





## **SUMMARY BASIS OF DECISION (SBD)**

**FABRAZYME®**

**Agalsidase beta, 5 mg and 35 mg**

**Lyophilized Powder for Reconstitution**

**Control No. 072889**



|             |            |
|-------------|------------|
| Date Issued | 2004/04/30 |
|-------------|------------|

**Health Products and Food Branch**

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*Health Canada*

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- Promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.

*Health Products and Food Branch*

***Également disponible en français sous le titre:*** SUMMARY BASIS OF DECISION (SBD)  
Fabrazyme<sup>®</sup> Agalsidase bêta, 5 mg et 35 mg de poudre lyophilisée pour une reconstitution N° de contrôle 072889

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## 1 PRODUCT AND SUBMISSION INFORMATION

|                                       |  |
|---------------------------------------|--|
| Brand Name                            | Fabrazyme®   |
| Manufacturer/ Sponsor                 | Genzyme Canada Inc.  |
| Medicinal Ingredient                  | agalsidase beta  |
| International Nonproprietary Name     |  |
| Strength(s)                           | 5 mg and 35 mg   |
| Dosage Form(s)                        | Lyophilized powder for reconstitution  |
| Route(s)                              | IV infusion  |
| DIN(s)                                | 02248965 (5 mg/vial), 02248966 (35 mg/vial)  |
| Pharmaco-therapeutic group (ATC Code) |  |
| Non-medicinal Ingredients             | Mannitol, Sodium Phosphate (monobasic, monohydrate and dibasic, heptahydrate), Nitrogen  |
| Submission Type and Control No.       | NDS Control No. 072889   |
| Date of Submission                    | August 2, 2001   |
| Date of Approval                      | January 23, 2004   |
| Overview of Submission                | The New Drug Submission for Fabrazyme® was given a Notice of Compliance (NOC) on January 23, 2004 in Canada, for enzyme replacement therapy in patients with Fabry's Disease, administered intravenously at a dosage of 1.0 mg/kg body weight infused every two weeks. The NOC covered both the 5 mg and 35 mg strengths of agalsidase beta, also containing varying amounts mannitol, sodium phosphate monobasic, monohydrate, and sodium phosphate dibasic, heptahydrate, depending upon the strength. |

## 2 SCIENTIFIC AND REGULATORY BASIS FOR DECISION

### 2.1 Introduction

Fabrazyme® (agalsidase beta) is a highly purified recombinant form of the human alpha-galactosidase A enzyme (r-hα-GAL). It is intended as replacement therapy for enzyme-deficiency in patients with Fabry's Disease and administered intravenously at a dosage of 1.0 mg/kg body weight infused every two weeks.

Fabry's disease is a genetic disorder that results in the accumulation of glycosphingolipids (GL-3) in the endothelium of vessels and affects, in particular, vital organs such as the kidneys, the heart and the Central Nervous System causing renal failure, cardiomyopathy and cerebrovascular disease. Clinical manifestations also include peripheral neuritis, angiokeratoma corporis diffusum universale, renal failure, myocardial and cerebral infarction. In clinical trials, Fabrazyme® effectively cleared GL-3 deposits from the renal vascular endothelium and decreased assay levels of GL-3 in biopsied kidney tissue.

There is currently no specific curative treatment for Fabry's Disease. Patient management had, to date, been limited to symptom control and supportive measures. While Fabry's Disease affects only a very small percentage of the global population, it is a severely debilitating disease leading to severe morbidity and early mortality. All of these characteristics qualified Fabrazyme® to be reviewed under the Priority Review policy.

The drug is supplied as a sterile, non-pyrogenic, white to off-white lyophilized cake or powder for reconstitution with Sterile Water for Injection, USP. Each vial of the final product will contain either 5 mg or 35 mg of agalsidase beta, and varying amounts of mannitol, sodium phosphate monobasic, monohydrate, and sodium phosphate dibasic, heptahydrate, depending on the strength.

### 2.2 Quality Basis for Decision

#### 2.2.1 Drug Substance (Medicinal Ingredient)

##### *Manufacturing Process and Process Controls*

The Drug Substance is manufactured using a recombinant cell culture expression system, followed by several purification steps. The manufacturing process begins when one to two vials of Working Cell Bank (WCB) are thawed and inoculated into a spinner flask with serum-containing medium. Expansion of the cells continues through a series of spinner flasks, into a seed bioreactor, and then into the production bioreactor.

Fermentation consists of a growth phase, a transition phase into serum-free medium, and a harvest phase.

The harvest fluid is clarified by microfiltration. The enzyme is subsequently purified through a 4 step column chromatography process which utilizes different principles of separation. Eluate from the last purification step undergoes ultrafiltration and diafiltration into a buffered solution. The purified enzyme is then nanofiltered (20 nm).

During the drug submission review, each part of the manufacturing process was found to be adequately validated at full-scale. The validation of the cell culture (fermentation) part of the process was satisfactorily performed for both proposed production scales. Several critical process parameters were monitored and the quality attributes were evaluated throughout the cell culture process from cell thawing to harvesting. In addition, *in vitro* viral testing was satisfactorily performed on harvest material produced at the end of each run. Data from the validation study indicated that the fermentation process was and can be appropriately controlled.

The validation of the purification process was satisfactorily executed by processing bioreactor harvest fluid through the clarification and purification steps to produce the Drug Substance. The process validation study on three consecutively manufactured batches of Drug Substance was evaluated and found to be satisfactory based upon the use of relevant in-process controls and successful release testing. For example, the critical quality attributes or controls evaluated at each step included purity of the product, levels of impurities present, yields of the enzyme, and microbial load. The review of the separate validation study for the nanofiltration step found that the protein purity/ impurity profile was not affected by nanofiltration.

Based upon the review of the process validation data presented, there is confidence that the recombinant human  $\alpha$ -galactosidase (r-h $\alpha$ GAL) purification process is reproducible and that it can be expected to consistently produce a Drug Substance which meets all Drug Substance release specifications.

During the On-Site Evaluation (OSE), controls surrounding the fermentation and a representative purification step (at each scale) were evaluated and found to be acceptable. The manufacturing activities were conducted in accordance with Good Manufacturing Practices. The quality and control of all materials used in the manufacture of the Drug Substance were reviewed and found to meet standards appropriate for their intended use. All animal-derived raw materials are sourced and/or tested appropriately. The vendor qualification program was evaluated during an OSE and found to be satisfactory.

