

1579 Montgomery Rd.
Allison Park, PA 15101
412-908-3268
allenblack@patentlawyersite.com

Mark Rohrbaugh, Ph.D., J.D.
Office of Technology Transfer
National Institutes of Health
6011 Executive Boulevard
Rockville, Maryland 20852

RE: Petition for Rehearing and Rulemaking Regarding *In the Case of Fabrazyme*,
Decided December 1, 2010

Dear Dr. Rohrbaugh:

Enclosed is a petition for rehearing and rulemaking regarding *In the Case of Fabrazyme*. The petition is based on new information from Genzyme as of March 25, 2011 indicating that it is not making progress in restoring the supply of Fabrazyme® as it originally represented to the NIH. The NIH stated in its original determination that it would revisit the petition upon receiving such information.

The instant petition also requests that the NIH promulgate rules regarding march-in so that the harm to patients from future supply disruptions to any life-saving Bayh-Dole invention can be mitigated. The original petitioners are joined by additional U.S. Fabry patients and their spouses, who are available to discuss their injuries during the shortage. Given the severity and grave nature of the latest delay by Genzyme, expedited review is requested.

Sincerely,



C. Allen Black, Jr., Ph.D.
Counsel for Petitioners

PETITION FOR REHEARING AND RULEMAKING REGARDING
IN THE CASE OF FABRAZYME® Decided December 1, 2010

April 5, 2011

Petitioners:

Joseph M. Carik, Barbara Carik, Michael Masula, Erin Masula, Anita Hochendoner, Earl Hochendoner, Anita Bova, Thomas Olszewski, Darlene Cookingham, David Roberts, Shawn Britton, Cheryl Britton, and Amber Britton

Represented By
C. Allen Black, Ph.D., J.D.
1579 Montgomery Rd.
Allison Park, PA, 15101
412-908-3268

Before the
Department of Health and Human Services
National Institutes of Health
Washington, DC

PETITION FOR REHEARING)
AND RULEMAKING REGARDING)
IN THE CASE OF FABRAZYME®) Docket No. _____
DECIDED DECEMBER 1, 2010)
)
)
)
)
)
)
)

April 5, 2011

Mark Rohrbaugh, Ph.D., Director,
Office of Technology Transfer
National Institutes of Health
6011 Executive Boulevard
Rockville, Maryland 20852

PETITION

The undersigned counsel submits this petition on behalf of Joseph M. Carik, Barbara Carik, Michael Masula, Erin Masula, Anita Hochendoner, Earl Hochendoner, Anita Bova, Thomas Olszewski, Darlene Cookingham, David Roberts, Shawn Britton, Cheryl Britton, and Amber Britton to the National Institutes of Health “NIH” to rehear the case *In The Case of Fabrazyme* decided December 1, 2010 and engage rulemaking to prevent future undersupply of Bayh-Dole inventions and compensate those citizens that are injured by such undersupply by allocating Bayh-Dole royalties to mitigate suffering.

I. ACTION REQUESTED

The undersigned on behalf of the petitioners requests that the Secretary of Health and Human Services initiate march-in due to Genzyme's new policy of allocating drug away from U.S. citizens in favor of overseas patients and in light of Genzyme's latest manufacturing failure reported on March 25, 2011. 35 U.S.C. § 203(a)(2). Petitioners further request the recusal of any Health and Human Service administrators that may have a financial interest in Bayh-Dole royalties.

Independent of the rehearing request, the petitioners also request rulemaking regarding the agency's response to situations where misuse of a Bayh-Dole invention results in (or could reasonably result in) undersupply of the invention at the cost of human health and life. There is currently no administrative guidance as to when, if ever, march-in should be initiated under the Bayh-Dole act.

II. STATEMENT OF GROUNDS

A. Interests of the parties

Joseph M. Carik, Michael Masula, Anita Hochendoner, Anita Bova, Thomas Olszewski, David Roberts, Shawn Britton, and Amber Britton are private U.S. citizens who have Fabry disease. Barbara Carik, Earl Hochendoner, Cheryl Britton, and Erin Masula are spouses of the listed Fabry patients. For almost two years, no patients in the U.S. have been given the prescribed dosage due the patentee's and licensee's inability to produce enough drug to treat all of the Fabry's patients that have been prescribed

Fabrazyme®.¹ Instead of licensing others to produce the drug or even turning over allocation decisions to public health professionals such as the FDA, Genzyme Corporation instituted across-the-board rationing. Genzyme reduced the dose for all patients being treated to less than one-third of the required dose as of June 2009 and banned subsequently diagnosed patients from receiving the drug. Within the past two months, the dose was increased to 50% and some new patients were allowed to receive this dose. However on March 25, 2011, Genzyme announced having to destroy another lot of Fabrazyme® due to manufacturing errors.² As a result, further rationing, ban of access, and delays are expected.

Fabrazyme® is a medically necessary drug and no alternative treatment is available in the U.S.³ Genzyme's lowered dose of Fabrazyme® is untested and not FDA approved. The European Medicines Agency has found that the lowered dose is dangerous (accelerates disease) and non-efficacious (most patients have had a severe return of symptoms including increased risk of heart attack, stroke, and renal failure).⁴ (Attached as Exhibit 1). Notably, a minority of patients were found to tolerate the low dose; however, the petitioners having Fabry disease, like most patients, are not in that lucky few. Consequently, U.S. Fabry disease patients face imminent and ongoing harm.

¹ As discussed in *In the Case of Fabrazyme* (decided December 1, 2010) Mt. Sinai Medical Center holds patent no. 5,356,804, which is licensed to Genzyme Corp. to manufacture Fabrazyme®, an invention funded by NIH grant no. DK 34045. The original march-in petition is incorporated by reference in its entirety.

² See, 03/23/2011 statement at <http://supplyupdate.genzyme.com/weblog/fabrazyme/>

³ See, <http://www.fda.gov/drugs/drugsafety/drugshortages/default.htm>. Fabrazyme® is used to treat a serious disease and there is no other available source of that product or alternative drug or therapy that is judged to be an adequate substitute.

⁴ EMA Assessment Report for Fabrazyme® available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/11/WC500099241.pdf

B. Procedural posture

Mr. Carik has previously requested that the NIH grant an open license under the Bayh-Dole act for other parties to manufacture agalsidase beta in order to alleviate the shortage and provide a second source of manufacture to mitigate future shortages. *In the Case of Fabrazyme*® (NIH, decided Dec. 1, 2010).⁵ Ms. Amber Britton formally supported the petition. The additional petitioners join in the instant request.⁶

On December 1, 2010, the march-in petition was denied by the NIH citing the FDA regulations as the primary obstruction to a new manufacturer entering the market to alleviate the shortage under a march-in license. *Id.* Specifically, the NIH stated that “[n]o remedy that is available under the march-in provision would address the problems identified by the requestors... because years of clinical studies would be required before an alternative source could be approved by the FDA.” *Id.* at 9.

C. Jurisdiction

NIH has kept the Fabrazyme® case open specifically where new information is presented for consideration. *Id.* at 2. This petition presents new facts and issues for rehearing that were not addressed in the original petition.

Independent of the rehearing request, the petitioners also request that regulations be promulgated. It is vital to human health and safety for the NIH to provide guidance as to when and how the remedy of march-in would apply for Bayh-Dole inventions

⁵ *In the Case of Fabrazyme* (NIH, decided Dec. 1, 2010) is available at <http://www.ott.nih.gov/policy/March-in-Fabrazyme.pdf>

⁶ Petitioners also have filed suit against Genzyme Corporation and Mt. Sinai Medical Center, Western District of Pennsylvania, Case 2:05-mc-02025 Document 292 Filed 03/09/11. Joseph Carik and Amber Britton filed a Citizen Petition with the FDA on 01/19/2011 assigned docket no. FDA-2011-P-0055-0001/CP to prevent further export of Fabrazyme®.

regulated by the FDA because the sole express statutory remedy for non-use and unreasonable use of Bayh-Dole inventions is march-in.⁷ Thus, where march-in is not available, the burden rests on the NIH to promulgate regulations that would prevent such a deadly disruption from happening again for any Bayh-Dole invention.

II. REQUEST FOR REHEARING REGARDING NEW FACTS

A. Genzyme's testimony to NIH regarding when the supply would be restored was factually untrue

The previous decision for march-in rested on “facts” that are now known to be untrue. The NIH stated that it will “re-evaluate this determination immediately upon receiving any information that suggest progress toward restoring the supply of Fabrazyme® to meet patient demand is not proceeding as represented.”⁸ By its own admission, Genzyme has misrepresented to the NIH when the shortage would be rectified.

