

**PETITION TO USE AUTHORITY UNDER THE BAYH-DOLE ACT TO PROMOTE ACCESS TO FABRYZYME® (AGALSIDASE BETA), AN INVENTION SUPPORTED BY AND LICENSED BY THE NATIONAL INSTITUTES OF HEALTH UNDER GRANT NO. DK-34045**

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## **1. Executive Summary**

Joseph M. Carik, Anita Hochendoner, and Anita Bova request the Secretary to exercise Bayh-Dole march-in rights and grant an open license to use patents related to the manufacture of Fabrazyme® (agalsidase beta). The grounds for the request are that the patent owner and its exclusive licensee have harmed the public health by severely rationing the supply of agalsidase beta, the only approved therapeutic treatment for Fabry disease.

The license should be open to any qualified application including a grant for the right to make, use, import, export and sell agalsidase beta, either as a standalone treatment or as a component a combination of treatments. The license should include a five percent royalty to the patent owner, calculated on the basis of reasonable sale price for agalsidase beta products.

## **2. Petitioners**

Joseph M. Carik, Anita Hochendoner, and Anita Bova are private individuals who have Fabry disease. They are prescribed Fabrazyme® to treat the disease, but they have not (and are not) receiving the prescribed dosage due the patentee's and licensee's inability to produce enough drug to treat all of the Fabry patients that have been prescribed Fabrazyme®. Their symptoms have worsened, and they are at greater risk of morbidity and death due to complications from the disease because of the severe and ongoing restriction in the supply of Fabrazyme®. Their position is identical to all Fabry patients because all patients are being rationed the drug by Genzyme.

The Bayh-Dole Act allows any "responsible applicant" to request march-in rights under 35 U.S.C. § 203. The Bayh-Dole act's language is liberal, and while the term "responsible" is not explicitly defined, the petitioners assert that they are responsible applicants within the context of the statute. First, they are primary stakeholders in ensuring Fabrazyme® is available because they suffer from the disease. Secondly, they are highly motivated to bring access of the drug to all victims as soon as possible since their own health and the health of their families are at stake. Finally, they have no interests such as personal or corporate financial gain that would conflict with restoring access to Fabrazyme® to the public.

## **3. Request for licenses to patents on Fabrazyme®**

Joseph M. Carik, Anita Hochendoner, and Anita Bova seek an open license under the Bayh-Dole Act that would allow supply of agalsidase beta in the U.S. and abroad to treat Fabry patients. Specifically, this petition requests that NIH authorize responsible entities and individuals to use U.S. Patent No. 5,356,804 and U.S. Patent No. 5,580,757 in order to manufacture, import, export or sell agalsidase beta.

## **4. Background on Fabry disease**

Fabry disease (also known as Fabry's disease, Anderson-Fabry disease, angiokeratoma corporis diffusum, and alpha-galactosidase A deficiency) is an X-linked recessive (inherited) lysosomal storage disease, which can cause a wide range of systemic symptoms including:

Renal disease: Proteinuria (which causes foamy urine) is often the first sign of kidney involvement. Renal insufficiency and renal failure may worsen throughout life. End stage renal failure in males can typically occur in the third decade of life, and is a common cause of death due to the disease.

Heart disease: Cardiac complications occur when glycolipids build up in different heart cells; heart related effects worsen with age and may lead to increased risk of heart disease. Hypertension (high blood pressure) and cardiomyopathy are commonly observed.

Dermatological manifestations: Angiokeratomas (tiny, painless papules that can appear on any region of the body, but are predominant on the thighs, around the belly-button, buttocks, lower abdomen, and groin) are a common symptom. Anhidrosis (lack of sweating) is a common symptom, and less commonly hyperhidrosis (excessive sweating).

Ocular disease: Ocular involvement may be present showing cornea verticillata, i.e. clouding of the corneas. Keratopathy may be the presenting feature in asymptomatic carriers. Other ocular symptoms include conjunctival aneurysms, posterior spoke-like cataracts, papilloedema, macular edema, optic atrophy, and retinal vascular dilation.

Additional symptoms include: Fatigue, neuropathy (in particular, burning extremity pain), cerebrovascular effects leading to an increased risk of stroke, tinnitus (ringing in the ears), vertigo, nausea, inability to gain weight, and diarrhea.

Mortality and morbidity: Fabry disease significantly shortens the life of its sufferers. In one NIH study where patients were not treated by enzyme replacement therapy, researchers found from survival analysis that 50% of patients developed End Stage Renal Disease (ESRD) by 53 years, with a range of 21 to 56 years.<sup>1</sup> Importantly, all NIH patients in the study who lived into their 50s developed ESRD.<sup>2</sup>

## **5. Government role in funding research and development**

NIH has been instrumental in funding and conducting research into Fabry disease, involving, for example, efforts from the Kidney Disease Section, National Institute of Diabetes and Digestive and Kidney Diseases, and the Developmental and Metabolic Neurology Branch of the National Institute of Neurologic Disorders and Stroke.

NIH is one of the largest funding entities for Fabry research, and is heavily invested in securing the well-being of Fabry patients. A July 22, 2010 search of the NIH Research Portfolio Online Reporting Tools (RePORT) database using the keyword "Fabry" identified 372 NIH grants.<sup>3</sup> A July 23, 2010 search of clinicaltrials.gov using the key words "Fabry's Disease" identified 54 clinical trials, including 14 that were funded by the NIH, 16

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<sup>1</sup> Branton et al., Natural History and Treatment of Renal Involvement in Fabry Disease; *J Am Soc Nephrol* 13:S139-S143 (2002).

