genzyme

Genzyme Corporation
One Kendall Square
Cambridge, MA 02139-1562, U.S.A.
T 617-252-7500
F 617-374-7470

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Subject: **Docket Nos. 02N-0528**
"Draft Concept Papers on Risk Management"

May 28, 2003

Dear Sir/Madam:

Thank you for the opportunity to comment on the "Draft Concept Papers on Risk Management" published in the Federal Register on March 7, 2003. Below are Genzyme's comments for your consideration

I. Pre-marketing Risk Assessment Draft Concept Paper

A. Generation and acquisition of safety data during development

1. The Draft Concept Paper is overwhelmingly oriented to risk management issues and strategies appropriate to traditional, systemically absorbed drugs used for common chronic diseases. Special consideration needs to be given to biological products, non-systemically absorbed drugs and drugs or biologics used for the treatment of orphan and ultra-orphan diseases (patient populations < 2000). For example, the Draft Concept Paper recommends that QTc prolongation be assessed for all drug development programs. This is generally not appropriate for biological products. Risk assessment strategies for pharmaceutical products do not necessarily apply to biological products. Risk assessment strategies for such products need to be delineated.

Risk assessment is the product of a series of judgments made during pre-clinical and clinical development as well as in the post-approval market setting. The most rigorous pre-marketing testing cannot identify all risks even when large numbers of patients are available for study. Development and availability of new products, particularly those for unmet medical needs, should not be delayed or unduly burdened by resources expended for unnecessary or inappropriate pre-marketing risk assessments.

The Draft Concept Paper on Pre-marketing Risk Assessment has the potential to compel major changes in the way safety and effectiveness are established. For example, the Draft Concept Paper recommends the use of Large Simple Safety Trials (LSST) in the pre-marketing phases of clinical development to aid in the assessment of risk. Although such studies have a role in some post-approval settings, they are not appropriate in the pre-approval setting. By nature and intent they should reflect the broader, more diverse drug usage post-marketing. They are time consuming and costly studies which will invariably delay approval. Their introduction prior to approval qualitatively alters the nature of the evidence required for approval. Furthermore LSSTs are not possible for products for ultra-orphan diseases (patient population < 2000). This was not the intent of the PUDFA III negotiations and is inconsistent with Commissioner McClellan's statements concerning the use of Phase 4, post-marketing studies to expedite the development and approval of newer treatments. Such studies are better alternatives to the use of LSSTs in the pre-approval Phases of development.

2. The Draft Concept Paper should not erect unnecessary or inappropriate pre-marketing barriers for products for unmet medical needs or for products that provide improved medical treatment even if there is existing therapy.

The characteristics of the pre-marketing risk assessment databases called for in the Draft Concept Paper are not applicable to products for:

- acute diseases,
- serious life-threatening illnesses,
- conditions with major unmet medical needs,
- orphan diseases, particularly ultra-orphan diseases, and innovative therapies

These must be considered on a case-by-case basis. We request that the guidance clearly acknowledge these distinctions

3. Inclusion of diverse patient populations in pre-marketing clinical studies presents problems with regard to data interpretation, e.g., heterogeneity or small subgroups. This has the potential to obscure rather than elucidate real safety signals — it could result in more false positives — and confound determination of effectiveness. Pivotal studies are neither designed nor powered to distinguish among "levels of risk" in heterogeneous patient populations or at different doses. Additional study arms present problems with patient recruitment and the overall time to organize, manage and complete clinical trials. Moreover, how is the concept of "level of risk" defined? In addition, we believe that drug development efforts would be enhanced if Agency personnel in the Review and Support Divisions were more receptive to creative clinical and statistical strategies in evaluating data on efficacy and safety, in particular for products with the above listed characteristics.

4. The Draft Concept Paper provides reasonable suggestions and recommendations but lacks clarity and details about how risk assessment ought to be incorporated into development plans. Several suggestions as noted above have the potential to change the standards for approval.