The NIH decision rested on Genzyme's statement that the shortage would end by first half of 2011.⁹ However, Genzyme has since revised its “promise” to now restore the supply in the second half 2011. At this point, it would be irrational to give any weight to any subsequent “predictions” by Genzyme as to when the shortage will end because all predictions by Genzyme have been unreliable. As such, the statement to NIH to restore the supply by the first half of 2011 was clearly not made in good faith.

Specifically, Genzyme promised the NIH that a full supply of Fabrazyme® would be available in the first half of 2011, but this is now known to be untrue. In fact, this is

⁷ 35 U.S.C. § 200 *et seq.*

⁸ *In the Case of Fabrazyme*, p. 2 (NIH, decided Dec. 1, 2010)

⁹ *Id.* at 9.

the ninth consecutive time that Genzyme has pushed back its projections in order to stave off intervention. The NIH must now presume, for the protection of Fabry patients, that Genzyme will de facto never be able to reliably supply Fabrazyme®. As such even if it takes years to establish, the licensing another manufacturer to provide a second source of Fabrazyme® is the only rational approach left to protect the safety of the American people.

In support, petitioners present a timeline of Genzyme's unending misrepresentations to patients, investors, and now the NIH:

June 24, 2009: "The company currently expects the period of shortage for Cerezyme and Fabrazyme to last approximately 6-8 weeks. This period is expected to begin in August for Cerezyme and in October for Fabrazyme." ¹⁰

July 22, 2009: "Genzyme has now completed the sanitization of the Allston facility and is on-track to resume production of both drugs there this month. Genzyme expects new Cerezyme and Fabrazyme supply from Allston by the end of the year." ¹¹

October 21, 2009: "Genzyme has completed the first production cycles for Fabrazyme, is preparing to begin the next, and anticipates that the first shipments of new Fabrazyme will take place in late-December. The company expects that it will be able to fully meet anticipated demand for these therapies in the first quarter of 2010." ¹²

February 22, 2010: "[W]e have not achieved the expected Fabrazyme inventory level needed to support our goal of meeting 70% of global demand in April. We have taken steps to increase and stabilize the production of Fabrazyme and if these efforts are

¹⁰ See <http://supplyupdate.genzyme.com/weblog/archives.html>

¹¹ *Id.*

¹² *Id.*

successful, we anticipate that we will be able to increase Fabrazyme availability to patients for the second half of 2010.”¹³

April 21, 2010: “Genzyme has made progress in increasing the productivity of the Fabrazyme manufacturing process. The first run of a new working cell bank (WCB) resulted in a 30 percent increase in productivity, and a second run is underway. Genzyme’s goal is to increase productivity an additional 30 percent. Genzyme estimates that it will need to continue the 30 percent shipping allocation through the third quarter.”¹⁴

July 21, 2010: “We do expect that supply will change in a meaningful way by the end of September, and in the October through December 2010 time period additional supply will be available to support increases in Fabrazyme dose or infusion frequency.”¹⁵

December 1, 2010: “Genzyme has expressed its commitment to provide a full supply of Fabrazyme® in the first half of 2011.”¹⁶

March 25, 2011: “[w]e want to assure you that we are still on track to return to normal supply of Fabrazyme in the second half of 2011 with the expected approval of our new manufacturing facility in Framingham, Massachusetts.”¹⁷ (Attached as Exhibit 2)

B. Genzyme is now reducing access of Fabrazyme® to U.S. citizens in favor of overseas patients

On March 25, 2011, Genzyme issued its latest supply report to Fabry patients (attached as Exhibit 1). The report states: "Still, in order to help share the impact of this

¹³ *Id.*

¹⁴ *Id.*

¹⁵ *Id.*

¹⁶ *In the Case of Fabrazyme*, p.10 (NIH, decided Dec. 1, 2010) available at <http://www.ott.nih.gov/policy/March-in-Fabrazyme.pdf>

¹⁷ See <http://supplyupdate.genzyme.com/weblog/archives.html>

loss, some Fabrazyme that was originally destined for patients treated in the U.S. will be diverted to patients elsewhere." *Id.* This change in corporate policy is highly material to whether march-in is necessary to protect the health and safety of American citizens.

The stated motive to "share the loss" is disingenuous and contradicts the NIH conclusion that Genzyme is "diligently" trying to restore access of the drug to U.S. citizens.¹⁸ Replagal®, manufactured by Shire Pharmaceuticals, is available to overseas patients as an alternative to Fabrazyme® unlike in the U.S. In fact, the European Medicines Agency has recommended that patients switch to Replagal® from the low dose of Fabrazyme®.¹⁹ Shire has been able to meet the demand for Fabry patients that switch from Fabrazyme® and has shown that it is safe to switch.²⁰ However, Genzyme has lost significant market share overseas and patients that have switched to Replagal are unlikely to switch back to Fabrazyme®.

Thus, the diversion of drug away from U.S. patients appears to be motivated by retaining market share overseas. If Shire is able to absorb the patients that Genzyme is losing, then there is no public health advantage to reducing doses of U.S. citizens. In fact the reallocation is a perverted result of giving Genzyme a patent monopoly in the U.S. but not overseas. Americans have no alternative drug available, but Europeans do. Thus, Genzyme is attempting to compete in the European market by divesting the captive U.S. market of Fabrazyme® absent any health or safety reason.

Obviously, the only way to protect U.S. citizens from Genzyme's reallocation plan is to allow another manufacturer to supply the U.S. market. As Genzyme loses more market share in Europe, it will continue to be highly motivated to divest even more drug

¹⁸ *In the Case of Fabrazyme*, p.2 (NIH, decided Dec. 1, 2010)

¹⁹ *Id.* at 5.

²⁰ See <http://www.shire.com/shireplc/en/investors/investorsnews/irshirenews?id=459>

from U.S. patients in order to maintain market share overseas, even if Replagal® is approved in the U.S. As such, march-in is absolutely required to protect U.S. citizens in the current situation.

C. Genzyme has caused of two other recent drug shortages

Specifically, Genzyme announced on March 23, 2011 that it cannot supply enough Thyrogen® to treat all of the thyroid cancer patients.²¹ Thyrogen® is also a Bayh-Dole invention. Thyrogen is protected by U.S. Patent No. 5,840,566, which is licensed from Sloan-Kettering Institute for Cancer Research. The invention was made with support under Grant number CA-23185 from the National Institutes of Health, U.S. Department of Health and Human resources. It is sincerely hoped that the NIH knew of this shortage prior to the instant petition. However, if it did not, then the NIH should immediately implement oversight of Sloan-Kettering as it did with Mt. Sinai and further consider march-in for this drug as well since the shortage appears to be due to the same underlying manufacturing problems as Fabrazyme®.

On January 21, 2011 Genzyme announced that it had rectified the year long shortage of Cerezyme® which is used to treat Gaucher's disease, another lysosomal storage disorder.²² Genzyme stated that patients were still not entirely safe, though. "We are still working on rebuilding the inventory of Cerezyme that we need to ensure that this type of supply shortage does not happen again."²³ The Cerezyme® shortage was similarly due to the underlying manufacturing problems that also caused shortages of Fabrazyme® and Thyrogen®

²¹ See <http://www.thyrogen.com/pdfs/supplyupdate-2011.pdf>

²² <http://supplyupdate.genzyme.com/weblog/cerezyme/>

²³ *Id.*

Thus, Genzyme has created no less than three recent drug shortages. Such a consistent, ongoing, and widespread inability to provide patients with drug access across many critical drug markets should demonstrate conclusively to the NIH that trusting Genzyme to be the sole source of manufacturing for any life-saving drug is not only irrational but also likely deadly to American citizens.

D. Denying march-in is now irrational in the current situation

The Bayh-Dole act states that “It is the policy and objective of the Congress... [to] protect the public against nonuse or unreasonable use of inventions....” 35 U.S.C. §200. The only express remedy Congress provides in the Bayh-Dole act for nonuse and unreasonable use of an invention is march-in. 35 U.S.C. § 203(a)(2). While the text of the statute is permissive regarding when march-in may be exercised by a funding agency, it is irrational for the NIH to interpret the statutory remedy march-in as being unworthy of trying in the current situation.

First, use of low dose Fabrazyme® that has been untested by the FDA meets the criterion of “unreasonable use” of an invention under the Bayh-Dole act. Secondly, the ban of access of the drug to American citizens is per se “non-use” of the invention. The NIH does not dispute that Genzyme violated the Bayh-Dole act’s prohibition of unreasonable use and non-use of publicly funded invention.

