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

**Subject: Docket No. 01D-0489 Draft "Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees"**

19 February 2002

Dear Sir/Madam:

Thank you for the opportunity to comment on the *Draft "Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees"* published in the Federal Register on 20 November 2001.

Genzyme Corporation is a Biotechnology company with products that are classified as drugs, biologicals, medical devices and *in vitro* diagnostics and include cell, gene and tissue therapies. Genzyme has currently over 70 active clinical trials on these products and utilizes Data Monitoring Committees whenever practical. Genzyme applauds the work FDA has put into this Guidance but is suggesting some areas for improvement or reconsideration.

Our first concern is combining all trials, regardless of sponsorship, into one document without differentiation is inappropriate. We think that there should be a separate approach for studies done under a drug development IND (or device development PMA) and other studies which are of a larger scale similar to those done by the VA or NIH. The issues are not identical. In particular, since the expertise lies largely with the manufacturers for studies under development INDs/PMAs, the role of the DMC and other supporting groups in the decision making processes may be quite different.

Genzyme regrets that there is no discussion of the down side and limitations of a DMC, either practical or theoretical. There are practical issues, costs, expertise, and organizational problems but also theoretical issues including those that result from potential bias within the DMC, an issue not acknowledged within the document. Another issue that is poorly dealt with is handling of safety issues. While this is repeatedly referred to in the document, the discussion is sometimes internally contradictory and very

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far from the reality of product safety monitoring. The Manufacturer's legal, regulatory, and ethical responsibilities for safety monitoring and assessment are not clearly depicted and the implicit assumption is that it is impossible for the Sponsor to act in a manner which protects the well-being of patient's if presumed financial interests are at stake.

In general this document departs from the traditional concern that individuals involved in the design and conduct of a trial may not be able to be fully objective in reviewing the interim data for any emerging concerns, to an implicit assumption that they cannot act in a responsible manner with regard to these concerns. Traditionally the data monitoring board is an adjunct to the trial leadership to ensure review of data in an "unbiased" way. This document goes beyond that conception and eliminates the sponsor from the decision making process. While the document arises out of concerns for early termination for efficacy in a specific trial, we feel that the Guidance moves beyond this in its impact and proposes a role for the DMC in drug/device development.

Outlined below are Genzyme's specific comments for your consideration.

In Section 1.2 There are differences between such trials. Industry sponsored trials are more likely to be on new agents where the expertise on the product is limited to the company. The failure to distinguish between a clinical trial being undertaken in the context of drug development and one which is undertaken in the phase iv setting is a significant problem. These are not the same situations. Guidelines suitable for a single study in an academic setting are not the same as those needed in the setting of innovative drug development.

The application to Part 11 in Section 1.2 is not obvious, and we suggest that it should be removed.

In Section 2.3, we note that while decisions made without knowledge of the unblinded interim data may be unbiased by knowledge of the data, they are guided by assumptions about how those data look – which may not be correct. In such cases the proposed recommendation may be wrong both for the company and for the patients. Under many charters, it is likely that the recommendation of the company would be submitted for approval to the DMC who would evaluate it on the basis of the unblinded data

The need for such information in intelligent decision making is supported later in the document when the recommendation is made that the unblinded DMC make the same sort of recommendations. The assumption is that the DMC's freedom from presumed financial interest in the outcome is the most critical factor in the acceptability of recommendations. While there are certainly circumstances in which external factors might lead to decisions that are inappropriate, it is inappropriate to construct a watch dog system based on the assumption that the sponsor cannot act ethically. This is implicit in much of this document. One must be aware of the law of unintended consequences. The

inherent conservatism of a DMC that, unlike patients, practitioners and sponsors has no vested interest in the outcome of a study may lead to a bias towards excessive caution. This is particularly the case in the setting where the DMC is potentially liable. They therefore have risk in the presence of a trial which is continued in the presence of a safety concern but none if the trial is stopped and the development aborted. The risks in that case are born entirely by the sponsor. Moreover patients lose any opportunity to benefit from the continuation of the trial. Decisions about early stopping for efficacy or futility are less problematic.