5. The Draft Concept Paper indicates that risk assessment be conducted to ensure that the product's trade name, established name, labels, cartons and package insert not contribute to medication errors. The Paper recommends first-hand information from Health Care Practitioners and consumers prior to approval. There are practical and regulatory issues that need to be addressed. The Agency normally does not clear a trade name until the time of approval. This will not afford a sponsor sufficient time to test the names, packaging and labeling without delaying launch. Pre-approval testing of the trade name and labeling could have implications with regard to pre-approval promotion.

B. Data Presentation and Analysis

1. The multiplicity of analyses creates increased probability of false signals. Multiple analyses must be considered exploratory at best and should not automatically require further studies or labeling changes. The results must be considered in the context of the totality of the data. Sound judgment is required to avoid disproportionate reaction to very small and/or potentially false signals.

2. The use of grouped terms and case definitions must be uniformly adopted if sponsors are to lump and/or split MedDRA terms for analyses. This is necessary in order to make valid comparisons among drugs within a class and across classes, important for determination of labeling. Inconsistency in analyses could results in unfair and misleading labeling.

II. Risk Management Programs

A. Risk Management Planning and Risk Management Programs

1. Risk Management Programs and interventions should balance access to the product with the level of concern. Specific risk reduction objectives should be customized to the specific risks of concern and the individual product benefits. RMP must be based on scientific evidence and rely on systems-based interventions that are applied consistently across Programs.

According to the Draft Concept Paper—Risk Management Programs, a sponsor could at any time during development or after approval voluntarily submit a proposed RMP or FDA could propose to the sponsor that a RMP merits consideration and discussion. The discussion of a RMP would be based on benefits and demonstrated risk profile as characterized by the clinical development program, post-marketing surveillance,

Phase 4 trials or other risk information. The RMP would be broached when the number and severity of a product's risks appear to undermine the magnitude of its benefits in an important segment of potential or actual users. As the Agency points out in the Paper, there is no ready formula for this and the Agency expects the decision to develop, submit and implement an RMP to be made on a case-by-case basis.

The Agency also anticipates that risk management planning will be handled through modifications in the PI. In addition, the Concept Paper indicates that the package insert and post-marketing surveillance will be sufficient in most cases. Specific criteria as well as examples are necessary to guide Sponsors as to when RMPs beyond the package insert would need to be considered. Likewise criteria are needed to determine which level is appropriate. What is the value to the patient? Levels based only on risk alone, rather then risk and benefit, will not serve patients well. It is important that RMPs beyond the PI are the exception rather than the rule.

Criteria are needed to ensure consistency across products in a class or across classes of products. Criteria are also essential to ensure consistency between Centers and within Centers of the FDA. There must be some safeguards for sponsors such as appeal mechanisms that would include review by Advisory Committees to avoid unilateral imposition of RMPs. RMPs may carry significant time and resource costs for both industry and health care practitioners. Given current concerns over rising health care costs, care is needed not to over burden the healthcare system.

2. We believe that the use of RMPs may have an effect on the use and availability of products that could go beyond the intended reduction of risk. For example, the fact that a product is subject to an RMP might cause prescribers to use another product that has similar or other equally important risks. Also, restricted access could negatively affect use by patients who need and would benefit from the product, but may be frightened by the existence or scope of the product's RMP without understanding the underlying risk/benefit analysis. Additionally, providers and patients with chronic diseases may have to contend with multiple products with RMPs, a circumstance that could be confusing and burdensome. We note that patient and physician groups were not well represented at the April Workshop. We believe that their input is vital and must be sought prior to the development of Draft Guidances.

3. There was general consensus at the April Workshop that Risk Management Programs must be system-based. RMPs should be as simple as possible to avoid confusing patients and healthcare providers and must not overburden the healthcare system and consume substantial resources. Consideration must be given to these unintended consequences.

4. The Guidances must include objective, standardized criteria for determination of the various "levels" into which RMPs will be categorized. The selection of categories should be based on the risk/benefit balance rather than on risk

alone. The Guidance should describe what value each level will add to patient protection. Ways must be devised to avoid misinterpretation of "levels" that could stigmatize products by negative connotation associated with higher levels.