Instead, the NIH states that if the march-in license was granted then it “is unlikely to increase (emphasis added) the supply of alpha-galactosidase A... because years of

clinical studies would be required before an alternative source could be approved by the FDA.”²⁴ This conclusion is incorrect for the following reasons:

1) The NIH decision incorrectly frames the problems facing Fabry patients as being limited to increasing the immediate short-term supply of Fabrazyme®. The NIH misunderstands the scope of the problem facing patients. Specifically, the underlying and far more dangerous problem than a single shortage is that there is only one source of drug manufacture. As a consequence, any manufacturing disruption (whether due to negligence, natural disaster or bankruptcy) has a catastrophic and deadly impact on patients as seen in the instant case. Also as seen in the instant case, Genzyme is highly motivated to divert drug into competitive markets away from U.S. patients. There is simply no safety net for the American people. Thus, march-in is required to ensure that any future disruptions of supply are mitigated by a second source of manufacture of the drug. It would be irrational to assume that even if Genzyme rectifies the short term shortage, it will be also be able to guarantee an uninterrupted supply over the term of the patent.

Fabry patients have already suffered and died because there is no second supplier of Fabrazyme®. Thus, no matter when the current shortage is “fixed,” Genzyme has demonstrated that it cannot ensure the safety of the American people. It is unconscionable to continue to place these patients’ lives solely in the hands of the exact same manufacturer that has already harmed them, especially when the Bayh-Dole remedy of march-in could protect these Americans from another supply disruption from Genzyme. After a contractor has breached the public trust so profoundly, it is irrational

²⁴ *In the Case of Fabrazyme*, p. 9 (NIH, decided Dec. 1, 2010)

to ignore Congressional guidance and deny these patients a second source of manufacture that can prevent or mitigate future supply chain interruptions that are likely to occur.

2) The NIH decision was predicated on an illogical belief that there is a conflict of law between the Bayh-Dole act and the Food, Drug and Cosmetics Act “FDCA”, both of which are designed to save lives, not sacrifice them. By pitting the two statutes against each other, the NIH has asserted that it is impossible to both “protect the public against nonuse or unreasonable use of inventions” mandated by the Bayh-Dole act and ensure a safe drug supply under the FDCA.²⁵ Such an interpretation of the Bayh-Dole act is irrational. There should be no toleration by the NIH for any manufacturer that violates the Bayh-Dole act whether or not the invention is regulated by the FDA as well. By failing to grant march-in, the NIH is rewarding Genzyme with ongoing monopolistic profits even after it has expressly violated the Bayh-Dole act and breached the public trust.

3) The NIH exceeds its jurisdiction in attempting to interpret FDA regulations as rendering march-in futile. Specifically, the FDA has broad powers under the FDCA to protect the health of American citizens, especially during a health crisis. If the NIH is truly concerned about the conflict between the FDCA and the Bayh-Dole act then it should request an opinion from the FDA establishing as a factual matter how long it would likely take for emergency approval of a second manufacturer for Fabrazyme®. The FDA has intimate knowledge of the manufacturing problems at Genzyme under its consent decree. Thus, the FDA’s input is invaluable. Instead, the NIH cynically presumes that the FDA cannot act expeditiously under the FDCA or its consent decree during this nationwide health crisis.

²⁵ 35 U.S.C. § 200

4) The uncertain future of the industry with regard to “alternative treatments” supports initiating march-in.²⁶ While the NIH may be “encouraged that the world-wide supply of drugs or biologics will increase in the long term,” none of these treatments are guaranteed to succeed in treating Fabry disease; whereas, Fabrazyme® is. The only way the future for Fabry patients can be secured is by having Fabrazyme® available if these treatments fail.

It is irrational to exclude a second source of Fabrazyme® to gamble on the success of untested treatments. It is a fact that Fabrazyme® at its correct dose is relatively safe and effective. Conversely, there are no facts which indicate which of the alternative drugs will be safe and efficacious, much less a suitable replacement for Fabrazyme®. Thus, every effort should be made to ensure a reliable supply chain of Fabrazyme® until such treatments come to market. Therefore, the solution to the current problem is to create a second source of Fabrazyme®, not simply hope that new treatments make it to market.

5) Refusing march-in during a health crisis is not in the best interest of patients. The NIH states that its mission is “protecting and improving health.”²⁷ However, the NIH fails to describe how denying march-in protects or improves the health of patients. The NIH decision simply states that march-in is unlikely to increase the supply of Fabrazyme® during the term of the patent.²⁸ Ironically, by refusing march-in, the chance that patients might be helped by a second supplier drops from being unlikely to assuredly.

²⁶ *In the Case of Fabrazyme*, p. 7 (NIH, decided Dec. 1, 2010)

²⁷ See <http://www.nih.gov/about/mission.htm>

²⁸ *Id.* at 9.

Moreover, the NIH reduces the Bayh-Dole act remedy of march-in to a cruel calculus, in which dying patients must demonstrate a likelihood of success before the NIH will act. Congress provided a statutory remedy. Congress did not require an agency to only implement the remedy when the odds of success are high. The NIH has reached an irrational conclusion that it is in the best interest of patients to not license the invention, even though it admits that march-in could perhaps help patients.

Thus, the burden is properly on the NIH to prove that it is in the best interest of patient's health to deny march-in. The NIH has not proffered any evidence that march-in would be detrimental to Fabry patients. Instead the NIH is asking dying patients to undertake an economic analysis of the Fabrazyme® market, provide a patent invalidity (or validity opinion) in anticipation of Hatch-Waxman litigation, contact manufacturers regarding the analysis, subsequently solicit manufacturer and investor support, and generate clinical data under the safe-harbor provision of the Hatch-Waxman act so that a manufacturer is "ready" to step in under march-in when a supply disruption occurs. Placing such a burden on dying patients who as taxpayers paid for the invention, paid the monopolistic prices, and now are paying the ultimate price with their lives is simply unconscionable.

6) Denying march-in because no company is currently "ready" to step in undermines the Congressional intent of the Bayh-Dole incentives. The NIH has improperly created a procedural barrier to letting additional manufacturers enter the market by requiring that a manufacturer "be ready" to supply the invention before such a party will be considered for a license. Such a barrier is irrational because it creates a Catch-22 situation that Congress never intended: without a license there is no financial

motive to invest in the clinical research to enter the market, but to enter the market a manufacturer must first invest in the clinical research to have a chance of obtaining a license. Even more daunting is that 21 U.S.C. § 355 clearly states that it is an act of infringement to file a new drug application on a validly patented invention. Thus, absent a license, even if a company invests in clinical research under safe harbor, it will still face patent infringement litigation which it will likely lose, absent a march-in license, which has never been granted in the 30 year history of the Bayh-Dole act. The “readiness” requirement thus deters manufacturers from entering the market instead of promoting entry as Congress intended.

Undertaking clinical research is extremely expensive and without a guarantee that the company will not be sued under Hatch-Waxman when the Abbreviated New Drug Application “ANDA” is filed, manufacturers are understandably deterred from engaging in clinical research in the first place. However, the NIH asks manufacturers to “be ready with clinical data before the NIH will consider march-in” even though no rational businessman would recommend investing in such research until there is a license in place.²⁹ Thus, by interpreting a “readiness” prerequisite into the Bayh-Dole act, the NIH has effectively eliminated the incentive scheme that Congress devised with march-in.

III. REQUEST REHEARING REGARDING NEW PROCEDURAL ISSUES

A. The NIH Decision incorrectly assumed that because manufacturers did not have a pending research for filing an Abbreviated New Drug Application, no qualified party is available to manufacture Fabrazyme®

²⁹

Specifically, the NIH stated that it has no information that suggests a “qualified third party is ready to supply” Fabrazyme®, but will consider future license requests to manufacture Fabrazyme®.³⁰ The adjudication, however, was not subject to notice and comment. If the NIH is seriously considering licensing the patent, it has a duty to make the public aware of its desire to license the invention to the widest extent possible. Requests for proposals for research grants that lead to Bayh-Dole inventions are published in the Federal Register, so it is completely irrational not to similarly publicize requests for licensees of these inventions, especially when human lives are at stake. Absent a notice and comment period, it will be impossible for the NIH to distinguish between manufacturer disinterest versus simple lack of notice.