Particular attention was paid to the biologically-sourced materials used in the manufacturing process. Details of the construction and sequencing of the recombinant expression vector, containing the cDNA coding region from the human alpha-galactosidase, were reviewed and found to be acceptable. The Chinese Hamster Ovary (CHO) cells containing the expression vector DNA produced the r-hαGAL protein which is secreted into the cell culture media.

The cell banking system used for the production of r-hαGAL consists of a two-tiered cell bank, in which the Master Cell Bank (MCB) was used to generate Working Cell Banks, to support the fermentation scales. The source, control, and stability of the cell line during production and storage were evaluated and found to be acceptable. All cell banks (i.e. MCB, WCB and the end- of-production cells) were characterized and tested for the presence of endogenous and adventitious agents, according to the International Conference on Harmonization (ICH) guidelines Q5A<sup>1</sup>, Q5B<sup>2</sup>, and Q5D<sup>3</sup>. Cells were confirmed to be of Chinese hamster origin and free of bacterial, fungal and mycoplasma contamination. Electronic microscopy detected only the presence of endogenous A- and C-type retroviral particles which are unable to infect either CHO or human cells. The control and storage conditions of the cell banks were verified during the OSE.

### **Characterisation**

The results from the various structural analyses and tests used to identify the primary, secondary and tertiary structure, as well as, post-translational modifications and biochemical properties of agalsidase beta, were evaluated in several drug substance lots and primary reference standards and found to be acceptable. Alpha-galactosidase A is a lysosomal hydrolase enzyme of about 100 KDa. This enzyme is a non-covalently linked homodimeric glycoprotein. Each subunit consists of 398 amino acids with three N-linked glycosylation sites at asparagines 108, 161 and 184. The theoretical mass of the peptide (excluding the mass of the carbohydrate chains) is 45,349 Daltons.

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<sup>1</sup> ICH Harmonised Tripartite Guideline, *Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*

<sup>2</sup> ICH Harmonised Tripartite Guideline, *Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products*

<sup>3</sup> ICH Harmonised Tripartite Guideline, *Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/ Biological Products*

Several techniques were used to study the enzyme. The biological activity was established using an enzyme assay which measures the hydrolysis of the terminal  $\alpha$ -galactose from a relevant synthetic substrate. To complement the activity assay, the manufacturer developed a cell uptake assay, to demonstrate that the enzyme can be taken up by the appropriate cells via mannose 6-phosphate receptors.

The report regarding the full amino acid sequencing of the enzyme was reviewed and found to be acceptable at the OSE. Sequencing by different techniques confirmed the sequence of the protein. The glycosylation pattern of the enzyme was confirmed using appropriate methods. Other methods were used to determine the purity and presence of impurities or modified forms of the enzyme. The results of these studies were found to be satisfactory, and consistent in both the drug substance lots and reference standards tested. The review found that sufficient studies were done to characterize the purified enzyme.

Based upon the review of the degradation pathway study, it was found that the degradation of r-h $\alpha$ GAL is negligible under normal pH and storage conditions. However, physical and chemical degradation may occur under other specific conditions.

### ***Control of Drug Substance***

Methods used for the release testing were chosen based on the knowledge obtained during characterisation of the protein and as experience with the manufacturing process was gained. The Drug Substance is tested for purity, identity, biological activity, safety, and bioburden. In addition, methods are used for the detection and quantification of impurities, as well as, other tests are used to ensure appropriate glycosylation of the protein. All methods used for these purposes have been validated as recommended by ICH guidelines Q2A<sup>4</sup> and Q2B<sup>5</sup>.

Specifications were set based on manufacturing history and data from batch analyses. Specifications for the Drug Substance from other jurisdictions were evaluated. By doing so, more stringent specifications were agreed upon during the review process and these will be used for Fabrazyme® lots manufactured for the Canadian market, post-approval.

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<sup>4</sup> ICH Harmonised Tripartite Guideline, *Text on Validation of Analytical Procedures*

<sup>5</sup> ICH Harmonised Tripartite Guideline, *Validation of Analytical Procedures: Methodology*

The Quality Control (QC) labs were inspected during the OSE. Sample receipt and storage were considered to be satisfactory. Samples are tested in a timely manner by appropriately trained staff. A complete QC test package for a lot of Drug Substance was reviewed and found to be acceptable.

Since no international standard was available for this product, the manufacturer developed an in-house reference standard which was adequately characterized using the same tests as those used for the release of the Drug Substance, as well as, some additional tests. The use of this in-house standard for testing Drug Substance, was considered to be acceptable. It was found that appropriate storage conditions for the reference standard were assigned, based upon the results of the stability studies conducted.

### ***Stability***

The stability study test methods chosen were a subset of the QC release test methods. From accelerated stability studies, forced degradation studies, and manufacturing history, these particular test methods were shown to be appropriate to evaluate the stability of the Drug Substance. Based upon the real-time stability study data submitted, the proposed hold times and storage conditions for the key intermediates were supported and considered to be satisfactory. Based upon the real-time and accelerated stability study data submitted, the proposed shelf-life storage and shipping conditions for the drug substance were supported and considered to be satisfactory.

### ***2.2.2 Drug Product***

#### ***Description and Composition***

Fabrazyme® is a sterile, lyophilized powder available in two strengths, 5 and 35 mg. The 5 and 35 mg strengths are filled respectively in 5 and 20 cc Type I glass vials, with 20 mm gray butyl stoppers and aluminum flip off caps. The powder is reconstituted with Sterile Water for Injection and it is further diluted into an infusion bag containing 0.9% sodium chloride, for immediate use.

#### **Composition**

Each 35 mg vial contains:

- Agalsidase beta 37 mg\* (total amount)
- Mannitol 222 mg
- Sodium Phosphate Monobasic, Monohydrate 20.4 mg
- Sodium Phosphate Dibasic, Heptahydrate 59.2 mg

\*Extractable dose of 35 mg/vial

Each 5 mg vial contains:      Agalsidase beta 5.5 mg\* (total amount)  
   Mannitol 33 mg  
   Sodium Phosphate Monobasic, Monohydrate 3.0 mg  
   Sodium Phosphate Dibasic, Heptahydrate 8.8 mg

\*Extractable dose of 5 mg/vial

Fabrazyme® does not contain any preservatives.

