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March 13, 2000

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

Re: Docket No. 99D-5199

Dear Sir/Madam:

Genzyme is submitting comments to the Food and Drug Administration's (FDA), "Draft Guidance for Resorbable Adhesion Barrier Devices for Use in Abdominal and/or Pelvic Surgery" which was released for comment on December 16, 1999. Please note that these comments are being provided to FDA in addition to the comments that Genzyme provided through the Adhesion Barrier Task Force, an *ad hoc* group comprised of representatives from adhesion barrier device manufacturers.

Genzyme appreciates FDA's effort in putting together this draft guidance document. Genzyme's comments are targeted at improving the adhesion barrier guidance document so that it provides a comprehensive, consistent, scientific and least burdensome framework for developing safe and effective adhesion barrier products. We look forward to collaborating with the FDA to finalize the document so that it will prove to be a valuable resource for future FDA reviewers and industry members involved in the premarket approval of adhesion barrier devices.

Need for a Consistent Approach by FDA in Evaluating Devices:

Genzyme is concerned by the inconsistency of various product-specific guidance documents in evaluating the safety and effectiveness of devices with similar technological characteristics, specifically bioresorbable implants. Genzyme encourages FDA to compare the safety and effectiveness recommendations in guidance documents for similar or other implantable bioresorbable devices with presumably similar risks to those in the adhesion barrier guidance document. If FDA determines that adhesion barrier devices are different from other bioresorbable devices, then FDA should document the basis of their concerns and justify the request for additional studies in the adhesion barrier guidance document.

For example, in the section titled, "Pharmacokinetic Studies," in the adhesion barrier guidance document, FDA has suggested that absorption, distribution, metabolism and excretion (ADME) studies be conducted on the device and its metabolic components. However, in the guidance document titled, "**Draft Guidance for Preclinical and Clinical Investigations of Urethral Bulking Agents used in the Treatment of Urinary Incontinence,**" which discusses devices with presumably similar risks, FDA states, "*Some of the studies cited above (e.g., pharmacokinetics, reproductive and developmental toxicity, and carcinogenesis) are required only for materials that are suspected of causing serious adverse effects...*"

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Bioabsorption can be assessed from the same studies (chronic toxicity) designed to evaluate the long-term tissue reaction at the implant site, or from the injection of the radio-labeled biological material and determination of the radioactivity remaining at the injected site at different time periods after the injection."

Genzyme suggests that language similar to this be used in the adhesion barrier guidance document. FDA should include the phrase "*required only for materials that are suspected of causing serious adverse effects*" and remove any implication that ADME studies must be conducted *a priori* for all adhesion barriers. Further, the adhesion barrier guidance document has introduced the following new test specification without sufficient justification for bioabsorption limits: "*studies should be carried out to time points beyond which there is no detectable level of the product and if the product is metabolized or otherwise broken down into smaller molecular components, then the pharmacokinetic studies should address the fate of each of the components over time.*" Genzyme recommends that this language be removed from the guidance document since it would be scientifically impossible to study the fate of each of the break-down components.

Another instance where there is inconsistency in product specific guidances is FDA's "**Guidance Document for Dura Substitute Devices**" where FDA states that for products which remain in the body for greater than 30 days, "*long-term carcinogenicity studies should be performed with any device in which **a positive genotoxicity test result was obtained.***" This recommendation is again in direct contradiction with that in the adhesion barrier guidance document where FDA indicates that "*if the contact is longer than 30 days,carcinogenicity studies (i.e., 2-year rat implantation) are also recommended.*" FDA has eliminated genotoxicity testing as a screen for carcinogenicity studies in the adhesion barrier guidance document. Genzyme suggests that language in the adhesion barrier guidance be added to indicate that long-term carcinogenicity studies be conducted only if the device is suspected to be carcinogenic as a result of a positive genotoxicity test result or other documented evidence in the literature which would raise concerns about carcinogenicity.

Finally, the appropriateness of accelerated stability testing is recognized in the adhesion barrier guidance document. However, Genzyme disagrees with the following statement in the guidance document: "*accelerated stability test data may only be used to extend product expiration dating for six months beyond the date demonstrated by real time stability testing. If real time data support an expiration date of 12 months, then an expiration date of 18 months is appropriate as long as accelerated stability test data support this.*" In other words, using a hypothetical situation, if a manufacturer has real time data to support an expiration date of 12 months, and accelerated test data that supports 24 month expiration, then according to the guidance document, the manufacturer can still only claim 18 months expiration. However, in another FDA guidance document specifically for implant devices, "**Neurological Embolization Devices,**" FDA states that "*if a shelf-life is proposed for a device, performance testing should include, at the least, the worst case set of parameters, i.e., accelerated aging test samples that correspond to the maximum shelf-life proposed. Assuming these test values meet release criteria specifications and an adequate accelerated aging protocol is followed, **real-time shelf-life testing may not be needed.** However, some materials may require **real-time comparison testing to support the accelerated aging protocol.***" Genzyme suggests that language in the adhesion barrier guidance be altered to indicate the same requirement such that real-time testing be required only on a product-by-product basis, and that in the instances that it is required by the FDA, that it be used **to support** accelerated aging data instead of *vice versa*.