B. The appearance of a potential conflict of interest exists in the NIH adjudication of In the Case of Fabrazyme®

In the Case of Fabrazyme® was decided by Dr. Francis Collins. While the petitioners recognize and appreciate the efforts of Dr. Collins as a scientist, humanitarian, and an administrator, Dr. Collins is also an inventor of at least nineteen inventions in which Bayh-Dole royalties apply.³¹ It appears from the public record that Dr. Collins

³⁰ *In the Case of Fabrazyme* p.9. (Decided December 1, 2010)

³¹ (U.S. Patent No. 7,838,531; Farnesyltransferase inhibitors for treatment of laminopathies, cellular aging and atherosclerosis); (U.S. Patent No. 7,358,347; MEN1, the gene associated with multiple endocrine neoplasia type 1, menin polypeptides and uses thereof); (U.S. Patent No. 7,297,492 ; LMNA gene and its involvement in Hutchinson-Gilford Progeria Syndrome (HGPS) and arteriosclerosis); (U.S. Patent No. 6,984,487; Cystic fibrosis gene); (U.S. Patent No. 6,902,907; Cystic fibrosis gene); (U.S. Patent No. 6,730,777; Cystic fibrosis gene); (U.S. Patent No. 6,627,745; Pyrin gene and mutants thereof, which cause familial Mediterranean fever); (U.S. Patent No. 6,342,355; Probe-based analysis of heterozygous mutations using two-color labeling); (U.S. Patent No. 6,238,861; Neurofibromatosis gene); (U.S. Patent No. 6,201,107; Cystic fibrosis gene); (U.S. Patent No. 6,013,449; Probe-based analysis of heterozygous mutations using two-color labeling); (U.S. Patent No. 5,869,611; Markers for detection of chromosome 16 rearrangements); (U.S. Patent No. 5,859,195; Neurofibromatosis gene); (U.S. Patent No. 5,837,457; Markers for detection of chromosome 16 rearrangements); (U.S. Patent No. 5,777,093; cDNAs associated with ataxia-telangiectasia); (U.S. Patent No. 5,776,677; Methods of detecting cystic fibrosis gene by

either receives compensation or expects to receive compensation through the Bayh-Dole grant of statutory royalties in at least some of these inventions.

The adjudication process of *In the Case of Fabrazyme*® had at least the appearance of a conflict of interest because the decision was made by a financial stakeholder in the revenue of Bayh-Dole inventions. Again, while the petitioners do not question the skill and dedication of Dr. Collins, the petitioners believe that the adjudication process itself should be free of even the appearance of conflict. Thus, the petitioners request that Dr. Collins recuse himself from participating in re-hearing. Such sensitivity to the fairness of the process should be promoted where public health concerns may conflict with the private financial interests of recipients of Bayh-Dole invention royalties.

It is also noted that former NIH Director Elias Zerhouni is now the director of Research and Development for Sanofi-Aventis, which is purchasing Genzyme. Obviously, Sanofi-Aventis and Dr. Zerhouni would suffer a significant financial loss if march-in rights were granted. It is hoped that the NIH will establish measures to avoid being influenced by Dr. Zerhouni and his financial interests in Genzyme or interests that his colleagues that remained at NIH may have.

IV. Regulations Regarding March-In Should be Promulgated to Prevent Future Death and Suffering of Patients That are Denied Access in Contravention to the Bayh-Dole Act.

nucleic acid hybridization); (U.S. Patent No. 5,728,807; Mutated proteins associated with ataxia-telangiectasia); (U.S. Patent No. 5,434,086; Method of testing potential cystic fibrosis treating compounds using cells in culture); (U.S. Patent No. 5,240,846; Gene therapy vector for cystic fibrosis).

The NIH as much as admits that it is powerless to assist in the current drug crisis of Fabrazyme®. However, the inability of NIH to protect the health and safety of U.S. citizens against misuse of Bayh-Dole inventions in the instant case should be used as a guide to promulgate regulations that empower the NIH. Such regulations can mitigate and prevent future deaths and suffering of U.S. citizens that are at risk of being denied access to Bayh-Dole inventions, which the NIH licenses. Thus, in order to remedy the de facto powerlessness of the NIH to meet the needs of patients that are denied access to Bayh-Dole inventions, the petitioners request that the following issues be addressed by engaging in rule-making:

1. The NIH has no reliable mechanism to identify possible non-use or unreasonable use of Bayh-Dole inventions and should promulgate rules to promote rapid disclosure of problems.

From the communications with the NIH, it appears that the NIH did not know that one of its inventions was being undersupplied to the U.S. public, which resulted in suffering and death. The timing of the response by the NIH was fatally delayed. The Fabrazyme® shortage began almost two years before NIH even considered the problem. If the trigger event for march-in had been the violation of the Bayh-Dole act (denial or reduction of patient access to an invention), then a second supplier would be close to producing Fabrazyme® if not already producing it at this point, even under a term of years required for FDA approval. From the instant case, it should be apparent that a rapid response to a Bayh-Dole violation is critical to ensure human health and safety.

To address the problem of notification and response time, the petitioners request the following regulations be promulgated:

- a. The petitioners request that the NIH promulgate a regulation to require Bayh-Dole contractors to provide notice to the NIH immediately when a shortage occurs or is likely to occur independent any other reporting requirements, including public disclosure of real time inventory levels and demand.
- b. Where such a shortage has occurred or is imminent, the petitioners secondly request that the NIH promote a regulation to create a codified NIH response plan. While the nature of the plan can be in any form, petitioners suggest a similar approach that the FDA has by creating a Drug Shortage Manual of Policies and Procedures.
- c. Third, the petitioners request that the NIH promote an internal regulation to require that the agency publicize the shortage on a publicly accessible NIH website, which is updated regularly, so that third parties can seek march-in licenses as soon as possible.
- d. Fourth, the petitioners request that the regulations imposed on Mt. Sinai in the instant case be promulgated industry-wide to apply to all Bayh-Dole contractors and licensees. Specifically, 1) where a shortage has occurred, the contractor provide monthly reports on the progress in addressing the supply shortage; 2) the contractor provide monthly reports on allotment and allocation of the invention to persons in need of the invention, and 3) notify the agency within 48 hours after a query into a license for the Bayh-Dole invention is received.

e. Fifth, where there is a clear threat to human health and where there is a violation of the Bayh-Dole act prohibition of unreasonable use and non-use of an invention, the NIH should immediately issue a march-in license. If there is administrative error, then the Bayh-Dole act provides an administrative path for a contractor to appeal such a decision. The NIH is reminded that patients do not have such an express right under Bayh-Dole to appeal a decision to deny them access to a drug, even though the harm to patients greatly transcends any economic injury that any contractor might incur.³²

2. *The NIH can avoid Bayh-Dole invention misuse by granting non-exclusive licenses to market entrants unless the contractors can show an overriding need for an exclusive license and should promulgate rules in accordance.*

The overly generous grant of exclusive licenses drives innovators out of the U.S. market and creates unreasonable health and price burdens for U.S. patients. Obviously, the intent of Congress with Bayh-Dole was to promote innovation, not to use Bayh-Dole rights to drive life saving drugs out of the U.S. market and, thereby, restrict American access to life saving technologies, as has occurred in the case of Fabrazyme®.

As a consequence of the current situation, the petitioners request that:

a. The NIH promulgate regulations that first convert all current exclusive licenses of Bayh-Dole inventions into non-exclusive licenses, unless, by petition, the contractor shows an overriding need for exclusive licensing royalties to supply the market. Potential infringers who desire to serve the market should not be sued

³² 35 U.S.C. § 203(b)

out of the market by contractors but rather invited to license public inventions non-exclusively from the NIH.

b. The NIH promulgate regulations, that going forward, only non-exclusive licenses be granted unless the contractor shows an overriding need for an exclusive license in order to supply the market.

c. The NIH promulgate regulations barring Bayh-Dole licensees from applying for additional exclusivity exceeding the scope of the Bayh-Dole patent grant including seeking additional exclusivity under the Orphan Drug Act for Bayh-Dole inventions, unless a overriding need for such exclusivity is demonstrated in order to supply the market.

3. *The NIH can mitigate supply-line interruption to Bayh-Dole inventions by requiring exclusive licenses to provide a second source of manufacture and should promulgate rules in accordance.*

Where an exclusive license is required to supply a market of a Bayh-Dole invention, the petitioners request that a rule be promulgated to require such exclusive licensees to provide a second source of manufacture. In mission critical supply chains, such as with military contractors, industry is required to “second source” manufacture of patented products so that a manufacturing failure does not destroy a supply chain. There is currently no similar safety net for the supply chain of life-saving drugs developed with taxpayer dollars. The Bayh-Dole act gives the NIH jurisdiction to control health-critical supply chains through its ability to control the licensing of Bayh-Dole inventions. Thus, the petitioners request that the NIH promulgate regulations to require exclusive licensees

of Bayh-Dole inventions to “second source” manufacturing in order to protect the lives of patients that rely on the supply chain.