### ***Pharmaceutical Development***

A lyophilized dosage form for Fabrazyme® was chosen in order to maximize its shelf life. The formulation was chosen based on the results of preformulation studies. The formulation is comprised of r-hαGAL at 5 mg/mL in a sodium phosphate buffer, and mannitol. The inclusion of mannitol provides additional stabilization, serves as a tonicity modifier, and as a suitable bulking agent during lyophilization.

Since the preparation of an individual patient dose is based upon weight, two strengths were developed to minimize product waste.

Container closure validation studies were satisfactorily conducted using bacteriological challenge and sterility testing to ensure integrity of the container closure system. The Type I glass vial (USP/EP) and the siliconized gray butyl rubber closure were determined to be suitable components as they are highly resistant to hydrolysis and therefore minimize any potential chemical interactions with the product. Using this container closure system, Fabrazyme® has been satisfactorily demonstrated to be sterile and stable.

### ***Manufacturing Process and Process Controls***

Recombinant human α-galactosidase (r-hαGAL) Drug Substance is formulated with mannitol, sterile filtered and aseptically filled into vials. In order to retain the sterility of the filtered Drug Product, it is filled into depyrogenated glass vials, stoppered and sealed in rooms with the appropriate air classification.

The validation of this part of the manufacturing process was satisfactorily executed by manufacturing three consecutive Drug Product lots of both the 5 and 35 mg strengths. In addition to the validation of the compounding, sterile filtration, vial filling and lyophilization, the manufacturer demonstrated adequately, their ability to fill aseptically by performing the appropriate media fill studies.

The sterile filtration step, the filling line set up, and the filling operation were observed during the OSE. In addition, the facilities used to prepare the components and the transfer vessels were inspected. In-Process controls including both pre- and post-use filter integrity testing, and initial and periodic weight checks for filled vials are performed. All operations were found to be satisfactory.

### ***Control of Drug Product***

Standard Pharmacopoeial tests are performed on the lyophilized Drug Product and the reconstituted product using the acceptable in-house reference standard. In addition, the reconstituted Drug Product is tested using several identification and quantitative analytical tests, which adequately cover the main attributes of the product: identity, purity, biological activity, excipients, bacterial endotoxin, and sterility.

The validation reports provided for these methods were reviewed and found to be satisfactory. All methods were validated according to the recommendations of ICH guidelines Q2A and Q2B.

### ***Stability***

Accelerated and real-time stability data which support an expiry dating of 24 months at 2 to 8 °C for both the 5 and 35 mg strengths, were supplied.

### ***2.2.3 Facilities and Equipment***

The manufacturing process of Fabrazyme® occurs at two Genzyme sites. The buildings at these two sites are designed and operated as multi-product facilities. The Heating, Ventilation, and Air Conditioning (HVAC) systems in both facilities are appropriately designed for the work carried out (e.g. separate air handlers for cell culture area and for each purification suite and for filling room). Each building has a Water For Injection (WFI) system that is adequately designed and maintained to produce WFI for use in manufacturing.

Upstream and downstream processing steps are performed in separate purification suites. The potential for cross-contamination is minimized through the use of dedicated product contact equipment (e.g. cell culture spinner flasks and resins), via the use of dedicated suites (e.g. purification), and temporal segregation with appropriate cleaning procedures in between production runs (e.g. filling line). These procedures were reviewed in-house during the OSE and were found to be satisfactory. The suites are constructed of

appropriate materials. The environmental monitoring data reviewed during the OSE demonstrated that all facilities were and are expected to be appropriately controlled with respect to microbial and particulate levels.

The cleaning validation data of both dedicated and shared product contact equipment used in the manufacturing of the Drug Product was reviewed and found to be acceptable in terms of removal of residues and microbiological control.

The facilities involved in the manufacture of the Drug Substance and Drug Product were evaluated by a team, consisting of a Lead Inspector and a Product Specialist from the Biologics and Genetic Therapies Directorate, Health Canada. During the OSE, the facilities were found to be compliant with Divisions 1, 2, 4 and 8 of the *Food and Drug Regulations*. The responses to the Inspection Exit Notices were reviewed, all Observations were satisfactorily resolved, and Amended Inspection Exit Notices were issued.

#### ***2.2.4 Adventitious Agents Safety Evaluation***

Viral clearance validation of the manufacturing process, including the chromatography and nanofiltration steps, was done according to ICH guideline Q5A, and with the use of appropriate model viruses. These studies were performed using scale-down models of the manufacturing process, and included new and used chromatography resins. Appropriate rationales were provided to determine which viruses would be tested at each step. Sufficient viral clearance was obtained based on the viral load from the endogenous retroviral particle determination. Appropriate clearance was also obtained for the other model viruses and relevant viruses. Results for new and used chromatography resins were similar.

The viral safety of Fabrazyme® was adequately demonstrated through the overall Quality Control and testing strategy of the biological materials used, the cell banking system, and bioreactor harvest, as well as, the capacity of the manufacturing process to reduce and/or remove potential viral contaminants, as shown from the viral clearance studies.

#### ***2.2.5 Quality Summary and Conclusion***

From a chemistry and manufacturing perspective, a Notice of Compliance was issued based upon the following:

- the drug submission information was reviewed and all outstanding issues were satisfactorily resolved;

- an OSE was conducted, the facilities were found to be complaint, and all Observations have been resolved; and
- the laboratory testing of the consistency lots was satisfactory.

The Drug Substance and Drug Product Specifications were accepted based on the manufacturing history. The protein impurity specification was based on a statistical evaluation of the data but a few high results appeared to skew the results. As a result, the company made the commitment to revise the protein impurity specification after analysing the data from 20 lots of Drug Product, and to submit this information post-approval.

The expiry dating for both strengths was approved for 24 months at 2 - 8 °C based upon the results of real-time stability studies of 5 and 35 mg lots manufactured from Drug Substance produced at the small scale, and 35 mg lots manufactured using Drug Substance produced at the large scale. The company made the commitment to provide the stability data for the 5 mg strength made from drug substance produced at the large scale.