5. Risk Management Programs will be costly and resource-intensive for manufacturers, healthcare providers and patients. The Draft Concept Paper appears to place the burden for enforcing appropriate prescriber and patient behavior on the manufacturer whereas the manufacturer has neither the authority nor the wherewithal to accomplish this. Although flexibility, case-by-case determinations and tailoring RMPs to the type and magnitude of the risk were endorsed by the Agency at the Public Workshop, RMPs and the elements of intervention plans should be reserved for the most serious cases.

III. Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

1. The quality of spontaneous reporting could be improved by better education and involvement of healthcare providers and patients. It was notable that neither of these groups was well represented at the Public Workshop. While the pharmaceutical and biotechnology industries are regulated, they are intermediaries. The Agency must promote public awareness and influence professional associations to take part in the system. This could be effective in terms of influencing patients and physicians to dialog about potential drug/biologic therapies. It could also be effective in influencing better dialog and reporting of adverse events, including improved quality of reports. The Agency also needs to comment on the impact of the recently implemented HIPAA legislation as is affects the ability of Sponsors to follow-up on spontaneously reported adverse events. The regulations allow for the pursuit of this information, but this does not appear to be clearly understood by reporters. Genzyme has encountered substantial difficulties securing information because reporters cite HIPAA as a reason not to respond.

2. Data-mining may, under certain circumstances, be useful as an adjunct to traditional pharmacovigilance methods. However, the limitations of data mining must be recognized, such as the potential for raising numerous "signals" which require extensive evaluation to disprove. In particular, the variable nature of the information contained in adverse reporting databases will make results difficult to interpret. Criteria for identifying which "signals" are worthy of additional attention need to be articulated. Discretion is essential in the interpretation and utilization of these techniques. Data mining in U. S. adverse event data bases should be not be viewed as an established procedure.

will make results difficult to interpret. Criteria for identifying which "signals" are worthy of additional attention need to be articulated. Discretion is essential in the interpretation and utilization of these techniques. Data mining in U. S. adverse event data bases should be not be viewed as an established procedure.

3. The limitations of causality assessments on individual cases are well known. With the possible exception of cases with positive rechallenge, causality assessment of individual cases should not play a decisive role in regulatory decision making. The inadequacy of data and lack of consistent methodology in assessing individual spontaneous reports are problematic with regard to causality determinations. This could readily result in misinterpretation. The Agency, in its recently published proposed rule, has changed the standard for positive causality to "cannot be ruled out" which still further diminishes the value of causality assessments.

Use of Registries for collecting safety information:

Registries are useful as a surveillance tool when the information gathered can be used to provide direct and pertinent benefit to practitioners, patients, and/or sponsors. It is particularly important in the case of rare diseases where information contained in registries may represent the main source of structured, comparable cross-patient data on a disease progression, thereby assisting facilities in benchmarking efforts and focusing scientific and clinical research. Registries can support physician education and can assist practitioners in making better treatment decisions for their patients. Registries can also link practitioners to each other, often across significant geographical distances. In such cases the practitioner and patient benefit is direct and undeniable.

However, registries cease to be useful in a variety of circumstances. Some of the circumstances include:

- lack of longitudinal trends over the particular time period appropriate to the data
- data is limited or incomplete
- data is biased, for example by regional or, cultural factors or by, SES groups disproportionately represented relative to the population under study
- data collection is particularly burdensome to the patient or physician

It is always important when data is being requested by the Agency, the reason and the collection methodologies meet scientifically rigorous criteria.
Lastly, sections of registries may become invalid due to evolution in prescribing practices, changes in diagnosis, and other alterations in patient population. As such, registries must be fluid to provide maximum benefit to all the parties for whom the data is intended.

In other instances, registries focused on safety monitoring or surveillance and that are implemented to allow access to treatment that would otherwise be restricted due to

long term or otherwise unknown risks (e.g. xenotransplantation products posing threat of transfer of endogenous retroviruses). The need for such registries, or their breadth, should be reviewed on an ongoing basis in response to evolving technology and new scientific or clinical evidence.

Sincerely,

Alison Lawton
Senior Vice President, Regulatory Affairs
and Corporate Quality Systems