<sup>2</sup> Id.

<sup>3</sup> Public and Private Sector Funded Research for Fabry's Disease, KEI Research Note 2010:2, <http://www.keionline.org/rn2010-2>.

identified as having received funding from Universities or other non-profit organizations, and 27 trials that received funding from industry.<sup>4</sup>

## **6. Invention of agalsidase beta treatment**

While no cure is yet available, one of the greatest breakthroughs in scientific research on Fabry disease has been the discovery that enzyme replacement therapy with agalsidase beta (Fabrazyme®) can effectively treat Fabry patients.<sup>5</sup> The breakthrough was a direct result of NIH funding of grant no. DK 34045 awarded to Dr. Robert J. Desnick at the Mount Sinai School of Medicine of New York University. The adoption of Fabrazyme® treatment has been widespread and is currently the gold standard of care for patients in the U.S. exhibiting symptoms.

## **7. Ownership and licensing of Fabrazyme®**

Currently, Fabrazyme® treatment is the only FDA approved enzyme replacement therapy in the United States. Genzyme, Inc. is the exclusive licensee to produce Fabrazyme®.<sup>6</sup> Based on public records, the NIH also has a confirmatory license for Patent Nos. 5,580,757 and 5,356,804.<sup>7</sup> The petitioners are unable to determine whether the license with Genzyme is between Mt. Sinai or NIH and includes only one or both of the patents. However, applicant does not believe that the distinction is relevant for the purposes of the petition as Genzyme currently claims an exclusive license to patent no. 5,356,804.<sup>8</sup> However, in the event the NIH determines that such information is necessary for its decision, applicant requests that NIH immediately undertake to determine the nature of the license in order to expedite the petition.

## **8. Genzyme's failure to produce Fabrazyme® factual background**

The initial production of Fabrazyme® was sufficient to meet the needs of all patients in the United States. However, in mid-2009, Genzyme decreased production as a result of a viral infection of their Allston, MA manufacturing plant.<sup>9</sup> Further, in November 2009, Fabrazyme® was produced which contained contaminants. The FDA initiated action against Genzyme which resulted in a consent decree including \$175 million dollars fines as profit disgorgement and oversight of the manufacture of Fabrazyme® for at least 7 years.<sup>10</sup>

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<sup>4</sup> Id.

<sup>5</sup> Desnick RJ, Banikazemi M., Fabry disease: clinical spectrum and evidence-based enzyme replacement therapy, *Nephrol Ther.* 2006 Jan; 2 Suppl 2:S172-85.

<sup>6</sup> Genzyme Corp, 10-K, 2009, page 17 available online at [http://www.genzyme.com/corp/investors/GENZYME\\_CORP\\_10K\\_20090302.pdf](http://www.genzyme.com/corp/investors/GENZYME_CORP_10K_20090302.pdf).

<sup>7</sup> Confirmatory license to U.S. Patent No. 5,580,757 recorded at Reel/Frame:[020928/0711](http://www.uspto.gov/assignments/q?db=pat); available through <http://assignments.uspto.gov/assignments/q?db=pat>; Confirmatory license to U.S. Patent No. 5,356,804 recorded at Reel/Frame:[020928/0707](http://www.uspto.gov/assignments/q?db=pat); available through <http://assignments.uspto.gov/assignments/q?db=pat>.

<sup>8</sup> Genzyme Corp, 10-K, 2009, page 17 available online at [http://www.genzyme.com/corp/investors/GENZYME\\_CORP\\_10K\\_20090302.pdf](http://www.genzyme.com/corp/investors/GENZYME_CORP_10K_20090302.pdf).

<sup>9</sup> Weisman, Supervision of 7-8 years ordered for Genzyme: Quality-control problems prompt accord with FDA, *Boston Globe*, May 25, 2010 available at [http://www.boston.com/business/healthcare/articles/2010/05/25/supervision\\_of\\_7\\_8\\_years\\_ordered\\_for\\_genzyme/?s\\_campaign=8315](http://www.boston.com/business/healthcare/articles/2010/05/25/supervision_of_7_8_years_ordered_for_genzyme/?s_campaign=8315).

<sup>10</sup> Id.

Genzyme is only producing 30% of Fabrazyme estimated to meet the needs of patients.<sup>11</sup> Current patients cannot have dosage increases, and no new patients being diagnosed are eligible to receive therapy. Although the most recent communication from Genzyme indicates that it expects to increase production by late 2011, there is no substantial guarantee that the projected date will be met.<sup>12</sup>

## **9. Health impact of Genzyme's rationing of Fabrazyme®**

No cumulative data on the impact of Fabrazyme® rationing is yet available; however, anecdotal data indicate that patients are struggling and at least one patient may have died due to reduced dosage (Genzyme disputes that the death was due to rationing).<sup>13</sup> In addition, the petitioners have suffered immediate and significant harm due to the rationing. Specifically, Mr. Carik, Ms. Hochendoner, and Ms. Bova have had their dosage cut by 70%. They have had a return of symptoms and are now at far greater risk for cardiac disease and renal failure than before rationing began.