Post- approval, Fabrazyme® was placed in Lot Release Group 4<sup>6</sup> (i.e. annual notification of lots sold in Canada), based upon the data provided in the paper submission, the results of the OSE, and the in-house laboratory testing.

## 2.3 Preclinical Basis for Decision

### 2.3.1 Pharmacodynamics

Three pre-clinical studies set out to determine the efficacy of agalsidase beta in reducing and/or eliminating GL-3 collected in the kidney, heart, spleen, liver, lung, skin, and plasma. The experiments also set out to determine the most effective dosage.

All of the studies indicated that agalsidase beta reaches the lysosomes in an active form and reduces GL-3 levels in organs and tissues, and in all doses tested, in a time- and dose-dependent manner. The r-hαGAL is particularly effective in the liver, heart and spleen where GL-3 reductions were most pronounced. Cumulative doses of 0.5 to 0.6 mg/kg of r-hαGAL completely reduced GL-3 in the liver after one to two days. It took more cumulative doses of r-hαGAL—5 to 6 mg/kg—to do the same in the kidney, heart and spleen.

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<sup>6</sup> Reference: *Evaluation Groups and Lot Testing Requirements and Review/Testing Approval of Biological Drug Lots*

There were no undesirable pharmacodynamic effects observed in either of the trial studies. Even though these studies do not offer any data to support an effect on the clinical course of Fabry's Disease (the mice are phenotypically normal), they do support the hypothesis that intravenously administering r-h $\alpha$ GAL will positively affect bodily tissues by depleting GL-3 deposits. Thus the studies confirm the pathophysiological and biochemical bases for the use of r-h $\alpha$ GAL as an enzyme replacement therapy in humans. These studies confirmed the proposed clinical dosage as useful in decreasing GL-3 levels.

### **2.3.2 Pharmacokinetics**

Three pharmacokinetic (PK) studies were conducted on rats and canine models. Doses varied, in the first two studies, from single IV bolus injections of 3 mg/kg to escalating IV bolus doses with a  $\geq$ 48-hour wash-out at minimum between doses that varied from 3mg/kg, to 9 mg/kg and 27 mg/kg. There appeared to be no differences in PK parameters for either sex in the canine models. The third study applied a weekly bolus (27 times for 26 weeks) with the dose varying from 3 mg/kg, 10 mg/kg, and 30 mg/kg.

The pharmacokinetics profile of r-h $\alpha$ GAL was linear at the lower dose (3 mg/kg) and non-linear at the higher doses (9 and 27 mg/kg) in both the rats and the dogs. Because r-h $\alpha$ GAL was cleared at a slower rate in its higher doses, to facilitate a more rapid clearance, a threshold was identified at 50 micrograms/ml for rats and 100 micrograms/ml for dogs, below which more rapid clearance of the drug took place.

It was observed that r-h $\alpha$ GAL appears to accumulate in rat livers 24 hours after the last of 27 weekly doses of 30 mg/kg—the only dose tested for accumulation in that organ. No reasons for the increase were given; however, no histopathologic or liver enzyme changes were associated with this accumulation. Most of the drug activity was located in the liver of normal mice and rats given single intravenous bolus doses of 0.25 to 3.0 mg/kg, followed by the spleen, kidneys, lungs, heart, and brain. There appeared to be no difference in the biodistribution of r-h $\alpha$ GAL in rats when a 3 mg/kg dose was administered either as a bolus or as a two-hour infusion.

### **2.3.3 Toxicology**

There were four different studies performed with the Sprague-Dawley rats and one with beagle dogs. Various parameters were evaluated. Doses varied from a single IV bolus, a weekly IV bolus times 14 and 27 weeks, a weekly IV bolus times 12 and 24 weeks, and every other week, IV infusion for 25 weeks with a two week recovery.

No treatment-related findings in clinical pathology, microscopic and macroscopic, or in organ weights were observed. However, severe hypoactivity generally associated with cyanosis, as well as, laboured breathing and swelling of the extremities was observed after the third dose of r-h $\alpha$ GAL in Week 3 in one of the studies conducted on the rats in which the animals received a weekly injection of up to 30 mg/kg r-h $\alpha$ GAL for 27 weeks. This was not unexpected considering that a human protein was administered to rats in this study. This was interpreted as a hypersensitivity reaction that was managed by treatment with diphenhydramine (DPH). For the duration of the study, therefore, the rats were injected with 5 mg/kg DPH as a prophylactic which successfully blocked the hypersensitive response. As a result of the preclinical studies, hypersensitivity was identified as the most likely adverse reaction. However, in the clinical trials, patients who experienced symptoms suggestive of hypersensitivity have been effectively managed through a reduction in the rate of infusion and/or pre-treatment with oral antihistamines, antipyretics, non-steroidal anti-inflammatory drugs and/or corticosteroids.

There were no studies done to determine the safety profile of the drug on pregnancy, nor were there studies of reproductive function or perinatal toxicity.

Maximum clearance of GL-3 was observed one to two weeks following the administration of a single dose of r-h $\alpha$ GAL. Reaccumulation did not occur for approximately one month post-dose. As well, clearance of the agalsidase beta was reduced at higher dosages. Study data also indicated that there exists the potential for tolerization (through the development of antibodies) to agalsidase beta with its repeated use.

There were no studies done to assess the mutagenic potential of the drug. However, such a potential is not anticipated. Also, the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to drugs derived from biotechnology, and, therefore, were not considered as contributory.

No studies were done for carcinogenicity, even though agalsidase beta is designed for long-term treatment, with a total exposure over a lifetime exceeding six months. However, because the drug structure is based on a recombinant human glycoprotein structure combined with mannitol and phosphate as excipients, there is no anticipated carcinogenic potential. The biochemical properties of  $\alpha$ Galactosidase are well documented with no known DNA interactions. Given the shortened lifespan of patients suffering from Fabry's Disease, the potential benefits would in all cases outweigh the risks from enzyme replacement and the toxicity profile of Fabrazyme®

### **2.3.4 Preclinical Summary and Conclusion**

Intravenous application of agalsidase beta appears to target key organs and tissues with GL-3 deposits, reaching the lysosomes in an active form. The pharmacodynamic and pharmacokinetic studies conducted on mice, rats and dogs indicate, overall, that agalsidase beta is effective in reducing GL-3 deposits in tissues and organs of the body.