Regarding Committee Composition in Section 4.1, we note that experience in clinical trials is very different from experience in drug development. In many situations the experts are committed either to a point of view, a company or a product. The idea that there is a pool of independent, neutral, objective experts with a deep understanding of what it means to develop a product, particularly a novel medicinal product is not realistic in many situations. To the extent that DMC members may be potentially liable for their decisions the condition that “potential DMC members should be free of financial interests that could be substantially affected by the outcome of the trial” will not be possible to achieve. The DMC members will be operating under another set of biases. These may be prejudicial to the best interests of study subjects and others involved in the study. Further, DMC members are sometimes drawn from institutions that are participating in the study. Not infrequently there are only a limited number of institutions that have the patient populations and expertise to conduct a study, particularly when one is dealing with rare diseases or highly specialized medical techniques.

In section 4.1 Committee composition the guidance discusses the usefulness of ethicists or non scientists who bring the perspectives of a population under study gender ethnicity, geographical or even someone with the disease under study. This is an overlap with the IRB/ethics review committee responsibilities and such redundancies should be avoided. Such issues should be addressed by giving the DMC a detailed charter with specific rules and boundaries. Such charters will address the often difficult independence issues. When these boundaries are exceeded, certain prescribed actions take place (stopping rules, expansion rules etc). These rules and boundaries are previously agreed to by the sponsor, IRB/ethics boards and investigators ( and perhaps FDA). They will have considered the statistical, ethical and scientific ramifications of each action in advance. In this case the DMC should not have decision authority only analysis, and reporting responsibilities. When thresholds are approached or exceeded certain pre-agreed upon steps will be taken.

To accomplish this, 4.3.1.3 should be expanded to include the development of a charter for the DMC that delineates a set of operating rules, boundaries, and actions in relation to those rules and boundaries. This charter process should be given considerable detailed guidance in this document.

The statement in Section 4.2 that “(k)nowledge of unblinded interim comparisons from a clinical trial is not necessary for those conducting or those sponsoring the trial . . .” is not completely true for safety issues. For the analysis of safety issues, particularly for new agents, it may be necessary for the sponsor to have this information to identify high-risk subgroups for example. There may be for example interactions between treatment group

and risk for some or all patients. Examples include drug interactions (example) and the prior treatment (Herceptin and anthracyclins). These problems can often not be assessed statistically. There may not be any significant difference in the various groups. There needs to be a distinction in this document between decisions based on efficacy and those based on safety.

We suggest that Section 4.3.1.2 be presented as more of an iterative process between committee and study sponsor/lead investigators. In many situations the recommendations need further discussion and should not be presented as an entirely open and closed matter. This is particularly true given the general absence of knowledge about drug development on the DMC.

In Section 4.4.1.2, the hypothesis-testing model used to test the primary end points in a study, is not directly applicable to the exploratory analysis of adverse event data collected in an open format. While statistical analysis can sometimes be of use in detecting differences in adverse events between arms, often the identification and characterization of adverse events involves data driven exploration. This cannot always be done in a blinded fashion. This DMC model does not allow for the identification and characterization of new safety issues.

As a result this guidance undercuts the companies pharmacovigilance department's ability to fulfill its responsibility for evaluating safety issues. This conflicts with the sponsor's obligations to conduct safety evaluation with due diligence. These responsibilities cannot be simply delegated to the DMC. The sponsor is likely to have greater expertise and experience in managing such issues than the members of the DMC. One needs to evaluate the possible liability issues as well. What happens if the DMC fails to handle a safety issue appropriately? The responsibility presumably still lies with the sponsor. Please recall that already serious unexpected adverse events are unblinded and managed within the company to meet ICH requirements. In some many countries the interpretation of the ICH E2A document is that only unblinded cases be submitted.