The Petitioners recognize that proof of harm and the extent of that harm may impact the NIH determination of whether march-in provisions should be implemented. However, as the NIH understands, the petitioners' medical records should not be made part of the public record. In balancing these concerns, the petitioners thus agree to provide their medical records upon request for in camera review.

## **10. Statutory background of the Bayh-Dole Act**

The NIH has previously reviewed other petitions for Bayh-Dole march-in rights to date.<sup>14</sup> The NIH determination of the scope of those rights are stated in the NIH response to the petition *In re Norvir*.<sup>15</sup>

Specifically, the stated policy and objective of the Bayh-Dole Act is:

to use the patent system to promote the utilization of inventions arising from federally supported research or development; to encourage maximum participation of small business firms in federally supported research and development efforts; to promote collaboration between commercial concerns and nonprofit organizations, including universities; to ensure that inventions made by nonprofit organizations and small business firms are used in a manner to promote free competition and enterprise without unduly encumbering future research and discovery; to promote the commercialization and public availability of inventions made in the United States

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<sup>11</sup> Douglas and Gryta, 3<sup>rd</sup> Update: Genzyme shortage to last until year end-EMA, Wall Street Journal Online, Business, July 6, 2010, available at <http://online.wsj.com/article/BT-CO-20100706-709873.html>.

<sup>12</sup> Genzyme Corp, communication to Fabry Community, June 30, 2010. Attached Appendix A.

<sup>13</sup> A. Pollack, Genzyme Drug Shortage Leaves Users Feeling Betrayed, New York Times, Business, April 15, 2010 available at <http://www.nytimes.com/2010/04/16/business/16genzyme.html>.

<sup>14</sup> *In re Norvir*, <http://www.ott.nih.gov/policy/March-In-Norvir.pdf> ; *In re* Petition of CellPro, Inc., <http://www.nih.gov/news/pr/aug97/nihb-01.htm>; *In re* Xalatan, <http://www.ott.nih.gov/policy/March-In-Xalatan.pdf>.

<sup>15</sup> NIH Determination of *In Re Norvir*, available at <http://www.ott.nih.gov/policy/March-In-Norvir.pdf>.

by United States industry and labor; 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; and to minimize the costs of administering policies in this area.

*Act at § 200.* Toward this goal, the Act addresses not only rules governing the licensing of Government-owned inventions, but also addresses the rights of Federal contractors to elect title to inventions made with Federal funding. In giving contractors the right to elect title to inventions made with Federal funding, the Act also includes various safeguards on the public investment in the research. For example, the Federal agency retains a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any subject invention throughout the world. See 35 U.S.C. § 202(c)(4). In addition, the Act includes march-in rights which provide a Federal agency with the authority, in certain very limited and specified circumstances, to make sure that a federally funded invention is made available to the public. The march-in provisions are set out in Section 203(a), which states that:

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.

The Department of Commerce regulations implementing the Act and specifying the procedures that govern the exercise of march-in proceedings are set forth at 37 C.F.R. §

401.6. The regulations provide that whenever an agency receives information that it believes might warrant the exercise of march-in rights, it may initiate a march-in proceeding after notification of the contractor and a request to the contractor for informal written or oral comments.

## **11. The patents are “subject inventions” under the Bayh-Dole Act**

The Bayh-Dole Act, 35 U.S.C. § 200 et seq, authorizes the Federal Government to grant licenses to any party to use any patented invention conceived or first actually reduced to practice in the performance of work under a [Federal] funding agreement. 35 U.S.C. § 202(a); 35 U.S.C. 201(e).

As described above, Fabrazyme® was conceived and reduced to practice in performance of grant No. DK-34045 awarded by the National Institutes of Health. The Federal regulations implementing the Bayh-Dole Act require that contractors identify all inventions conceived or reduced to practice in the performance of a Federal grant by including on all patent applications and any patent issuing, the statement: “This invention was made with government support under (identify contract) awarded by (identify the Federal agency). The government has certain rights in the invention.” 34 C.F.R. § 401.14(f)(4).

Patent No. 5,356,804 is licensed to the NIH and states<sup>16</sup>: “This invention was made with Government support under grant No. DK-34045 awarded by the National Institutes of Health. The Government has certain rights in the invention.”

Patent No. 5,580,757 does not have a disclosure regarding government interests on the published patent, although it too is subject to a confirmatory license to the NIH.<sup>17</sup> The NIH RePORT database identifies patent 5,580,757, as one of seven patented inventions associated with NIH core project number R01DK034045. (See Appendix B).

## **12. The inventions are subject to march-in under 35 U.S.C. § 203(a)(2)**

The march-in rights provided in Section 203 of Title 35 of the U.S. Code authorize the funding agency to require the patent assignee or exclusive licensee to grant a license to a responsible applicant or applicants upon terms that are reasonable under the circumstances. If the assignee or exclusive licensee refuses such request, the agency may grant the license itself if it determines that one of several grounds for a march-in exists.

The instant petition is directed to whether action is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or their licensees as provided in 35 U.S.C. Section 203(a)(2). The petitioners wish to alleviate the physical suffering that the rationing has caused and simply desire to restore access to Fabrazyme® to themselves and all of the patients who need it.

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<sup>16</sup> Confirmatory license recorded at Reel/Frame:[020928/0711](http://assignments.uspto.gov/assignments/q?db=pat); available through <http://assignments.uspto.gov/assignments/q?db=pat>.

