme® that would expedite the production and reduce duplication of manufacturing and product development efforts by a third party. Support of the Request has been received from other patients and interested parties.

Determination

Based upon the information currently available, NIH has determined that a march-in proceeding under 35 U.S.C. § 203(a)(2) is not warranted at the present time because any licensing plan that might result from such a proceeding would not, in our judgment, address the problem identified by the Requestors. A march-in proceeding resulting in the grant of patent use rights to a third party will not increase the supply of Fabrazyme® in the short term because years of clinical studies and regulatory approval would be required before another manufacturer's product could become available to meet patients' needs in the United States. NIH has no information that a company is expecting imminent FDA approval of a competing version of an agalsidase beta product. Secondarily, the '804 patent is not an obstacle for a company to conduct clinical trials in the United States in furtherance of regulatory approval for a competing drug, because such clinical trials are exempt from infringement under the Hatch-Waxman statutory safe harbor provision. (35 U.S.C. § 271(e)) Finally, Genzyme has indicated that it expects the production of Fabrazyme® to be back to full supply levels in the first half of

[1] Information about Fabry disease is available at http://www.ninds.nih.gov/disorders/fabrys/fabrys.htm.

2011. Genzyme appears to be working diligently and in good faith to address the Fabrazyme® shortage.

Notwithstanding the foregoing, NIH will continue to carefully monitor the shortage of Fabrazyme® and will re-evaluate this determination immediately upon receiving any information that suggests progress toward restoring the supply of Fabrazyme® to meet patient demand is not proceeding as represented.

Further, in the unlikely event that NIH receives information that a third party has a viable plan to obtain FDA approval to market agalsidase beta during the period in which Genzyme is not able to meet patient demand for Fabrazyme®, and, that third party requires commercial rights to the '804 patent in order to proceed with its plan, NIH will immediately re-consider its decision to exercise its march-in authority. Toward this end, NIH has asked Mount Sinai to: (1) provide monthly reports on the status of Genzyme's progress toward addressing the supply shortage of Fabrazyme® until such time as U.S. Fabry patients' needs have been met; (2) provide a copy of Genzyme's reports on the allotment of Fabrazyme to Fabry patients; and, (3) notify NIH within two business days after receiving any request from a third party for a license to the '804 patent to market agalsidase beta during the Fabrazyme® shortage.

The Requestors have also asked NIH to include in any license to the patent "the cell line producing Fabrazyme® and any technical know-how developed in conjunction with producing the drug." The march-in provision is, however, only directed to Bayh-Dole Act subject inventions and not to tangible materials or unpatented technical know-how. NIH's determination decision is directed solely to use of its march-in authority to the subject invention.

Statutory Background and Criteria

The stated policy and objective of the Bayh Dole Act is:

> [T]o use the patent system to promote the utilization of inventions arising from federally supported research or development; . . . to ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions; . . . . (35 U. S.C. § 200)

Toward this goal, the Bayh-Dole Act provides a Federal agency with march-in rights authority in certain limited circumstances, to ensure that a federally funded invention is available to the public. More specifically:

> With respect to any subject invention in which a small business firm or nonprofit organization has acquired title under this chapter, the Federal agency under whose funding agreement the subject invention was made shall have the right, in accordance with such procedures as are provided in regulations promulgated hereunder to require

the contractor, an assignee or exclusive licensee of a subject invention to grant a nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant or applicants, upon terms that are reasonable under the circumstances, and if the contractor, assignee, or exclusive licensee refuses such request, to grant such a license itself, if the Federal agency determines that such—

(1) action is necessary because the contractor or assignee has not taken, or is not expected to take within a reasonable time, effective steps to achieve practical application of the subject invention in such field of use;
(2) action is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or their licensees;
(3) action is necessary to meet requirements for public use specified by Federal regulations and such requirements are not reasonably satisfied by the contractor, assignee, or licensees; or
(4) action is necessary because the agreement required by section 204 has not been obtained or waived or because a licensee of the exclusive right to use or sell any subject invention in the United States is in breach of its agreement obtained pursuant to section 204. (35 U.S.C. § 203(a))

With respect to the use of march-in, the regulations state at 37 C.F.R. § 401.6(b):

> Whenever an agency receives information that it believes might warrant the exercise of march-in rights, before initiating any march-in proceeding, it shall notify the contractor in writing of the information and request informal written or oral comments from the contractor as well as information relevant to the matter.