We suggest that you remove the suggestion in Section 4.4.1.4. It delegates to the DMC critical decisions on drug development that are inherently those of the sponsor. The DMC may make assessments within the rules designed for assessing the conduct of a specific study. This goes far beyond that responsibility and impinges fully on the development of a pharmaceutical product. This is not the responsibility of the DMC. The overall assessment of safety issues go beyond the data available in a single trial. These include in vitro and in vivo experience and data drawn from other, trials including ongoing and confidential studies. Incorporation of such information into the decision making process rapidly goes beyond both the remit and the competence of the DMC. We believe that DMC's decision making role should be limited to pre-specified questions. Where safety issues are involved the company is both the responsible party and at least equally competent to assess the problem. In fact there are circumstances in which the sponsor may be more conservative than the DMC. An example is when a product to be commercially viable must have a better safety profile than the market standard. This may

lead to the DMC continuing with a trial that the sponsor might stop on the basis of the risk profile.

The comments in Section 4.4.1.5 can be applied to the previous discussion of adverse event evaluation and safety analysis. This section is inherently not compatible with that outlined in 4.4.1.4. In fact this dichotomy is not realistic since data driven safety issues which are primarily clinical may arise at any point.

Unfortunately, the situations detailed in Section 4.4.2 are not infrequent and are increasing to the extent that drug development moves into new therapeutic areas with new modalities. The increasing use of innovative therapies is a frequent motivation. In these situations the model from previous sections of the rigid isolation of sponsor and DMC are not appropriate and should not be mandated. More flexibility is needed. There is considerable value in the use of such expert boards but not in the same model as with those reviewing data to determine whether stopping rules have been reached. In some cases for example the DSMB may be asked to determine whether it is possible to proceed to a higher dose level or to evaluate accumulating safety data. In these cases the rigid separation of the DMC from the sponsor is not the optimal model.

We note that Section 4.4.3.1 makes it clear that the responsibility remains that of the sponsor, a point not clear in earlier sections of the guidance. This section also emphasizes the need for the DMC to provide adequate justification for any recommendations that go beyond its primary mandate to advise on study continuation or termination.

In Section 4.4.3.2, who would have access to such minutes? Are they discoverable in the case of litigation?

In Section 5, we disagree with your statement that "(s)uch recommendations would be presumptively based on findings that would meet the definition of a serious and unexpected adverse event." As an example, we note that a sufficiently high rate of minor adverse events may be related to excessive discontinuation of study drug. These may be due to active treatment but need not be serious. Lack of efficacy may also appear as an increase in certain adverse events in the placebo or low dose group.

In Section 6 we suggest that you introduce a means of having a representative of the sponsor involved with the DMC for managing safety issues without this being regarded as undermining the independence of the DMC. This may give the sponsor's safety representative for example access to selected safety data on an unblinded basis.

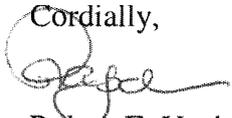
We believe that Section 6.1 suggests an assumption is that the sponsor's interests are inherently in conflict with those of the patient.

We would appreciate some elaboration on the potential advantages that accrue from the relationship between the sponsor and the DMC.

We question as to whether the statements in Section 6.4 apply only to efficacy. We believe that one must consider safety as well. This is an example of why a charter with predefined rules and boundaries would eliminate these types of biases.

Genzyme appreciates the opportunity to comment on the **Draft “Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees.”** Please contact me at (617) 374-7275 , Juliette Shih at (617) 761-8929 or Joanna Haas, MD at (617) 768-8023 should you have any questions regarding this letter.

Cordially,



Robert E. Yocher  
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Regulatory Affairs

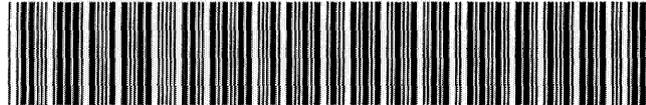
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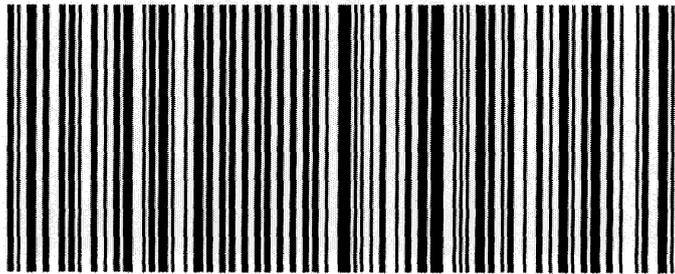
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