<sup>17</sup> Confirmatory license recorded at Reel/Frame:[020928/0707](http://assignments.uspto.gov/assignments/q?db=pat); available through <http://assignments.uspto.gov/assignments/q?db=pat>.

### **13. Agency role in determining the health and safety needs of Fabry patients**

The NIH is perfectly situated to access the specific health impact of drug rationing on Fabry patients because it has the agency expertise and access to medical experts who can verify and examine the scope of medical harm that drug rationing has caused. In fact, NIH physicians directly oversee and conduct research on Fabry patients. As stated in the NIH website: “The National Institute of Neurological Disorders and Stroke (NINDS), a component of the National Institutes of Health, conducts and supports research to find ways to treat and prevent lipid storage diseases such as Fabry disease. This research includes clinical studies by the NINDS Developmental and Metabolic Neurology Branch.”<sup>18</sup>

As stated above, the lack of access to Fabrazyme® has directly impacted the health of Fabry patients in the form of increased morbidity, increased hospitalization rates, and increased risk of death. Thus, the petitioners request that in accordance with 37 C.F.R. § 401.6 regarding fact finding that the NIH interview its physicians and review its patient records where available to confirm the adverse impact that the rationing has had. As such, the petitioners earnestly believe a review of NIH’s own records will confirm what the petitioners have found: that rationing of drug has increased suffering, morbidity, and increased hospitalization. Additional affidavits on petitioners’ health state will be submitted upon request and grant of in camera review.

### **14. Genzyme has not satisfied and cannot reasonably satisfy the health and safety needs of Fabry patients by rationing drugs while preventing additional sources of manufacture**

Rationing drugs does not satisfy the health and safety needs of individuals because there is no alternative treatment, and absent rationing all patients would receive their recommended treatment. The Bayh-Dole Act requires that Genzyme reasonably satisfy the health and safety needs of patients, which it has not done.

The term “reasonably satisfied” has not been specifically defined in the context of 35 U.S.C. Section 203(a)(2); however, it is only necessary to examine the definition of “reasonable” to determine its interpretation. Specifically, Black’s Law Dictionary states that “reasonable” is “[f]air, proper, or moderate under the circumstances.”<sup>19</sup> Based on the above construction, Genzyme has failed to reasonably satisfy the health and safety needs of Fabry patients for the following reasons:

- 1) It is an unreasonable, improper, and even catastrophic to limit patient access to a drug where such a limitation causes morbidity and death. The idea that drug access should be limited where there is a way to mitigate or prevent that limitation is anathema to virtually all ethical and scientific principles. Currently, 100% of Fabry patients have either limited access, or no access at all to Fabrazyme® or any alternative treatment. Limiting access instead of encouraging others to make up

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<sup>18</sup> Available at <http://www.ninds.nih.gov/disorders/fabrys/fabrys.htm> (July 19, 2010).

<sup>19</sup> Black’s Law Dictionary (2004, 8<sup>th</sup> ed.).

the shortfall in manufacturing is the worst conceivable public health solution to supply shortages of publically funded inventions.

- 2) It is further unreasonable and unfair to limit patient access to drug where the only impediment to its full production is a patent monopoly that was paid for in part from the tax dollars of the patients themselves. In fact, the exception regarding health and safety concerns in Bayh-Dole Act ensures that patent laws do not trump health and safety concerns. Thus, absent an overwhelming argument that patent exclusivity is more important than drug access (e.g., critical national security concerns), there is no medically or ethically justifiable reason to limit access to Fabrazyme® where a statutory remedy to the rationing exists.
- 3) To the extent that economic policy is to be balanced against the public need, it is further unreasonable to deny march-in rights where the petitioners or other licensees will not compete against the patentee. Specifically, granting march-in rights will not discourage industry investment in drug development, because licensees will normally not ration drug thus avoiding the instant situation altogether. Further, by granting march-in rights, Genzyme's revenues will actually increase since Genzyme sells every dose of Fabrazyme® that it currently manufactures, but only meets 30% of the demand. By being granted march-in rights, the licensee will pay a reasonable 5% royalty rate to Genzyme to sell drug that Genzyme cannot otherwise produce.
- 4) Further it is unwise economic policy (and further unreasonable) to protect, or otherwise favor the licensee where the licensee caused the health crisis in the first place. While there is no specific remedy in the Bayh-Dole Act for licensees with "unclean hands," the drafters never anticipated that a licensee would breach the public trust by limiting access to drug that could otherwise be manufactured. Specifically, the Bayh-Dole Act has operated seamlessly and successfully for the invention of Fabrazyme® until the drug was produced. The only dysfunction in the process has been Genzyme's negligent manufacture of drug and the failure to obey FDA regulations. Thus, where the licensee actually caused the crisis (whether willfully or not), it is inconsistent with the objectives of Bayh-Dole to continue to reward the patentee with further patent exclusivity as it attempts to fix its own mistakes, especially while patients are suffering without a remedy.
- 5) It is unreasonable to deny march-in-rights where it is likely that manufacturers are motivated and encouraged to use the publically funded patent monopoly to shift the economic costs of its errors directly to patients who, in part, funded the invention. Under the current economic strain of FDA fines and capital investment requirements, Genzyme is economically motivated to cover the increased costs by raising the price of Fabrazyme®. Genzyme can engage in "cost shifting" its own negligence by using its patent monopoly power to increase the price of drug to offset any fines and manufacturing losses. Simple economics dictate that decreased supply and increased demand lead to higher prices.