4. *The NIH has a moral, ethical, statutory, and Constitutional duty to mitigate the suffering of patients denied access to Fabrazyme® and other future victims of undersupply of Bayh-Dole inventions, and it should promulgate rules in accordance.*

The petitioners request that the NIH treat the patients that have suffered from denial of access to Bayh-Dole drugs with compassion by assisting them financially through the drug shortage. Taxpayers funded the discover of the invention, they paid the monopolistic price to use the invention, and, now that the invention is denied to them, they must personally bear the health and financial costs of the shortage, despite the duty of manufacturers and administrators to ensure a supply under the Bayh-Dole act. Shifting the costs of the shortage to the suffering patients and the families of the dead is fundamentally immoral, irrational, and implicates not only patients’ rights under the Bayh-Dole act, but the right of U.S. citizens to not be deprived of life and liberty under the 5th Amendment.

As such, the petitioners request that the NIH allocate a portion of the royalties from all Bayh-Dole inventions to establish a compensation fund for citizens that are denied access to Bayh-Dole inventions. While the NIH is powerless in the current situation to restore the supply of drug, it may be able to compensate patients that may be harmed by a shortage in the future. Such a compassionate use of Bayh-Dole royalties will not deter innovation, but rather ensure that victims of Bayh-Dole act violations be

compensated where the Bayh-Dole market system fails as it did in the case of Fabrazyme®.

While the NIH may consider any compensation system, the petitioners recommend modeling the compensation system on the Vaccine Injury Compensation Program. Access to the fund should be compassionate and generous without the need to resort to court litigation. Such a fund should be accessible pro se and also provide reasonable attorney fees to promote access to the fund. Moreover, the process should provide rapid adjudication in order to mitigate further financial hardships on patients. The fund can be created under the authority of the Bayh-Dole act.

5. *Questions that should be addressed in rule-making*

a. Standard of review: The NIH decision did not consider what standard, if any, applies to considering march-in for Bayh-Dole inventions. We believe that the legal standard for initiating march-in where a contractor violates the Bayh-Dole act should be that the Government action is in the best interest of those denied access to the invention, not second-guessing whether the statutory remedy would work well enough to increase short term supply. In the event another standard exists, the public should be informed.³³

b. Death count: The current death toll for misuse of Fabrazyme® appears to be at least three. We have asked the FDA to investigate these deaths.³⁴ While we do not believe that any deaths are acceptable from a Bayh-Dole violation, the NIH de

³³ While the issue is not expressly before the NIH, some have argued that initiating march-in will deter investment in new treatments, especially for orphan drugs. We believe that innovation and ensuring a reliable drug supply go hand in hand— you must accomplish both to save lives. Obviously, a child that is denied access to a life-saving drug by a shortage will die just as surely as if a drug company never invested in the first place. Nobody should have to choose between a having a reliable drug supply and promoting innovation. They are simply not mutually exclusive.

³⁴ Citizen Petition filed with the FDA on 01/19/2011 assigned docket no. FDA-2011-P-0055-0001/CP to prevent further export of Fabrazyme®

facto does not appear to place an upper limit on the number of deaths that need to occur before march-in is considered a worthy remedy. It is requested that the NIH inform the public of how many deaths are required beyond the current three that are required before march-in is initiated.

c. Injury and harm to American citizens: The European Medicines Agency has already documented the severe and life-threatening results of the non-FDA approved reduced Fabrazyme® dosage on Fabry disease patients. The petitioners and their doctors are also available to interview to confirm the severity of the harm to patients. The NIH acknowledges that the shortage is creating a health crisis; however such grave health issues are apparently insufficient to trigger use of march-in. Thus, it is requested that the NIH inform the public as to how much damage a patient population must suffer before march-in is considered as a worthy remedy.

d. Government action against Bayh-Dole contractors: The FDA has already filed a consent decree against Genzyme, initiated oversight, and fined the company \$175 million for its failure to observe safety standards. While we believe that such action by a Government agency should trigger march-in, the NIH has appeared to put a lower standard on the requirements of Bayh-Dole contractors than the FDA. Consequently, it is requested that the NIH inform the public as to how poorly, dangerously, and illegally a Bayh-Dole contractor must act before the NIH will consider march-in as a worthy remedy.

e. “Readiness Requirement:” Until the NIH decision, no one was on notice that march-in had a readiness requirement. We do not believe that such a requirement is in the best interest of public health. However, to the extent that the NIH

wishes to continue to place this constraint on issuing a march-in license, the public should be informed what is required for manufacturers to “be ready” for march-in for future shortages of Bayh-Dole inventions.³⁵ The “readiness requirement” is a substantive rule that does not appear in the statute or NIH regulations. Thus, the NIH is required to codify the “readiness” requirement under the Administrative Procedures Act. 5 U.S.C. § 552(a)(1)(D). Forcing manufacturers and patients to simply guess what actions they need to take to meet the readiness requirement serves no administrative or public health purpose.

f. FDA regulatory conflict of law: The NIH decision cites the FDCA and FDA regulations as the primary impediment to being able to use the march-in remedy. It is imperative that the NIH identify which regulations have rendered march-in futile. Obviously, if the FDA regulations preempt march-in (or renders march-in futile), then legislators will need to reform either the Bayh-Dole act and/or FDA regulations so that FDA regulated inventions are not exempted from the prohibition against non-use and unreasonable use mandated by Congress. As it stands, there appears to be no qualitative or quantitative amount of non-use or unreasonable use of a Bayh-Dole invention that would trigger march-in. Expressly banning Americans from access to an invention which could save their lives (even if it is regulated by the FDA) should automatically trigger the march-in remedy, if nothing else than to deter such gross misuse of Bayh-Dole inventions.

V. CONCLUSION

In the past, the NIH has appeared to act more as a revenue collector for Bayh-Dole inventions rather than a protector of U.S. citizens who rely on the supply chain of

³⁵ *In the Case of Fabrazyme®*, p.9 (decided December 1, 2010)

Bayh-Dole inventions for their life. In light of the suffering and death due to handling of the Fabrazyme® situation, the NIH has the opportunity to seize the reins and promote the interests of the health of U.S. citizens with its grant of power under Bayh-Dole. As acknowledged by the NIH decision, it is currently powerless to solve the current shortage even with the power of march-in.³⁶

However, the petitioners believe that the NIH is not powerless to act in preventing and mitigating future shortages by properly regulating Bayh-Dole inventions.

Promulgating regulations can help to avoid a repeat of the Fabrazyme® disaster.

Moreover, the NIH has the opportunity to demonstrate its compassion and concern for the patients harmed by the undersupply and denial of access to Fabrazyme® by using the royalties generated by all Bayh-Dole inventions to compensate the families of those who died during the shortage and the patients who have suffered unnecessarily.

Respectfully submitted,



C. Allen Black, Jr., Ph.D., J.D.
Counsel to Petitioners,

The Law Office of C. Allen Black, Jr.
1579 Montgomery Rd.
Allison Park, PA 15101
412-908-3268
allen@patentlawyersite.com

³⁶ *In the Case of Fabrazyme* (NIH, decided Dec. 1, 2010)

Exhibit 1: European Medicines Agency Study on Health Effects of Rationing Fabrazyme®.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

for

FABRAZYME

agalsidase beta

**Assessment report on the shortage of Fabrazyme'
Overview of Shortage Period: Spontaneous Reports from June 2009 through 15
September 2010 and Registry Data from June 2009 through 05 August 2010**

EMA/H/C/000370



I. INTRODUCTION

Fabry's disease is a lysosomal storage disorder due to a deficiency in alpha-galactosidase A. The natural course of the disease is illustrated in figure 1.