The drug appears to be most effective in the liver, heart and spleen, followed by the skin and lungs. With cumulative treatment, the kidney shows significant reduction of GL-3. The data also indicates that clearance of the agalsidase beta was reduced at higher doses of the drug.

Hypoactivity associated with hypersensitivity was evident at week 3 for some of the animals studied that received a weekly injection of up to 30 mg/kg r-h $\alpha$ GAL but was mitigated with the use of prophylactics. Any remaining concerns were carried forward to the clinical trial studies and recommendations were made for the design of the trial and patient follow-up, accordingly.

There was also an indication of the potential for the development of antibodies with long-term use of the drug.

There were no effects of agalsidase beta on embryo-fetal development. In conclusion, the pre-clinical data clearly support the use of Fabrazyme® at the dose of 1.0 mg/kg, every two weeks.

## **2.4 Clinical Basis for Decision**

Fabrazyme® is a recombinant human  $\alpha$ -GAL (r-h $\alpha$ GAL) enzyme intended as replacement therapy (ERT) for patients with the genetic disorder of Fabry's Disease. This exogenous source of  $\alpha$ GAL—produced by genetically engineered Chinese Hamster Ovary cells—is a highly purified recombinant form of the naturally-occurring human lysosomal hydrolase enzyme  $\alpha$ -GAL. It reduces and removes GL-3 deposits from the vascular endothelium of organs, tissues, urine and plasma of Fabry's Disease sufferers. In clinical trials, it effectively cleared glycosphingolipid (GL-3) deposits from the renal vascular endothelium and decreased assay levels of GL-3 in biopsied kidney tissue.

There is currently no specific curative treatment for Fabry's Disease, which results in peripheral neuritis, angiokeratoma corporis diffusum universale, renal failure, cardiomyopathy, cerebrovascular problems resulting in chronic morbidity and premature death. Patient management has, to date, been limited to symptom control and supportive measures.

### 2.4.1 Human Pharmacology

Two clinical studies were the primary source for clinical pharmacology data.

The Phase I/II Study, the only dose-finding study with ERT for Fabry's Disease, was a multi-dose, open-label study of 15 patients with Fabry's Disease. Conducted at one centre, the Mount Sinai School of Medicine in New York, the trial was organized around five dosing groups for a total of fifteen patients. They were treated with intravenous infusions of r-h $\alpha$ GAL, in two dosing regimens (every 14 days or every 48 hours) of varying amounts (0.3mg/kg, 1.0 mg/kg, 3.0 mg/kg).

**Dose Regimens**

| <b>Number of Patients</b> | <b>Dose</b>                          | <b>Dose Group</b> |
|---------------------------|--------------------------------------|-------------------|
| 3                         | 0.3 mg/kg every 14 days for 5 doses  | 1                 |
| 3                         | 1.0 mg/kg every 14 days for 5 doses  | 2                 |
| 3                         | 3.0 mg/kg every 14 days for 5 doses  | 3                 |
| 3                         | 1.0 mg/kg every 48 hours for 5 doses | 4                 |
| 3                         | 3.0 mg/kg every 48 hours for 5 doses | 5                 |

The patients were evaluated for vital signs (heart rate, blood pressure, respiration rate, body temperature, and pre- and post-study body weight). As well, they were assessed by magnetic resonance imaging (MRI) of the heart and abdomen, with thermal discrimination tests and ophthalmologic examinations. Those patients in the every 48-hours treatment group were also given sympathetic skin response tests. All of the patients were also assessed with electrocardiograms (ECG) and monitored for any adverse reactions, especially those suggestive of hypersensitivity. Lab analysis included blood chemistry, hematology, electrolytes, lipids, drugs of abuse, urinalysis, and IgG antibodies to r-h $\alpha$ GAL.

In the Phase I/II Study, r-h $\alpha$ GAL effectively cleared GL-3 from the endothelial cells of the liver, heart, and skin. The drug also decreased plasma GL-3 content and lowered urinary levels of GL-3.

The other study—the Phase III Study—was a multinational, multicentre, placebo-controlled, double blind, randomized study of 58 patients with Fabry’s Disease randomized at eight study centres in the United States and Europe, and treated for approximately 20 weeks. It was to-date, the largest study with the highest enrollment of patients with Fabry’s Disease. Twenty-nine patients were treated with 1.0 mg/kg (0.9 mg/kg to 1.1 mg/kg) of r-h $\alpha$ GAL while the other 29 were given placebo. The drug was administered intravenously at a rate that did not exceed 0.25 mg/min. over the course of about four to six hours. Dosage was administered every two weeks for a total of 11 infusions.

The Phase III Study data indicates that r-h $\alpha$ GAL has a global restorative effect on vascular endothelium. There was a highly statistically significant difference ( $p < 0.001$ ) between the Fabrazyme and placebo treatment groups (20/29 (69%) of patients treated with r-h $\alpha$ GAL achieved the primary endpoint of clearance of GL-3 inclusions from the capillary endothelium of the kidney after 20 weeks of treatment versus 0% in the placebo treatment group). The greater proportion of patients with a kidney majority score of “0” occurred in the Fabrazyme group. Heart biopsies in 21 of the patients (73%) displayed a near-normal anatomical appearance and achieved a zero score. Skin biopsies achieved 100% of a “near-normal” structure, zero score. Both the r-h $\alpha$ GAL-treated heart and skin endothelial changes were considered highly statistically significant when compared with the placebo group.

Both study trials support treating patients with Fabry’s Disease with agalsidase beta to clear glycosphingolipid (GL-3) deposits from the vascular endothelium of various tissues and renal vessels—their deposits being the major cause of morbidity and mortality in the population of patients with Fabry’s Disease. Data comparisons of treated patients to the placebo group indicates a reversal or halting of progressive renal disease in the treated group compared to the no change or worsening of patients with Fabry’s Disease in the placebo group.

The mobilization of the glycosphingolipids from the end organs appeared to result in reduced pain, thereby improving the quality of life for sufferers of Fabry’s Disease. The fact that the primary end-points were achieved would seem to confirm the efficacy of r-h $\alpha$ GAL.