The balance struck in the Bayh-Dole Act between public funding and private development is completely eviscerated where publically funded pharmaceutical/biological inventions can be rationed due to negligence but, ironically, prices can be increased beyond the FDA disgorgement fees to thereby avoid the economic damages caused by that negligence. Thus, the grant of march-in rights assures that Genzyme will not increase prices in response to the FDA fines further vitiating an already grave health crisis to recover lost profits.

- 6) It is unreasonable to deny march-in rights where granting the license would harmonize with FDA actions. Specifically, the FDA has fined Genzyme \$175 million dollars in disgorgement fees for its negligent manufacturing practices.<sup>20</sup> If Genzyme is allowed to use its patent monopoly to shift the cost of the FDA fine to Fabry patients, then the FDA fines have no effect other than increasing the price of already limited drug. Even worse, failure to grant march-in rights after an FDA fine has the net effect of punishing the victims, not the manufacturer. While there is no provision in the Bayh-Dole Act for regulating prices directly, the remedy of march-in rights assures that the patent monopoly from a publically funded invention cannot be misused to undermine FDA punishments for regulatory violations. Specifically, if Genzyme attempts to profiteer from the situation, patients will turn to the march-in licensees for drug. Absent the grant of march-in rights, the FDA fines will have no deterrent effect and, worse, force the victims pay for the manufacturer's breach of regulations. Thus, by granting march-in rights, the NIH can harmonize the Bayh-Dole Act with FDA regulations so that the two bodies of law can work together constructively to address the public health crisis.
- 7) In addition, it is reasonable, prudent, and necessary to allow second sourcing where initial demands cannot be met and/or where market disruptions are likely to continue. Although the current consent decree between Genzyme and the FDA includes oversight, it is clear that the FDA does not trust Genzyme to properly address the manufacturing issues. Given that Genzyme caused the health crisis and needs oversight, it is only prudent to allow a second independent source of production for at least the time that the FDA has oversight and/or the FDA can guarantee full access to the drug. Such second sourcing is common in industries where a market disruption would cause catastrophic consequences as in the computer chip industry. Obviously, the health impact of market supply disruption for pharmaceuticals/biological is far graver than any impact in the computer industry. A second independent source of Fabrazyme® will mitigate any future market disruptions, thereby further ensuring the future health of the American public who has already been catastrophically harmed.

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<sup>20</sup> Weisman, Supervision of 7-8 years ordered for Genzyme: Quality-control problems prompt accord with FDA, Boston Globe, May 25, 2010 available at [http://www.boston.com/business/healthcare/articles/2010/05/25/supervision\\_of\\_7\\_8\\_years\\_ordered\\_for\\_genzyme/?s\\_campaign=8315](http://www.boston.com/business/healthcare/articles/2010/05/25/supervision_of_7_8_years_ordered_for_genzyme/?s_campaign=8315).

- 8) Finally, it unreasonable to argue that inaction is preferable to action where a remedy is available. Specifically, two possible future developments could ameliorate the crisis, the return of normal production of Fabrazyme® (projected in late 2011) and/or the FDA approval of Replagal® (projected date unknown) by Shire pharmaceuticals.<sup>21,22</sup> Either development could restore access to effective enzyme replacement treatment for Fabry patients. Despite the fact that both results are hoped for by the petitioners, there is no guarantee that full access will be restored in the near future. In fact, both developments could be delayed by any number of factors. Absent an ironclad guarantee of success in the very near term for these developments, exercising march-in rights is the only immediate solution to the current problem. Because human health is at stake, it is critical for the Government act immediately to ensure that another alternative exists, even if the need for such an alternative may be hopefully mooted in longer term.

## **15. Grant of march-in rights is consistent with prior march-in determinations**

NIH has reviewed three previous petitions for march-in rights and denied exercise of the rights in each case. However, unlike previous petitions, the current petition is distinguishable for the following reasons.

Regarding interpretation of 35 U.S.C. § 203(a)(2) with regard to In re Cellpro, the NIH stated that reasonably satisfying a health need included “First, refraining from enforcing patent rights” and a pledge “to ensure that the product is as widely available as possible ... and to ensure patient access to the fullest extent possible.” Genzyme has failed to do either.<sup>23</sup>

As an initial matter, despite the ongoing health crisis world-wide, Genzyme has not stated that it will allow others to produce Fabrazyme®. Further, Genzyme’s 10-K states to shareholders that it considers its license to be critical to its assets, which can be inferred to mean that they will actively prosecute infringers.<sup>24</sup> Thus, unlike the Cellpro case, the manufacturer has not indicated it is willing to allow potential infringers to produce drug.

Secondly, in the Cellpro case, it was determined that the product was made as widely available as physically possible and that patient access was ensured to the fullest extent possible. Conversely, Genzyme has, through its own actions, limited access by violating FDA regulations. Further, Genzyme’s ability to manufacture drug is the sole limiting element in providing access. Thus, unlike the Cellpro case, Fabrazyme® access is not provided to the “fullest extent possible.” Rather, access is provided only to the extent

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<sup>21</sup> Replagal® is also an agalsidase enzyme replacement therapy; however, the protein has a different glycosylation pattern because it is produced in human cells.