Based on the available information, a Federal agency can either initiate march-in procedures set forth at 37 C.F.R. § 401.6(c) or notify the contractor that it will not pursue march in rights.[2] Consistent with 35 U.S.C. § 203(a) with respect to any subject invention, a Federal agency is authorized to:

> require the contractor, an assignee or exclusive licensee of a subject invention to grant a nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant or applicants, upon terms that are reasonable under the circumstances, and if the contractor, assignee, or exclusive licensee refuses such request, to grant such a license itself.

The NIH has the delegated authority to make the march-in determination in this case. NIH has received information from the Requestors, Genzyme, Mount Sinai, letters from patients who suffer from Fabry disease, and letters from other concerned members of the public, as well as other pertinent materials obtained by the NIH from public sources.

[2] See 37 C.F.R. § 401.6(b).

The Subject Invention

The patents in question are the '804 patent and the '757 patent. The '804 patent relates to the production of enzymatically active alpha-galactosidase A from a recombinant mammalian cell line. The '757 patent is similar but makes use of a fusion protein that must be cleaved before it is enzymatically active. This latter technology is not used in the manufacture of Fabrazyme®. Therefore, only the '804 patent is relevant to this determination.

Mount Sinai filed a patent application for the '804 patent on October 24, 1990. The patent issued on October 18, 1994 and, with term extensions, expires on September 27, 2015. Mount Sinai elected title to this invention and issued the Government a confirmatory license on September 13, 1991 as required by 37 C.F.R. § 401.14 (f)(1). There is no dispute that the '804 patent is a subject invention under 35 U.S.C. § 201(e) and 37 C.F.R. § 404.14 (a)(2).

Meeting Health or Safety Needs

The central inquiries in this case are whether there is an existing health need of Fabry patients associated with the exclusive licensing by Mount Sinai of the '804 patent to Genzyme and whether NIH, by exercising its march-in authority, could alleviate that problem. We have found the following information relevant:

(1) Until mid-June 2009, Genzyme produced sufficient quantities of Fabrazyme® to meet the needs of patients;

(2) In mid-June 2009, Genzyme interrupted its production of Fabrazyme® at its Allston, Massachusetts facility due to a viral contamination and further interrupted its production of Fabrazyme® due to a power outage;

(3) In May 2010, Genzyme entered into a Consent Decree with the FDA related to the production of Fabrazyme® and other products produced by Genzyme at its Allston plant; and

(4) Due to Genzyme's production difficulties at its Allston facility, Fabry patients, as of the date of this determination, are not able to obtain sufficient quantities of Fabrazyme®.

The Requestors state that, since Genzyme began rationing the dosages of Fabrazyme, they and other patients with Fabry disease "have suffered a return of symptoms including neuropathy, proteinuria, digestive disorders, heart disease, renal disease, morbidity, and increased risk of premature death."

In late October 2010, the European Medicines Agency (EMA), a European regulatory authority, issued a report to doctors urging that any Fabry patients on low doses of Fabrazyme® who are suffering adverse effects should receive full doses. The EMA reported that it initiated the review because of a trend of increased reports of adverse events correlating directly with the Fabrazyme® supply problems. These reports revealed a pattern suggesting that the decrease in the dose of Fabrazyme caused the Fabry disease to progress. The EMA observed that not everyone on a reduced dose suffered symptoms. Accordingly the EMA's report stated that continued low doses of Fabrazyme are acceptable for those patients whose condition remains stable.[3]

Based on the current information, the patients' required supply of Fabrazyme® cannot be met due to Genzyme's current manufacturing difficulties.