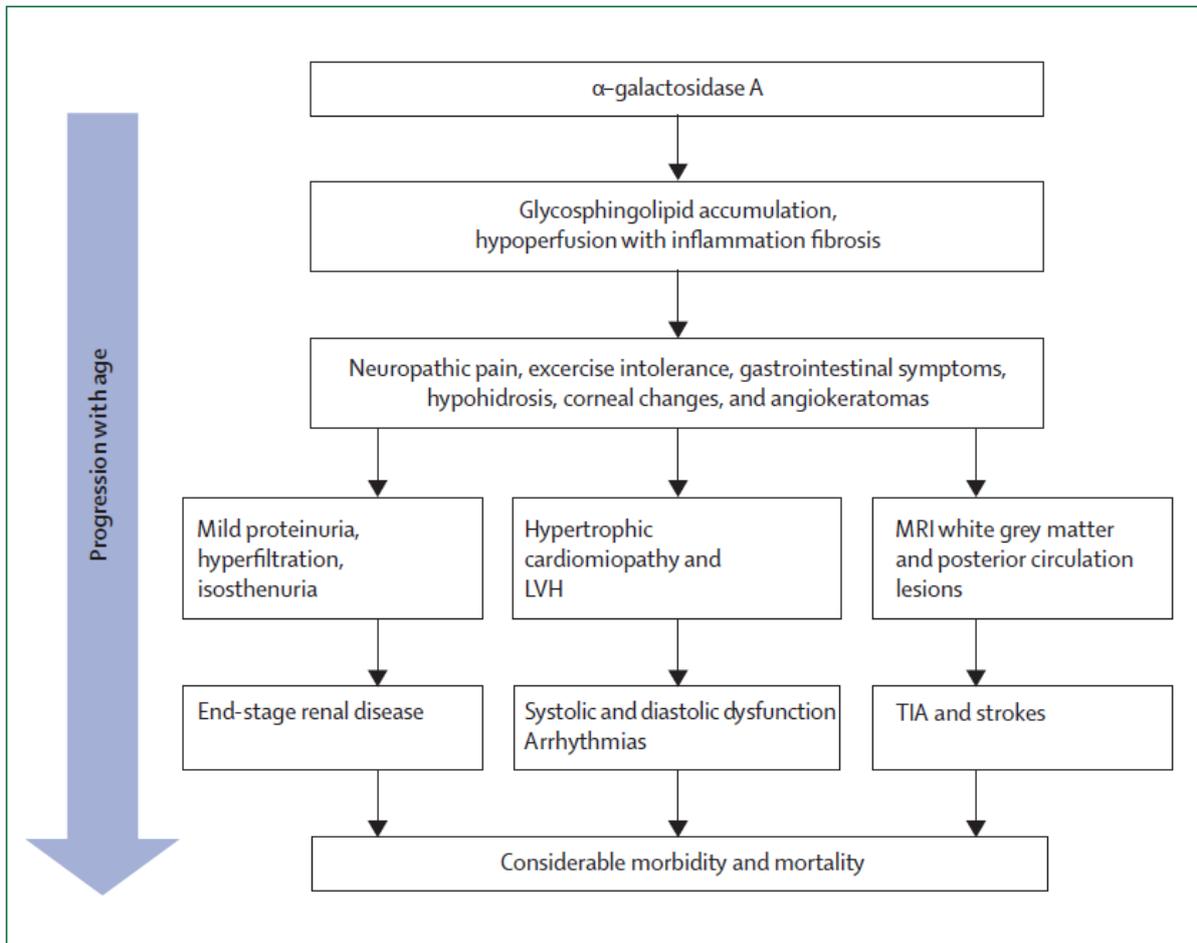


Figure 1: Progression of clinical findings in Fabry's disease with age

Progression of any of the paths depicted can proceed independently from the others, which means that for some patients, cardiac disease will be the most severe whereas for others renal or CNS disease can predominate. LVH=left ventricular hypertrophy. TIA=transient ischaemic stroke.

(Zarate & Hopkin. Lancet 2008;372:1427-35)

At the start of the disease (during the first decades of life), the main manifestations are pain (crises) and gastrointestinal symptoms. The long-term progression of Fabry disease is associated with chronic renal disease, cardiovascular disease, and cerebrovascular events (during fifth decade of life); this deterioration is a major cause of morbidity and mortality.

Fabrazyme® is an enzyme replacement therapy for Fabry's disease. The recommended dose and frequency in section 4.2 of the SmPC is 1 mg/kg every other week (eow).

Since June 2009 there has been a shortage of supply of Fabrazyme (agalasidase beta) because of production and quality (GMP) problems. To date four Direct Healthcare Professional Communications (DHPCs) with dose recommendations have been released in the European Union (EU):

25 June 2009:

- Children and adolescents less than 18 years old as well as adult male Fabry patients to continue with recommended Fabrazyme dosing and frequency.
- Adult female Fabry disease patients with no evidence of clinically significant end organ damage to be treated with a reduced dose of 0.3-0.5 mg/kg every 2 weeks.

28 September 2009:

- Children and adolescents less than 18 years old to continue with recommended Fabrazyme dosing and frequency.
- Adult male patients already treated and stabilized to receive 0.3 mg/kg every 2 weeks (as for adult female patients).
- Patients should be followed up every two months, and plasma or urinary globotriaosylceramide (GL-3) levels should be closely monitored.
- Patients who demonstrated a deterioration of disease should be switched back to their original dosage regimen with Fabrazyme.

22 April 2010:

- Treatment recommendations as communicated in the DHPC of September 2009 remained in place.
- For patients experiencing aggravation of disease symptoms and/or AEs ascribed to the lowered dose of Fabrazyme, physicians were advised to switch their treatment back to their original dosing regimen or initiate treatment with an alternative approved medicinal product.

09 July 2010:

- No new patients should be started on Fabrazyme, if alternative treatment is available.
- For patients on a dose lower than the recommended dose, physicians should consider switching to an alternative treatment, such as Replagal.
- Where alternative treatment is not available or where (continuation of) treatment with Fabrazyme is deemed medically necessary, it is important to note that an increase in clinical manifestations indicative of Fabry disease progression has been observed with the lowered dose.

In the United States all patients were asked to reduce their Fabrazyme use by spreading out their usual dose over a longer period of time.

During the shortage period, the MAH has updated the Rapporteur with reports on spontaneous reporting and data from the Fabry registry. These data and the Rapporteur's conclusions are summarized in this assessment report.

On 4 and 9 October 2010 a consensus meeting took place of representatives of physicians treating Fabry disease in the EU. At that meeting treatment recommendations in times of shortage were agreed. A representative of the EMA was present as an observer.

The purpose of this assessment report is to present an overview of the data received so far on patients on a lower dose of Fabrazyme.

II. POSSIBLE DETERIORATION IN PATIENTS ON THE LOWERED DOSE

The Rapporteur has reviewed all data from spontaneous reports regarding patients who reported adverse events (AEs) assessed to be suggestive of clinical deterioration on a lowered dose of Fabrazyme (from Genzyme's Global Patient Safety and Risk Management department (GPS&RM) database) for the period from 25 June 2009 through 15 September 2010.

In addition, all information from the Fabry Registry regarding certain clinical characteristics of patients whose doses of Fabrazyme were lowered during a period of approximately 13 months, from 25 June 2009 through 05 August 2010 have been reviewed and the data from both sources have been compared.

In all cases, it was assumed that these patients' doses were lowered in response to the reduction in the global supply of Fabrazyme during this period.

The MAH considered the following:

A. All spontaneous cases reported to GPS&RM and medically reviewed from 25 June 2009 through 15 September 2010 were considered for the analysis of patients experiencing clinical deterioration on a lower dose of Fabrazyme if they met the following three criteria:

1. The reported AE occurred after 25 June 2009,
2. The patient was on a lowered dose of Fabrazyme due to the supply shortage, and
3. The AE was not an infusion associated reaction (IAR).

B. After selecting the cases that met these criteria, the narratives were screened by the MAH for information with regard to evidence of clinical deterioration. A medical review of these cases, which included all relevant medical history and available laboratory data, was performed by GPS&RM to determine whether the AEs were suggestive of potential clinical deterioration. Due to the ongoing limited supply, cases of patients with clinical deterioration but without complete documentation of a lowered dose have also been incorporated into the reports; further efforts are being made with the patient's health care professional (HCP) to confirm the dose reduction in these cases.

C. Events assessed to be suggestive of potential clinical deterioration after medical review included, but were not limited to: cardiovascular events such as arrhythmia, coronary artery disease or heart failure; cerebrovascular events such as transient ischaemic attacks or cerebrovascular accidents; renal events such as renal impairment or renal failure; gastrointestinal events such as abdominal pain, nausea, vomiting, and diarrhoea; events consistent with Fabry disease-related pain such as paraesthesias, pain in extremities, or peripheral neuropathy; changes in hearing; and constitutional symptoms such as fatigue and malaise.