<sup>22</sup> See Appendix B, Letter to Fabry patients from the Fabry Support and Information Group regarding Replagal® treatment and the current state of the FDA approval process.

<sup>23</sup> In re Cellpro available at <http://www.nih.gov/news/pr/aug97/nihb-01.htm>.

<sup>24</sup> Genzyme Corp, 10-K, 2009, page 17 available online at [http://www.genzyme.com/corp/investors/GENZYME\\_CORP\\_10K\\_20090302.pdf](http://www.genzyme.com/corp/investors/GENZYME_CORP_10K_20090302.pdf).

Genzyme can manufacture drug, which falls woefully short of meeting even one third of the demand.

With regard to *In re Norvir* and *In Re Xalatan*, the NIH refrained from acting based on pricing concerns.<sup>25</sup> In both instances, the NIH determined that patients had reasonable physical access to drug, whether or not they could pay the price charged. In contrast, the instant case involves drastic drug rationing and profoundly limited physical access. There is simply not enough of the drug manufactured to treat everyone who needs it. While economic concerns are involved in the instant case and weigh heavily in favor of granting march-in rights, additional facts distinguish the instant case because physical access to the drug is the primary limiting factor preventing access.

## **16. Immediate action is needed to protect public health**

The Bayh-Dole Act allows march-in rights where there is a public health need. It is unarguable that there is a public health need for additional production of Fabrazyme®. Action by the U.S. Government in this case is necessary to alleviate the harm to the public because the current licensee physically cannot produce enough of the drug to alleviate the public health need. The public health situation is so grave that every remedy possible should be implemented to restore access. In the instant case, the critical public health need can be remedied by granting the request for march-in rights. Moreover, there are no factors weighing against granting the march-in rights since drug companies will not be deterred from licensing public inventions as long as they do not undersupply the market.

## **17. Remedy requested**

The Bayh-Dole Act authorizes the Secretary of the Department of Health and Human Services to require that Genzyme issue licenses under terms that are reasonable under the circumstances and, if Genzyme refuses the request, to grant such licenses itself. 35 U.S.C. § 203(a). The petitioners request that NIH use this authority to require Genzyme to issue an open license for use of the Fabrazyme® patents subject to this petition. The terms of the license should include a reasonable royalty to Genzyme.

## **18. Definition of an open license**

An open license is a non-exclusive license that is available to any petitioner willing to meet standard non-discriminatory terms.

## **19. Right to manufacture and export world-wide**

The open license should include the rights to use the patents to make, sell, use, import or export Fabrazyme® as either a standalone product or as a component. Additionally, the license should include access to the cell line producing Fabrazyme® and any technical know-how developed in conjunction with producing the drug in order to expedite production and reduce duplication of efforts. The license should include the right to export

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<sup>25</sup> *In re Norvir* available at <http://www.ott.nih.gov/policy/March-In-Norvir.pdf> ; *In re Xalatan* available at <http://www.ott.nih.gov/policy/March-In-Xalatan.pdf>.

Fabrazyme® to overseas markets. These rights are necessary to restore access not only in the U.S. but also meet global treatment needs.

## **20. Proposed terms of open license**

The Bayh-Dole requires that march-in licenses include terms that are reasonable under the circumstances. The petitioners propose terms that include a royalty paid directly to the patent holder.

## **21. Royalty to the patent owner**

Specifically, the petitioners propose that the open license provide to the owners of the Fabrazyme® patents a combined royalty of 5 percent of the net sales of the Fabrazyme®. The five percent royalty is roughly equal to the average US pharmaceutical royalty payment, as reported by the pharmaceutical manufacturing sector to the US Internal Revenue Service. This is more than adequate given that each of the patents in question were invented through a government funding agreement, and that Genzyme has earned approximately \$431 million from the sale of Fabrazyme® in 2009 alone.<sup>26</sup>

## **22. Term of license**

According to the consent decree, the FDA will oversee Genzyme's manufacturing of Fabrazyme® for at least seven to eight years. In order to harmonize the march-in rights with FDA oversight and guarantee an independent second source of production during this time, the petitioners request an initial license having an eight year term.

## **23. Conclusion**

The Bayh-Dole Act provides the Federal Government with the tools it needs to address the current public health crisis caused by Genzyme's drug rationing. Petitioners request that the march-in provisions of the Bayh-Dole Act be immediately implemented in order to restore access to critical treatment for Fabry disease victims

Respectfully submitted August 2, 2010,

C. Allen Black, Jr., Ph.D.,  
representing Joseph M. Carik, Anita Hochendoner, and Anita Bova, Fabry disease victims  
who are currently being rationed Fabrazyme®.

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<sup>26</sup> Genzyme press release, January 12, 2010 available at [http://www.businesswire.com/portal/site/genzyme/index.jsp?ndmViewId=news\\_view&ndmConfigId=1019673&newsId=20100112006676&newsLang=en](http://www.businesswire.com/portal/site/genzyme/index.jsp?ndmViewId=news_view&ndmConfigId=1019673&newsId=20100112006676&newsLang=en).

[www.patentlawyersite.com](http://www.patentlawyersite.com)

## **Appendix A – Genzyme communication regarding rationing**

Attached is the most recent communication to the Fabry community from Genzyme describing the rationing of Fabrazyme®.