Commercial Development of Biological Products

The process for bringing a biological product to market for use in humans requires substantial time, effort, and resources, irrespective of any patent rights. Any new product must proceed through the complete FDA Investigational New Drug ("IND") and Biologic License Application ("BLA") approval processes. These approval processes include, among other things, the following generalized steps:

(a) arranging appropriate safeguards, as required by 21 C.F.R. Parts 50, 54, and 56;
(b) arranging a supply of clinical-grade materials suited for clinical research, as required under 21 C.F.R. Parts 210, 211, 600, and 606;
(c) gathering all of the necessary preclinical (in vitro and in vivo) data to support the start of clinical research;
(d) filing the IND and waiting thirty (30) days to permit the FDA to impose a hold on clinical research, pursuant to 21 C.F.R. Part 312;
(e) conducting enough clinical studies (at least two of which the FDA requires to be pivotal) to establish parameters for human pharmacokinetics, efficacy, dosing, and safety; and
(f) filing the BLA pursuant to 21 C.F.R. Part 601.

Once the BLA has been filed, the FDA's internal goal is to complete the review within ten months or within six months if the application has priority status.[4] However, the process may be indefinitely longer if the initial review does not result in an approval.

Even for a company seeking to expand production of its own, existing product by constructing a second facility, the FDA still requires that the company demonstrate the lack of "adverse effect

[3] http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/10/WC500098370.pdf.

[4] FDA Performance Report to the President and Congress for the Prescription Drug User Fee Act, FY 2009 at 9-10 (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/UCM228022.pdf).

on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product,"[5] through whatever testing the FDA deems necessary – including a new round of clinical trials.[6] If a second company wants to make a similar, competing product, the competitor must file its own IND and BLA, just as if the competitor were the original innovator.

Genzyme's Development, Manufacture, and Sale of Fabrazyme®

Following Mount Sinai's grant of an exclusive license to Genzyme for the '804 patent, Genzyme made substantial investments in the development of Fabrazyme®. This effort included developing a recombinant cell line that produces the human enzyme alpha-galactosidase A under clinical conditions, and then conducting Phase I, II, III, and IV clinical studies with its enzyme product. Genzyme began marketing the drug Fabrazyme® in the European Union in 2001 and in the United States after it received FDA approval on April 24, 2003.[7] Genzyme is the only company that has been granted FDA approval in the United States to manufacture and sell an alpha-galactosidase A product. Fabrazyme® is the only approved therapeutic for Fabry disease in the United States.

On May 24, 2010, the FDA and Genzyme entered into a Consent Decree in a proceeding before the United States District Court for the District of Massachusetts to correct manufacturing quality violations at the company's Allston, Massachusetts manufacturing facility. Under this Consent Decree, Genzyme agreed, among other things, to adhere to an FDA approved timeline for making facility improvements to comply fully with current good manufacturing practice, periodic inspections by the FDA, and employment of an independent expert to inspect the Allston plant and issue recommendations. In addition, the Consent Decree provides a deadline for Genzyme to transfer its operations for filling drug vials from its Allston facility to other manufacturing sites but allows it to continue "to manufacture, process, test, pack, label, hold, and distribute . . . Fabrazyme®."

Prior to Genzyme's production difficulties it began constructing a new manufacturing facility in Framingham, Massachusetts, in order to expand the production of Fabrazyme®. According to Genzyme, this new plant will provide substantial additional capacity to support the anticipated increasing need for Fabrazyme®. Genzyme expects that its new Framingham manufacturing facility will be approved by the end of 2011.

Genzyme indicated to NIH that because Fabrazyme® inventories were not sufficient to avoid shortages during the period of suspended production and recovery, Genzyme immediately began working with regulatory authorities, physicians, and patient organization groups to carefully manage product supply with the goal of minimizing the impact of the shortage on the

[5] 21 C.F.R. § 601.12(b)(1).

[6] See generally 21 C.F.R. § 601.12.

[7] Reported on the FDA website, the FDA granted Orphan Drug Product status to Fabrazyme® on January 19, 1988; the market exclusivity associated with Orphan status expired April 24, 2010.

health of patients. Genzyme has further indicated that available Fabrazyme® has been and continues to be distributed equitably to all regions and without regard to charitable status.

Genzyme also stated that it has been allocating 38% of its available supply of Fabrazyme® to patients in the United States based on the U.S. percentage of Fabrazyme® usage prior to its supply interruption in mid-2009. Further, Genzyme expects to have the full supply of Fabrazyme® available in the first half of 2011.