### **2.4.2 Pharmacodynamics**

In the Phase I/II Study, the pharmacodynamic activity of r-h $\alpha$ GAL was studied by evaluating GL-3 clearance from tissue and plasma. Analysis indicated that concentrations of GL-3 in tissue were cleared with applications of r-h $\alpha$ GAL, and quite rapidly from plasma. In particular, GL-3 deposits were mobilized from renal vascular endothelium, skin and heart. As Fabry's Disease is characterized by an inherited deficiency in the lysosomal enzyme  $\alpha$ -galactosidase A which leads to progressive accumulation of glycosphingolipids (predominantly GL-3)—and which, over the years, can trigger severe responses such as renal failure, cardiomyopathy, and cerebrovascular problems leading to morbidity and premature death—the reduction of GL-3 in patients treated with r-h $\alpha$ GAL is strong evidence, based on surrogate markers that prove the efficacy of the drug.

Results were similar in the Phase III Study for the treated group. These same effects (the depletion of GL-3 deposits in tissue and skin) were not observed in the placebo group. The primary efficacy endpoint of this particular study was the reduction of GL-3 in the vascular endothelium of the kidney. This indicates that GL-3 mobilization in the tissue and organs of the treatment group were directly attributable to infusions of r-h $\alpha$ GAL.

### **2.4.3 Pharmacokinetics**

In the Phase I/II Study, GL-3 was reduced to minimal levels by the second infusion in the 1 and 3 mg/kg dosing groups of the 14-day schedule, and remained there for the duration of the study. Minimal levels of GL-3 were not reached until the third or fourth infusion with the 0.3 mg/kg dose. As area under the curve (AUC) values were disproportionate to the dose (increasing from approximately 80 to 500 to 4000 micrograms-min/mL as the dose was increased from 0.3 mg/kg to 1 to 3 mg/kg), this suggests that r-h $\alpha$ GAL was partially cleared via concentration-independent (first-order) kinetics. In contrast, the terminal elimination half-life ( $T_{1/2}$ ) appeared unaffected by dose. This too, is consistent with elimination being governed, in part, by first-order concentration-independent kinetics.

The Phase III Study collected blood samples for pharmacokinetic analysis and leukocyte enzyme uptake. Blood samples for the analysis and intake were obtained pre-infusion with r-h $\alpha$ GAL, and periodically after infusion beginning 30 minutes after the start of the infusion and ending 10 hours after the infusion was completed. Assessments took place at visits 1, 7 and 11.

The pharmacokinetics of r-h $\alpha$ GAL appeared to be affected by the formation of IgG antibodies to r-h $\alpha$ GAL, following repeat administration. As a result, intra- and inter-patient variability in parameters, such as area under the curve to the time of collection (AUC) and clearance (CL), were observed among the three pharmacokinetic assessments. The significance of a change related to antibody presence or titre is unclear. It is also not clear whether this effect is a true *in vivo* change in pharmacokinetics or an *in vitro* artifact produced by the potential interference of an immune complex present in an activity assay. The observed changes in pharmacokinetics did not appear to affect the efficacy outcomes.

Repeated infusions of r-h $\alpha$ GAL resulted in a progressive increase in the uptake of r-h $\alpha$ GAL in the leukocytes in the majority of the r-h $\alpha$ GAL treated patients.

It is unclear as to whether or not these changes in pharmacokinetics will affect the efficacy of the drug, nor is the significance of antibody presence understood; therefore, it is unclear whether long-term efficacy of the drug will be maintained since life-long replacement therapy will be necessary for these patients.

Agalsidase beta is a protein and, as such, is not expected to bind to other proteins; rather it is expected that it will degrade metabolically through peptide hydrolysis. Impaired liver function should therefore not affect its pharmacokinetics in any significant way, nor are drug-drug interactions expected. For those reasons, neither *in vitro* interaction studies nor *in vivo* clinical drug interaction studies were conducted.

#### **2.4.4 Clinical Efficacy (analysis of main studies)**

Fabry's Disease affects a very small segment of the population. Because of the rarity of the disease, the clinical trial studies offered their own challenges. There were a relatively small number of Fabry's Disease patients available, therefore, for participation in the clinical trials and this imposed narrow parameters on the studies. As well, there were no benchmarks for preventing or ameliorating the accumulation of GL-3 in organs and tissue. However, since the most significant manifestation of Fabry's Disease is renal failure, the primary endpoint selected for the studies was the measurable clearance of GL-3 from the renal vascular endothelium.

Two clinical trials were performed (Phase I/II and Phase III; see details, above). The Phase I/II study was primarily a clinical, pharmacodynamic, pharmacokinetic and safety study. The Phase III Study provided significant information on the clinical pharmacology of r-h $\alpha$ GAL. All of the patients continued into an extension study. In the Phase III study—a larger one composed of 58 patients (from 65 originally screened)—there were

no statistically significant differences observed between the placebo-treated and the r-h $\alpha$ GAL-treated groups in terms of age, age group, weight, height, gender, or ethnicity. Neither were differences noted in baseline levels of plasma GL-3, endogenous plasma  $\alpha$ GAL activity, endogenous leukocyte  $\alpha$ GAL concentration, and historical data regarding  $\alpha$ GAL activity. Both groups were comparable at baseline in demographics, history of Fabry's Disease, and baseline scores for primary, secondary and tertiary endpoints.

The studies indicate that the glycosphingolipids were mobilized from their accumulation in renal endothelium resulting in pain reduction and improved quality of life for sufferers of Fabry's Disease. Plasma GL-3 levels were significantly decreased to a greater extent for the drug-treated patients. These same effects of GL-3 mobilization and decrease in pain intensity was not observed in the placebo group. Primary endpoints were achieved and shifted to secondary endpoints. (The primary endpoints were the mobilization of GL-3 from the vascular endothelium of the kidney; secondary endpoints were the overall changes in the composite score of GL-3 deposits in the endothelium of the kidney, skin and heart through LM (light microscopy) assessments and ELISA (a whole-tissue assay) measurements. Pain reduction was also considered as a secondary endpoint.) Statistical significance was reached for the number of episode-free (pain-free) days recorded by the patients in their diaries, the neuropath symptoms and change scores favouring r-h $\alpha$ GAL-treated patients, the modest increase in sweat volume for treated patients (as opposed to a decrease in sweat volume for the placebo group), and a decrease from baseline for plasma GL-3 levels that was significantly greater for treated patients.