Physicians who enrol patients in the Fabry Registry are asked to monitor patients and submit clinical data according to a Minimum Recommended Schedule of Assessments. This schedule includes key clinical and laboratory parameters that should be evaluated and the frequency at which they should be reported to the Fabry Registry. However, Genzyme has found that these data are typically entered on a semi-annual or annual basis. In addition, not all changes in dosage have been reported to the Fabry Registry and changes in the average reported dose may not accurately reflect patients' actual treatment regimens.

Events of chronic renal disease, cardiovascular disease, cerebrovascular events, and deaths reported to the Fabry Registry were investigated in patients whose doses were lowered during the period from 25 June 2009 through 05 August 2010. In addition, data related to peripheral pain, abdominal pain, and diarrhoea were included. Reported plasma and urine levels of GL-3 were also analyzed in patients who are enrolled in the Fabry Registry.

III. REVIEW OF DATA FROM SPONTANEOUS REPORTS

The MAH submits bi-weekly reports on patients all over the world. Most reports are on non-EU patients. In every report, the MAH is required to discuss the EU patients separately.

In the EU, of the patients on Fabrazyme, approximately 4% was on a dose lower than 1 mg/kg/eow prior to the start of the supply shortage.

After a decline, the number of patients on Fabrazyme as well as the number of patients on the lowered dose seems to have stabilized. This is an indication that the recommendations are being followed to some extent and that no or a small number of new patients are being initiated on Fabrazyme.

In the figure below, the bars indicate the numbers of reported AEs. The figure only presents the unique patients, so the real number of AEs is higher because for some patients there are more AE reports in time received. There appears to be a stabilisation in the number of AEs, suggesting that patients who still are on the lowered dose, are relatively stable and are not adversely affected by the use of the lowered dose.

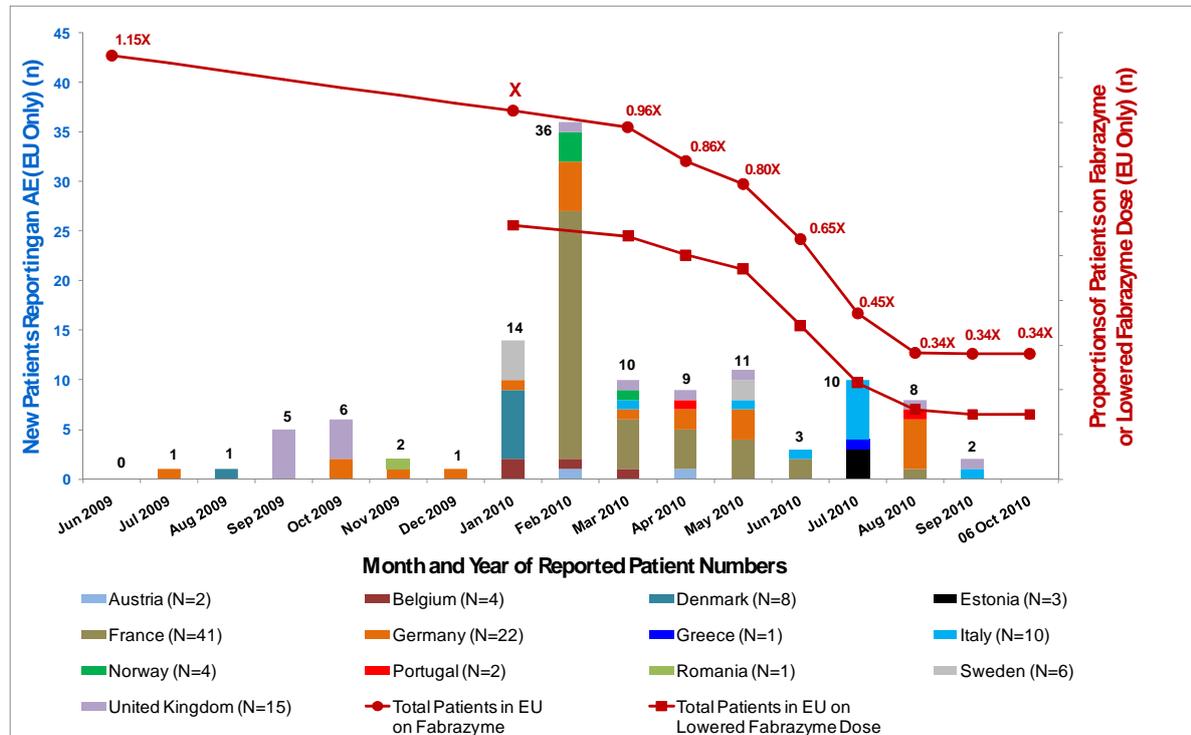
See table 1 and figure 2 below.

Table 1: Estimated Percentage of Patients in the European Union on a Lower Dose

Estimated Number of:	January 2010	March 2010	April 2010	May 2010	June 2010	July 2010	August 2010	Sept. 2010	06 Oct. 2010
Patients on Fabrazyme*	x	0.96x	0.86x	0.80x	0.65x	0.45x	0.34x	0.34x	0.34x
Patients on 1 mg/kg/eow	26%	26%	25%	23%	31%	37%	37%	41%	41%
Pediatric patients on 1 mg/kg/eow	5%	5%	5%	5%	5%	6%	7%	7%	7%
Patients on 0.5 mg/kg/eow	32%	22%	23%	22%	21%	6%	13%	12%	12%
Patients on 0.3 mg/kg/eow	36%	47%	47%	50%	43%	51%	42%	40%	40%

*Note that x=total number of patients on Fabrazyme per January 2010 (exact number not disclosed for confidentiality reasons). In time, this number gradually decreases.

Figure 2 New Unique Patients Reporting AEs Assessed to be Potentially Suggestive of Clinical Deterioration on a Lowered Dose of Fabrazyme by Country, and Proportions of Patients on Fabrazyme and Lowered Doses of Fabrazyme (EU Patients Only) Since the Start of the shortage



* Bar graph data in Figure 1 represent the total number of unique patients by month who are new to the analysis of case reports assessed to be suggestive of potential clinical deterioration on a lowered dose of Fabrazyme. All patients new to the analysis during the current biweekly period are presented in that month. However, in subsequent reports, the patients will be listed in the month of the worldwide receipt date (WWRD) of their AE report. For example, if a case was initially reported with a WWRD in February 2010, but the data confirming that the patient was on a lowered dose were not received and medically reviewed until 20 September 2010, the case would be presented for the first time in the 16 September 2010 through 30 September 2010 biweekly report in the column for 16-30 September 2010. This presentation shows how many new unique patients from the EU are reporting AEs assessed to be suggestive of clinical deterioration on a lowered dose of Fabrazyme during the recent biweekly period. However, in subsequent reports, the case would be presented in the February 2010 column based on the initial WWRD to the safety database. Further, each unique patient is counted in Figure 1 only once. Therefore, if a patient reports one AE in September 2009 and another separate AE in March 2010, the patient will be included in the calculations for September 2009 only.

** The AEs received and medically reviewed after 30 September 2010 are beyond the scope of this document and will be presented in future reports.

There is a clear trend of increasing reports of (serious) AEs since the shortage. The higher the percentage of patients receiving the lowered dose, the higher the number of AEs reported. After the recommendations to switch to Replagal or to return to a higher dose when clinical deterioration appeared, this percentage decreased, as well the absolute number of reports. A subgroup of patients seems to be doing well on the lower Fabrazyme dose.

The MAH did not provide comparable data for the period before the shortage and concluded that based on the limited data available, it is not possible to ascertain whether more patients are having serious clinical events while on lowered doses of Fabrazyme, compared with earlier data from patients on a full dose of Fabrazyme.

However, the MAH did provide and compare quarterly data from Q3 2009 (see table 1). The percentage of AEs ascribed to the lowered dose increased steeply. After the increase in AEs seen from Q4 2009 to Q1 2010, the number of reported AEs from Q1 2010 to Q2 2010 appears to have been either stabilizing or decreasing.

Over time, increases have been seen in serious cardiac and nervous AEs and, to a lesser extent, in renal events, while a decrease, albeit less steep, has been seen in reported AEs related to pain/paresthesias.

The reported AEs are summarised in table 2. This table concerns data up to Q3 2010.

Note that this table presents worldwide data.