June 30, 2010

Dear Fabry Community,

The purpose of this letter is to provide you with an update on the supply of Fabrazyme for the next few months, based on the best information we have at this time. In recent communications, we have stated that our supply of Fabrazyme in the coming months could be affected primarily by three factors: the ongoing impact of the production disruptions we reported in April, the effects of preparing to implement the FDA Consent Decree, and the productivity associated with the new Fabrazyme working cell bank. The effects of these factors combined with our low inventory levels mean that shipping delays should be expected until additional manufacturing capacity at our Framingham facility becomes operational (currently anticipated in late 2011), even as we look forward to increasing the overall supply of Fabrazyme.

What this means for US patients in July through September 2010:

- Patients can receive one full dose of Fabrazyme between July 19th and August 31st.
  - We expect orders to be released for fulfillment starting July 15th. Infusions should be scheduled no earlier than July 19th to account for shipping time.
  - Orders fulfilled in July cannot be shipped with an increased ratio of 5 mg vials, because of limited supply of these vials.
  - Beginning August 2nd, we plan to be able to accommodate requests for a higher ratio of 5 mg Fabrazyme vials.
- This dose must be shipped by August 31st as carry over from one shipping period to another will not be possible.
- In late August, we will provide specific details regarding a potential September shipment.
- We do not have sufficient supply of Fabrazyme to support a dose increase for any patient at this time. Please note that Fabrazyme is still not available for new patients to begin treatment during this period.

For support regarding Fabrazyme orders, insurance and billing issues, infusion agency questions, or additional information about the supply of Fabrazyme, healthcare providers and patients should contact their Genzyme Case Manager at 1 (800) 745-4447, Option 3 or Medical Information at 1 (800) 745-4447, Option 2.

This information gives our best estimate of Fabrazyme supply at the current time. Since we continue to work with extremely limited inventory, even minor changes to our current manufacturing plan can impact our ability to supply Fabrazyme. We

appreciate the Fabry community's ongoing patience as we work to resume more regular supply of Fabrazyme.

Sincerely,

Daniel Gruskin, MD  
Senior Director, US & Global Medical Affairs

Pamela di Cenzo, Vice President  
Patient & Product Services, PGH

## Appendix B– Patents associated with Federal grants on Fabry Disease

Attached is a report of patents associated with grants on Fabry's Disease, based upon July 22, 2010 search of NIH RePORT.

Patents associated with NIH grants on Fabry's disease July 22, 2010 search of NIH RePORT		
Core Project Number	Patent Number	Patent Title
M01RR000037	7138389	Oral androgen therapy using modulators of testosterone bioavailability
M01RR000039	6228839	Use of keratinocyte growth factor to improve oxidative status
M01RR000188	7160676	Method of determining sperm capacitation
M01RR000833	5106837	Adenosine derivatives with therapeutic activity
M01RR000833	5234811	Assay for a new Gaucher disease mutation
M01RR000833	5271931	Methods for increasing C1 inhibitor concentrations using interferon-gamma and/or interleukin-6
M01RR000833	5424296	2-Halo-2'-deoxyadenosines as therapeutic agents against malignant astrocytoma
M01RR000833	5506214	Use of substituted adenine derivatives for treating multiple sclerosis
P41RR002594	5280788	Devices and methods for optical diagnosis of tissue
P41RR002594	5312396	Pulsed laser system for the surgical removal of tissue
P41RR002594	5419323	Method for laser induced fluorescence of tissue
P41RR002594	5452723	Calibrated spectrographic imaging
P41RR002594	5562100	Method for laser induced fluorescence of tissue
P41RR002594	5919140	Optical imaging using time gated scattered light
P41RR002594	6321111	Optical imaging using time gated scattered light
P41RR002594	6404497	Polarized light scattering spectroscopy of tissue
P41RR002594	6537211	Fluorescence imaging endoscope
P41RR002594	6611339	Phase dispersive tomography
P41RR002594	6624890	Polarized light scattering spectroscopy of tissue
P41RR002594	6690966	Methods of molecular spectroscopy to provide for the diagnosis of tissue
P41RR002594	6697652	Fluorescence, reflectance and light scattering spectroscopy for measuring tissue
P41RR002594	6697665	Systems and methods of molecular spectroscopy to provide for the diagnosis of tissue
R01DK034045	5356804	Cloning and expression of biologically active human alpha-galactosidase A
R01DK034045	5382524	Cloning and expression of biologically active alpha-n-acetylgalactosaminidase

<b>Patents associated with NIH grants on Fabry's disease July 22, 2010 search of NIH RePORT</b>		
R01DK034045	5401650	Cloning and expression of biologically active alpha-galactosidase A
R01DK034045	5491075	Cloning and expression of biologically active alpha-N-acetylgalactosaminidase
R01DK034045	5580757	Cloning and expression of biologically active alpha-galactosidase A as a fusion protein
R01DK034045	6455037	Cells expressing an alpha gala nucleic acid and methods of xenotransplantation
R01DK055823	7148251	Amino ceramide-like compounds and therapeutic methods of use

## **Appendix C – Fabry Support and Information Group communication regarding the state of the crisis**

Attached is a letter from the director of the Fabry Support and Information Group detailing the current state of the crisis and measures currently being undertaken to restore access to treatment.