Immune reactivity was anticipated with those patients having low or undetectable levels of endogenous  $\alpha$ GAL. Patients were pretreated with acetaminophen (900 to 1,000 mg) and hydroxyzine (25 to 50 mg) to reduce the potential for hypersensitivity reactions. However, a number of the patients developed IgG antibodies. It is not known if such a development will alter the long-term efficacy of the drug.

In summary, consistent results in the clearance of GL-3 from the kidney, heart and skin were obtained in the patients under study. Biweekly intravenous injections of 1 mg/kg of r-h $\alpha$ GAL to patients with Fabry's Disease is an effective enzyme replacement therapy for removing GL-3 deposits from the capillary endothelium (vasculature) of various tissues and implies a considerable potential clinical benefit for the kidney and heart (implicated in the mortality of Fabry's Disease). The strongest evidence for the efficacy agalsidase beta was in the mobilization of GL-3 from the end organs. In the liver, the two principal reservoirs of glycosphingolipids—the endothelial cells of the sinusoids and the Kupffer cells—were virtually cleared of glycosphingolipids. This was confirmed by ELISA which demonstrated a greater than 84% mean clearance of GL-3 from this organ.

However, while there is evidence that GL-3 is mobilized from the liver, kidney, heart and skin, there is also evidence that antibodies against r-h $\alpha$ GAL do develop, and this factor is a concern for the long-term use of the drug. Nonetheless, patients treated with r-h $\alpha$ GAL suffered less pain and enjoyed an improved quality of life (although this also appeared to be a strong placebo effect; the same was true for the SF-36 Health Status Survey, a tertiary endpoint, where both the placebo-treated and drug-treated groups noted improvement from baseline indicators). Statistically significant, clinically credible primary endpoints were reached in a disease that has had no treatment available for it to-date. The recommended doses were determined to be adequate. The sponsor has committed to further study with ongoing monitoring, which will help to determine the long-term safety and efficacy of this replacement therapy, as well as, extending the studies.

#### **2.4.5 Clinical Safety**

Because of the relatively small number of the population afflicted with Fabry's Disease, there were few patients available for study purposes. The evaluation, therefore, of the clinical effect was intended to be exploratory in nature. Safety was measured by noting any adverse experiences, changes in vital signs, ECG and echocardiogram results, a full physical examination as a baseline, and clinical laboratory safety parameters.

In the Phase I/II Study, almost all of the adverse reactions were mild or moderate in severity. Even though the nature of these reactions were transient in presentation and some patients had a pre-existing history of high blood pressure (secondary to kidney disease related to Fabry's Disease), patients were still able to safely receive infusions of r-h $\alpha$ GAL. However, because the study was of short duration, the long-term effects of the drug on blood pressure could not be tested.

Fifty-three percent of the patients developed IgG antibodies specific to r-h $\alpha$ GAL by study completion as detected by seroconversion. An immunological response was detected as early as the second infusion. Additionally, 27% of the patients developed hypersensitivity reactions of a mild to moderate intensity. Of the eight patients who seroconverted, four patients developed symptoms suggestive of a hypersensitivity-type reaction. All patients responded to treatment and two patients were successfully rechallenged with r-h $\alpha$ GAL. In patients who experience hypersensitivity reactions, appropriate pre-treatment regimens, including antipyretics and antihistamines, as well as, a reduction in the rate of infusion, should be considered when appropriate.

In the larger Phase III placebo-controlled study, no deaths were reported in either treatment group. All of the participants experienced at least one adverse event but none were dropped from the study as a result. Five patients in each group suffered serious adverse events but they were due largely to biopsy procedures, underlying medical conditions or accidents that had no relation to the study. All of the affected patients recovered, with the exception of one patient from the placebo group who suffered a severe fall and is experiencing problems associated with head trauma. Three adverse events—rigors, fever and skeletal pain—occurred at a statistically significant higher frequency in the r-hαGAL-treated group compared to the placebo group. The first two were infusion-associated; the latter was not considered to be clinically relevant. All of these adverse events were successfully managed with pre-treatment medications and a reduction of the infusion rate.

The table, below, provides an overview of the most notable Adverse Reactions.

**Incidence of Related Adverse Events:**

Combined Trials, Phase III, Phase III Extension and Phase II Japan

| <b>Body System</b>                        | <b>5-10%</b>   | <b>10-50%</b>                                    | <b>&gt;50%</b> |
|---|--|--|----------------|
| <b>Body As A Whole - General</b>          | Pain, Fatigue, Leg pain, Asthenia, Malaise                                   | Temperature changed sensation, Fever, Chest pain | Rigors         |
| <b>Gastro-Intestinal System</b>           | Vomiting, Abdominal pain   | Nausea   | ---            |
| <b>Central/ Peripheral Nervous System</b> | Tremor, Dizziness, Paraesthesia  | Headache   | ---            |
| <b>Respiratory System</b>                 | Bronchospasm, Throat tightness   | Rhinitis, Dyspnea                                | ---            |
| <b>Cardiovascular - General</b>           | Edema in extremities, Heart valve disorders, Heart disorder, Cardiac failure | Hypertension                                     | ---            |
| <b>Secondary Terms</b>                    | ---  | Pain of Fabry's Disease (extremity pain)         | —              |
| <b>Heart Rate and Rhythm</b>              | Tachycardia, Bradycardia   | —  | ---            |
| <b>Musculoskeletal System</b>             | ---  | Myalgia  | —              |
| <b>Psychiatric</b>                        | ---  | Somnolence                                       | —              |
| <b>Red Blood Cell</b>                     | Anaemia  | —  | ---            |
| <b>Skin and Appendages</b>                | Pruritus   | —  | ---            |
| <b>Urinary System</b>                     | Renal function abnormal  | —  | ---            |
| <b>Vascular (Extracardiac)</b>            | ---  | Flushing   | ---            |
| <b>Vision</b>                             | Lacrimation abnormal   | —  | ---            |

In the Phase III Study, patient blood chemistry, hematology and urinalysis were monitored at baseline, visit 4, 7, 10 and 11 (week 20) for changes in value over the course of treatment. Values at baseline were normal for both treatment groups. The percent shift of chloride was greater in the r-hαGAL -treated group compared with the placebo group (11.5% versus 3.6%); however there was no demonstrable pattern to indicate that treatment will affect blood chemistries with any clinically relevant significance. Similar changes were noted in the hemoglobin/ hematocrit levels in both the placebo and treatments groups. The variations appear to have no clinical consequence for hematologic parameters. Changes were also observed in neutrophils, however, shifts in their increase or decrease are thought not to be of any clinical consequence.