In an August 20, 2010 letter to the Fabry community, Genzyme offered all patients currently treated with Fabrazyme® one full dose in September 2010 and one full dose in October 2010. More recently, Genzyme, in a letter to the Fabry community dated October 25, 2010, reported that: (1) patients currently treated with Fabrazyme who were infused biweekly prior to the shortage would receive two full doses in November 2010; and, (2) there was not a sufficient supply to support a dose increase for any patient nor would the drug be available for new patients to begin treatment in November. Genzyme advised that it is providing regular updates to its best estimate of Fabrazyme supply. Because it is working with a limited inventory, however, Genzyme further noted that even minor changes to its current manufacturing plan can impact the drug's availability and that it is committed to informing the Fabry community of shipping delays.

Commercial Development of Treatments for Fabry Disease

In considering this Request, we considered the '804 patent with respect to the development of alternative treatments of Fabrazyme. At least five other companies worldwide are known to be engaged in commercial development directed to alternative treatments for Fabry disease. At this time, based on the information available, we are encouraged that the worldwide supply of drugs or biologics for Fabry patients will increase in the medium- and long-term.

First, Shire plc, a UK company, obtained authorization to market its product Replagal® (agalsidase alpha), a form of alpha-galatosidase A, in the European Union in 2001. It is now available in forty-five countries but is not yet approved in the United States.[8] In the United States, Shire filed a BLA with the FDA in December 2009. By February 2010, however, Shire withdrew its BLA filing, replaced it with a rolling submission, and at the suggestion of the FDA, requested and received fast-track designation.[9] As of June 2010, enrollment was closed in its clinical studies. Shire has announced that it will actively manage emergency requests and will continue to provide the drug to U.S. patients who have been enrolled in the treatment IND and who obtained the drug for emergency use.[10] On August 3, 2010, Shire withdrew its BLA for Replagal® in order to consider updating its submission with additional clinical data.[11]

---

[8] Source: Shire webpage (see http://www.shire.com/shireplc/en/products/rare/fabrydisease/REPLAGAL).
[9] Source: Shire webpage (see http://www.shire.com/shireplc/en/investors/investorsnews/irshirenews?id=329).
[10] Source: Letter from Fabry Support & Information Group to Fabry community (Jul. 9, 2010) (see: http://www.fabry.org/fsig.nsf/PDFs/PDFs10/$File/FDA_Approval_Letter.pdf).
[11] Source: Shire Half-Year Report for the six months ended June 30, 2010 at 5 (see: http://www.shire.com/shireplc/en/investors/reports).

Shire represents that it currently supplies Replagal® to over 2,300 Fabry disease patients and anticipates being able to continue to accommodate additional Fabry patients in 2010 while carefully monitoring supply and demand.[12] Shire further states that it "will be in a position to make Replagal® available to at least 300 additional patients in 2011, phased throughout the year, based on current manufacturing capacity."[13] Finally, Shire has said that approval of a new manufacturing facility in Lexington, Massachusetts will allow treatment of several hundred more Fabry patients.[14]

The '804 patent is not a barrier to the availability of Replagal® in the United States as the drug has been held not to infringe the '804 patent.[15] Further, Genzyme has encouraged patients to switch to Replagal® during the supply shortage of Fabrazyme®. However, since Mount Sinai's European patent equivalent to the '804 patent (EP 1 942 189) was granted on April 14, 2010, Mount Sinai has initiated infringement actions in Germany and Sweden against Shire for its sale of Replagal®.[16] Infringement actions can be coupled with a demand for an injunction to halt use of a patented invention. In this case, a reduction in the supply of Replagal® during a period of shortage of Fabrazyme would increase demand for Fabrazyme® in Europe and further limit the doses available to individual patients in the US and Europe. Mount Sinai has assured us that it will not pursue an injunction against the marketing and sale of Replegal® during any period of an existing or future shortage of Fabrazyme®. We expect Mount Sinai and Shire to make the welfare of the patients their first priority as they resolve resolve their differences.
Second, Amicus Therapeutics, a US company, is developing Amigal® (migalastat HCl), an oral small molecule "chaperone" medication to treat Fabry disease, which has reached Phase II and Phase III clinical trials.[17] Both Mount Sinai and Genzyme have reported that Amicus would not require a license under the '804 patent, as its product is a small molecule, and the '804 patent is directed to recombinant protein production. Recently Amicus and GlaxoSmithKline announced an agreement to develop and commercialize Amigal®, including advancing clinical studies and exploring co-administration of Amigal® with enzyme replacement therapy to treat Fabry disease.[18]