Table 2 Summary of Patients and Adverse Events Spontaneously Reported to Genzyme's Global Patient Safety & Risk Management Database That Were Received and Medically Reviewed from 25 June 2009 through 30 September 2010 and Assessed as Being Suggestive of Clinical Deterioration while on a Lowered Dose of Fabrazyme (selection of SOCs)

Adverse event category Preferred Term	Q3 2009 (N=21)		Q4 2009 (N=34)		Q1 2010 (N=89)		Q2 2010 (N=90)		Q3 2010	
	Events (n)	Patients (n)	Events (n)	Patients (n)	Events (n)	Patients (n)	Events (n)	Patients (n)	Events (n)	Patients (n)
Cardiac disorders (arrhythmias, cardiac failure, cardiac occlusion, MI)	1	1	1	1	13	12	14	14	11	10
Cerebrovascular-stroke	1	1	2	2	7	7	2	2	10	7
Fabry disease related pain	10	9	10	9	41	41	35	35	24	21
Gastrointestinal pain	2	2	5	5	3	3	5	4	7	7
Gastrointestinal diarrhoea	2	2	5	5	5	5	4	4	1	1
Renal disorders (renal failure, renal failure chronic)	-	-	-	-	6	6	4	4	9	9

The above data come from: a) Genzyme's "Report on Fabry Registry Patients who received Fabrazyme Dose reductions between 25 June 2009 and 05 August 2010 and Comparison to Spontaneous reports to Global Patients Safety and Risk Management Database" dated 23 September 2010; b) data from the third quarter 2010 (obtained from the biweekly reports 01-15 July; 16-31 July; 01-15 August; 16-31 August; 01-15 September; 16-30 September 2010).

Patients returning to higher dose or switched to Replagal

Some information was received on patients who had been switched to Replagal. However, the data is limited and no conclusions can be drawn from them.

There were also switches between Replagal and Fabrazyme prior to the Fabrazyme supply shortage.

GL-3 levels

There are some data available on GL-3 levels measured in patients before and after their dose lowering. These data do not show any clear trend.

IV. REVIEW OF DATA FROM FABRY REGISTRY

In the Fabry Registry, 410 patients were reported to be on lowered dose (US 59% and Europe 22%).

As of 5 August 2010, the Registry had enrolled a total of 3,681 Fabry patients (1,808 males and 1,873 females), irrespective whether or not they received enzyme replacement therapy.

Cerebrovascular events: The stroke incident rates have increased slightly since 25 June 2009 (from 0.63 (95% CI: 0.31–1.12) per 100 person years of follow-up to 1.32 (95% CI: 0.36–3.37).

Renal events: Since the previous Registry report, one new case of a renal event was reported (initiation of chronic dialysis). The incidence rate in these very small numbers did not increase during the shortage.

Cardiovascular events: The number of patients who had cardiovascular events after 25 June 2009 was small (N=3) and the observation period was short. Therefore, no conclusion can be made on whether or not there is any meaningful difference in the incidence of cardiovascular events in Fabrazyme-treated patients before and after 25 June 2009.

Neurologic peripheral pain, abdominal pain, diarrhoea: There have been consistent reports of a higher percentage of patients reporting peripheral pain, abdominal pain and diarrhoea on a daily basis after 25 June 2009, compared with the period before that date.

Globotriaosylceramide (GL-3) levels: The findings on the plasma GL-3 data are comparable with those in the spontaneous reporting; there is no apparent change.

Regarding urine GL-3 levels, six of the seven patients had lower levels post June 2009 compared with pre June.

V. CONSENSUS MEETING

On 4 and 9 October 2010, a consensus meeting of treating physicians was held. The purpose of that meeting was to reach consensus on the proper management of Fabry disease during the period of shortage of enzyme replacement therapy (ERT) and to come up with clear treatment recommendations for physicians during the shortage period of Fabrazyme (shortage of agalsidase beta and subsequent constraints in supply of agalsidase alfa). The aim was also to have the agreed treatment recommendations published in a scientific journal.

The EMA was present as an observer and the CHMP was informed of the outcomes of the meeting by the physicians' representative.

The CHMP took the outcome of this consensus group of experts into account.

VI. CONCLUSIONS

- There is a clear trend of increasing reports of (serious) AEs since the start of the shortage. The higher the percentage of patients receiving the lowered dose, the higher the number of AEs reported. After the recommendations to switch to Replagal or to return to a higher dose when clinical deterioration appeared, this percentage, as well the absolute number of reports, decreased. This provides a picture of more and more patients at risk from the lowered dose switching back to higher dose or to Replagal.
- A certain patient subgroup seems to have no obvious clinical effects due to the lowered dose.
- The safety data on the registry period June 2009 to 05 August 2010 confirm the trends as seen in the spontaneous reports. Due to its voluntary-based and periodic reporting, the Registry is somewhat 'behind' in time and this is reflected in the data. In the Registry so far the increases and decreases described above are still developing.

- Taking into account the potential for increased awareness of the supply shortage among healthcare providers which could potentially lead to reporting biases, the limitations of spontaneous reporting and the small number of reports, there is an increase in reporting of adverse events possibly due to the lowered dose. In the early stages of the shortage the main increases in AEs were related to pain/paresthesia events, while later on in the shortage period, the main increases were in serious cardiac events such as myocardial infarction, in serious nervous disorders such as stroke, and – possibly to a lesser extent – in renal disorders. There have been consistent reports of a higher percentage of patients reporting peripheral pain, abdominal pain and diarrhoea on a daily basis after 25 June 2009 (start of the shortage).
- **This pattern of adverse events resembles the natural, but accelerated, course of Fabry's disease.**
- The CHMP requests the MAH to include this important data on long-term low dosage use in the SPC in section 5.1. The MAH should provide wording stating that during the shortage period, spontaneous reports on the following adverse events (indicating a deterioration of the disease) were received: Fabry disease-related pain, paresthesia, diarrhoea, cardiac disorders as arrhythmias and myocardial infarction, nervous system disorders as stroke, and renal disorders as renal failure.
- A yet unexplained finding is that the plasma GL-3 levels show no apparent change before and after dose lowering. Data on the urine GL-3 levels are scarce; in six of the seven patients there was a lowering after dose lowering.

Exhibit 2: March 25, 2011 Genzyme Supply Update Letter



Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
Tel 800-745-4447

March 25, 2011

RE: U.S. Supply of Fabrazyme® (agalsidase beta) for May 2011

Dear Patient,

Genzyme recently provided a global update on Fabrazyme supply via our supply website and we wanted to let you know what this means in the U.S. Recently one specific “lot,” a batch of finished vials, of Fabrazyme was rejected during quality assurance review because it did not meet release criteria. This loss of Fabrazyme was related to conditions in the area of our Allston Landing, Massachusetts facility where some of the Fabrazyme we make is freeze-dried and put into vials – the “fill/finish” suite. Fabrazyme sold in the U.S. is not filled and finished at Allston Landing, but rather at a contract manufacturing facility at another location. Still, in order to help share the impact of this loss, some Fabrazyme that was originally destined for patients treated in the U.S. will be diverted to patients elsewhere.

What this means for you:

- 1) In the U.S., there is **no change to the March and April allocation** that we communicated in our letter dated January 21, 2011. We will still be able to provide Fabrazyme as planned for the remainder of March and for April (one full 1mg/kg dose per patient, per month).
- 2) However, the loss of product described above means there is **a possibility that we will be unable to open the next Fabrazyme shipping window at the beginning of May 2011.** Because of this uncertainty regarding supply timing in the month of May, your healthcare provider may wish to consider adjusting your infusion schedule in the coming weeks. Should your healthcare provider choose flexible dosing, we expect to have sufficient 5mg Fabrazyme vials available in April to support dosing flexibility.
- 3) We realize that you are eager to have the information needed to plan your infusions. We will contact you as soon as we have additional information about the timing of Fabrazyme availability beyond April.

As you know, last month we initiated a request process to allow a limited number of new patients to start Fabrazyme treatment. We would like to remind the Fabry community that providing Fabrazyme treatment to a small number of new patients does not change the amount of Fabrazyme available for current patients. The Fabrazyme request process does not have any impact on the timing of Fabrazyme availability in May.

General Information

The information in this letter is based on our current best estimate of Fabrazyme supply. Increasing the availability of Fabrazyme remains our highest priority. At this time, we are still working with very limited inventory, so even minor changes to our current manufacturing plan can impact availability of Fabrazyme. We will continue to do our best to inform you of any shipping delays that might affect you or your infusion schedule.

For support regarding insurance and billing issues, infusion agency questions, or additional information about the supply of Fabrazyme, or to give Genzyme your feedback, please contact your Genzyme Case Manager at 1 (800) 745-4447, Option 3 or Medical Information at 1 (800) 745-4447, Option 2.

Sincerely,

A handwritten signature in black ink, appearing to read "Pamela di Cenzo". The signature is fluid and cursive, with a large initial "P" and "C".

Pamela di Cenzo, Vice President
Patient & Product Services