## Fabry Support & Information Group

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7/8/2010

Dear Fabry Community,

As most of you are aware the ongoing Fabrazyme® shortage is having a severe impact on the Fabry community and unfortunately is likely to continue for at least another year. As reported in the recent FSIG Connection newsletter much needed relief came from Shire HGT through their FDA approved Treatment Investigational New Drug (tIND) protocol (HGT-REP 059) designed to allow U.S. patient's early access to Replagal®.

This protocol was in direct response to the Fabrazyme supply shortly. Shortly after printing the newsletter FSIG was informed by Shire HGT of an amendment to the HGT-REP 059 tIND protocol.

There has recently been an overwhelming interest in this US treatment protocol by Fabry-patients and physicians. Due to this unprecedented demand coupled with uncertainty in any regulatory submission, Shire has decided to amend the current U.S. treatment protocol to limit the number of patients participating in this program.

What does this mean?

- All existing enrolled patients will be able to continue treatment at the full dose of Replagal as expected.
- All patients that have begun the pre-treatment screening process will be able to continue and receive treatment at the full dose of Replagal as expected.
- No new additional Fabry patients will be allowed to enroll into the HGT-REP 059 tIND protocol as of 6/25/10.

However, the Emergency Treatment Investigational New Drug (eIND) protocol is a treatment option which remains in effect for Fabry patients who qualify for this protocol.

We are grateful that Shire HGT has been able to respond to the needs of Fabry patients and provide Replagal to a large number of patients in the US through their early access program and we regretfully understand that they cannot provide access to all US patients still wanting treatment with Replagal.

I know this news will be disheartening to those who were undecided and considering the treatment protocol with Replagal. Before the extremely unfortunate manufacturing difficulties struck Genzyme, it took both Genzyme and Shire to meet the needs of the worldwide Fabry community and it is going to take the full efforts of both companies to meet those needs again.

FSIG is confident in Genzyme's ability to restore full supplies of Fabrazyme, but with uncertainty about when this will occur combined with shipment irregularity additional action is crucial for those in the U.S. with no other option for treatment with enzyme replacement therapy (ERT).

**Fabry Support & Information Group, 108 NE 2<sup>nd</sup> St., PO Box 510, Concordia, MO 64020**

**Web Site: [www.Fabry.org](http://www.Fabry.org) E-mail: [Info@Fabry.org](mailto:Info@Fabry.org)**

**phone (660) 463-1355 fax (660) 463-1356**

FSIG is asking for your help in this effort. Enclosed is a letter to the Associate Director for Rare Diseases at the FDA. The letter highlights the key points in this matter and will focus attention on the need for swift approval of Replagal. FSIG sees this as the most immediately available avenue and responsible course of action to alleviate the shortage of ERT for the treatment of Fabry disease for the U.S. patient population.

Please feel free to add any additional comments you may have. If you are a patient now on Replagal or a medical professional caring for those on Replagal and have a positive story to add this may also be of help. Please sign, date and mail this letter and add your voice to the combined voice of the Fabry community.

FSIG has a long standing history of supporting the option of choice in the care and treatment of Fabry disease. Hopefully this same desire expressed by the Fabry patient community will soon be realized.

Sincerely,

A handwritten signature in cursive script that reads "Jack Johnson".

Jack Johnson,  
Executive Director,  
FSIG

**Fabry Support & Information Group, 108 NE 2<sup>nd</sup> St., PO Box 510, Concordia, MO 64020**  
**Web Site: [www.Fabry.org](http://www.Fabry.org) E-mail: [Info@Fabry.org](mailto:Info@Fabry.org)**  
phone (660) 463-1355 fax (660) 463-1356

Dr. Anne Pariser  
Associate Director for Rare Diseases, OND, CDER, FDA  
10903 New Hampshire Avenue  
Building WO22, Room 6474  
Silver Spring, MD 20993

Dear Dr. Pariser,

I am forwarding this letter to you to advocate for the rights of individuals suffering with Fabry disease. As I am sure you are aware the care and treatment of Fabry disease patients has been greatly compromised as the result of the unfortunate reduction in supply of agalsidase beta (Fabrazyme®) produced by Genzyme.

You are probably also aware of an alternate product, agalsidase alpha (Replagal®) produced by Shire Human Genetic Therapies, Inc. (Shire HGT) that is currently under biologics license application (BLA) review at the request of the FDA. This was followed by the development of a Treatment Investigational New Drug (tIND) protocol (ClinicalTrials.gov identifier: NCT01031173) and an Emergency IND (eIND) protocol to allow early access to Replagal reducing some of the hardship resulting from the Fabrazyme shortage.

Access to these two treatment protocols has been encouraging and has offered vitally needed relief. However, since the tIND has recently closed to new patients that relief has been limited. It has become all too apparent that adequate supply of Fabrazyme will not be reestablished in the near term and will remain in jeopardy for the minimum of another year.

The value of Replagal has been established with nearly nine years of safety and efficacy data since its approval by the European Medicines Agency (EMA) and its use throughout Europe as well as many other countries.

I support this initiative to request urgently needed action for the granting of FDA marketing authorization for Replagal. I believe this to be the most responsible course of action to fulfill the desperate need for enzyme replacement therapy for the treatment of this disabling and life threatening disease.

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Additional Comments: \_\_\_\_\_

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