Three other companies have publicly reported pre-clinical development of alternative drugs to treat Fabry disease. Isu Abxis, a Korean company, reports that its ISU 303 drug is in clinical development.[19] Protalix, based in Israel, reports that it is engaged in pre-clinical development

---

[12] Source: Q3 2010 Shire plc Press Release at 4 (Oct. 29, 2010) (see: http://www.shire.com/shireplc/en/investors/investorsnews/irshirenews?id=421).
[13] Id.
[14] Id.
[15] Genzyme Corp. v. Transkaryotic Therapies, Inc., 346 F. 3rd 1094 (Fed. Cir. 2003).
[16] Source: Source: Shire Half-Year Report for the six months ended June 30, 2010 at 5 (see: http://www.shire.com/shireplc/en/investors/reports).
[17] Source: Amicus webpage (see: http://www.amicustherapeutics.com/clinicaltrials/at1001.asp).
[18] GSK Press Release (Oct. 29, 2010) (see: http://www.gsk.com/media/pressreleases/2010/2010_pressrelease_10118.htm).
[19] Source: Abxis webpage (see: http://www.abxis.com/eng/index.asp).

of a Fabry drug, PRX-102.[20] Finally, JCR Pharmaceuticals Co., Ltd., based in Japan, has reportedly partnered with GlaxoSmithKline to co-develop its JR-051.[21] As of November 24, 2010, no clinical trials of these drugs have been reported.[22]

With respect to ISU 303, PRX-102 and JR-051, Mount Sinai and Genzyme have stated that none of the companies developing such products currently need a license to make, use or sell their products in the United States because any pre-clinical or clinical development activities in the United States would enjoy the protection of the Hatch-Waxman safe harbor, 35 U.S.C. § 271(e)(1). More specifically, the information available shows that no supplier of an alternative enzyme replacement therapy has approached Mount Sinai or Genzyme to seek a license to supply such a therapy during the duration of the shortage.

Conclusion

NIH has determined that the information currently available does not warrant a march-in proceeding under 35 U.S.C. § 203(a)(2) because, no remedy that is available under the march-in provision would address the problems identified by the requestors due to the shortage of Fabrazyme®. The license that Requestors have sought, were it to be granted, is unlikely to increase the supply of alpha-galactosidase A during the term of the '804 patent because years of clinical studies would be required before an alternative source could be approved by the FDA.

Moreover, NIH has not received any information that suggests a qualified third party is ready to supply an alpha-galactosidase A-based therapy.

On the other hand, Genzyme has expressed its commitment to provide a full supply of Fabrazyme® in the first half of 2011.

NIH is concerned about the urgent health needs of Fabry patients who are unable to obtain the recommended dosage of Fabrazyme® during this interim supply shortage and will continue to monitor the issues related to Fabry patient's access to Fabrazyme®.

[20] Source: Protalix webpage (see: http://www.protalix.com).
[21] Source: JCR Pharmaceuticals webpage (see: http://jcrpharm.jp/en).
[22] Source: ClinicalTrials.gov (see: http://www.clinicaltrials.gov).

We have asked Mount Sinai to: (1) provide monthly reports on the status of Genzyme's progress toward addressing the supply shortage of Fabrazyme® until such time as U.S. Fabry patients' needs have been met; (2) provide monthly reports on Genzyme's allotment of Fabrazyme® to Fabry patients; and, (3) notify NIH within forty-eight hours after receiving any request from a third party for a license to the '804 patent in order to market agalsidase during the Fabrazyme® shortage.

If at any time new information becomes available that could change our determination, we will evaluate it as quickly as possible to determine whether our decision should be modified.

Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health

12/1/10

Date