Urinalysis (by reagent strip method) does not add to any conclusions regarding the safety of Fabrazyme®. There were no relevant findings at baseline or at visit 11 (week 20) for either treatment group other than the presence of protein—an anticipated finding in any case in patients with Fabry’s Disease resulting from deposits of glycosphingolipids in the basement membrane of renal glomeruli.

Vital signs remained within normal limits, even at week 20. Elevations in blood pressure experienced by three patients were attributed to an infusion-associated reaction and were not sustained. No related toxic effects between baseline and study completion were observed with r-hαGAL in either of the Phase I/II and Phase III Studies based on physical examinations, ECG or echocardiogram findings.

It is not known how agalsidase beta affects pregnant or lactating women.

There was no specific data to enable an assessment of the pediatric safety profile of the drug however, the risk/benefit considerations are even more favourable in this population as the replacement enzyme therapy would be given before there is as extensive accumulation of sphingolipids in the tissues of the affected children than in adults.

#### **2.4.6 Issues Outstanding**

The following five post-market commitments were agreed upon:

##### **Completion of Ongoing Clinical Trials:**

1. The final study report, AGAL-008 “A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Fabrazyme® on Progression of Renal Disease and Significant Clinical Events in Patients with Fabry’s Disease”, will be submitted by September 30, 2004.

2. The final study report, AGAL-016-01 “A Multicenter, Phase I/II Open-Label Study of Fabrazyme® Replacement Therapy in Pediatric Patients with Fabry’s Disease”, will be submitted by November 30, 2005.
3. The final study report AGAL-025-03 “A Multicenter, Open-Label, Phase IV Extension Study of the Safety and Efficacy of Fabrazyme® in Fabry’s Disease”, will be submitted by April 30, 2006.

**Continuation of the Fabry’s Disease Registry:**

4. The sponsor has already begun the Fabry Registry and commits to continuing it and to submitting the final study report to the Biologics and Genetic Therapies Directorate (BGTD) by September 30, 2020.

**Packaging Flexibility:**

5. A 35 mg vial sized dosage strength will be marketed in Canada, in addition to the 5 mg vial.

## **2.5 Benefit/ Risk Assessment and Recommendation**

### **2.5.1 Benefit/ Risk Assessment**

The current symptomatic treatments for Fabry’s Disease have been unable to prevent or impede the progressive vascular damage and resultant failure of organs such as the kidney, heart, and brain in patients with the disease.

The benefits of restored vascular endothelium in the kidney as well as the improvement in vascular endothelium, seen in both heart and skin biopsies of r-h GAL treated patients, can be taken as proof of the validity of the surrogate nature of the main trial endpoint and therefore, as indicators of ‘clinical benefit’.

Four of 15 patients in the Phase I/II study and 12 of 29 patients in the Phase III study reported symptoms that were suggestive of infusion-associated reactions during treatment with r-h GAL. All reactions in the Phase I/II study responded to antihistamines and/or steroids, while Phase III infusion-associated reactions were successfully managed with infusion rate reduction and various pretreatment regimens. None of these reactions precluded further treatment with r-h GAL and all Phase III patients continued treatment in the open-label extension study.

The data relevant to the pediatric population was limited due to the small size of the study population; however, the safety profile of the drug in the Pediatric population with Fabry's Disease can be implied. The risk of hypersensitivity reactions due to development of IgG antibodies is the same concern in paediatric patients as in the adults treated with Fabrazyme®. Furthermore, the implied clinical benefits of r-h GAL therapy must be weighed against the risks of not treating children who would continue to accumulate glycosphingolipids in their tissues, with organ failure as a consequence.

Further demonstration of the durability of response and safety of treatment will be obtained in the ongoing trials as per the post-marketing commitments.

Given the serious and usually lethal manifestations of Fabry's Disease and the relatively minor risks associated with r-h GAL treatment, the potential benefits of enzyme replacement with r-hαGAL outweigh the risks. While not entirely risk-free, Fabrazyme® is comparatively innocuous and its properties are well-characterised, allowing for a significant level of confidence when benefits and risks of Fabrazyme® are considered. The outcomes, both primary and secondary are based on surrogate endpoints; however, there is enough knowledge of the pathophysiology of the disease to allow extrapolation of clinical benefit from the measurements of the urinary excretion of cumulated sphingolipids and improved organ function to conclude that the merits of treating Fabry's Disease with enzyme replacement (Fabrazyme®) have been proven.

### **2.5.2 Recommendation**

Based on the review by Health Canada of data on quality, safety and efficacy, Health Canada considers that the benefit/ risk profile of agalsidase beta (Fabrazyme®) is favourable in the treatment of Fabry's Disease. This view is based on the nature of the disease, its chronicity, the lack of any disease-specific therapy, and the favourable outcomes in clinical trials. The New Drug Submission complies with the requirements of Sections C.08.002 and C.08.005.1 and therefore Health Canada has granted the Notice of Compliance pursuant to section C.08.004 of the *Food and Drug Regulations*.

While the Fabry Registry, sponsored by Genzyme Canada Inc., the drug sponsor—will facilitate the tracking of the natural history and outcomes of patients with Fabry's Disease, it will also assist in the understanding of the variability and progression of Fabry's Disease, including the effects of Fabrazyme® on heterozygous females. The Fabry Registry will also assist in evaluating the long-term safety and effectiveness of Fabrazyme®, which remains unresolved.

There are adequate studies being conducted that will contribute to the knowledge of Fabrazyme® and its efficacy and safety, in both adults and the pediatric population. (See Section 2.4.6 for details.)

### 3 SUBMISSION MILESTONES

| Submission Milestone               | Date             |
|------------------------------------|------------------|
| Request for priority status        |                  |
| Filed                              | May 7, 2001      |
| Approval issued by BGTD            | June 5, 2001     |
| Submission filed                   | August 2, 2001   |
| Screening 1                        |                  |
| Screening Acceptance Letter issued | October 24, 2001 |
| NOC issued by Director General     | January 23, 2004 |