In Vivo Assay for Product Lot Release:

The guidance document recommends that the final product release specifications include an *in vivo* assay to measure the level of adhesion reduction.

Genzyme believes that including an animal performance assay is excessively burdensome to manufacturers and, to our knowledge, is unprecedented in the medical device industry. Outside of the adhesion prevention area, we know of no product that is required to pass an *in vivo* performance assay for lot release. It is the experience of Genzyme that a biological test is not sufficient, quantitative, nor adequately reproducible to judge whether a product should be suitable for release.

Moreover, during the last decade, public awareness of the use of animals in biomedical research has significantly increased (i.e. the animal rights movement). The public and the scientific community are concerned that animals are used both humanely and wisely. A concerted effort by scientists to reduce the number of animals used in research and development is ongoing. Requiring adhesion reduction in an animal model as a final product release specification would be contrary to this effort.

Special Considerations for Adhesion Barriers:

In this section of the guidance document, FDA recommends that studies to evaluate the effect of the device on wound healing, infection, reproductive toxicology and tumor growth be performed for **all** adhesion barrier devices, irrespective of the risks they pose. Genzyme suggests that these studies only be performed when the safety of the device is suspect. As such, additional studies to evaluate the safety of the adhesion barrier should be performed only on a product-by-product basis and when insufficient information exists in the literature or other documented sources.

Further, in the section titled, "Tumor Growth/Metastasis Effects," the guidance document states, "*In the absence of testing in an oncology trial, the product will be **contraindicated** for patients with known or suspected malignancies.*" Genzyme agrees that this is a valid statement, but recommends that it be included as a precaution/warning and not as a contraindication. Per FDA's Blue Book Memorandum G91-1 "**Device Labeling Guidance**," unless there is a known hazard and a causal relationship to the device has been established, the product cannot be contraindicated. The guidance document appears to agree with this definition in Section VI titled "Labeling" where "Contraindications" is defined as "*those circumstances under which the device should never be used.*"

Clinical Investigational Plan - Feasibility study:

In this section, the guidance document correctly states that feasibility studies are "*usually small, non-randomized, one or two-site studies, intended to evaluate the procedures to be used in the pivotal study.....*" However, in the bullet list of the examples of specific adhesion barrier device-related issues to be addressed in the feasibility study, the FDA lists "*signs of increased infectivity and altered wound-healing.*" Genzyme agrees with the importance of assessing preliminary safety, especially for unknown products and materials. Genzyme contends, however, that a small feasibility study at one or two centers cannot effectively evaluate these parameters unless they

occur at a high rate. A request to assess these parameters in a “quantifiable” manner would require a large number of patients and may be overly burdensome to the Sponsor. Genzyme recommends that these parameters be assessed in the randomized, pivotal trial. The Sponsor should, however, collect all the safety data that are required for evaluation of the device.

Broadening the Label Indication:

Sponsors of adhesion barrier devices universally agree that there are limited clinical models available to measure adhesion reduction in a reproducible, “validated” fashion. Certain indications can never be evaluated for various reasons, such as the need for a second operation within a reasonable time frame, availability of assessment tools, morbidity associated with a second look procedure, and ethical issues. For example, in abdominal procedures, the possibility to go back in for a second look is rare and cannot be easily justified for ethical reasons. In gynecological surgeries, second look is available, but only for a limited number of procedures, which automatically restricts the Sponsor from expanding the indication. Current data support the fact that the etiology of adhesion formation is similar throughout the pelvis. Similarly, the adhesion formation process is consistent within the abdominal area. Therefore, limiting the label indication to only that data which have been collected from the clinical studies would deprive surgeons and the public of an effective treatment modality. Therefore, Genzyme recommends that the FDA not restrict the label to use only in the manner the product was studied in clinical trials. Implicit in this recommendation is that the label should describe where the product was shown to be effective, as long as the Sponsor is not restricted (within scientific rationale) from describing additional areas where the product would be effective.

Genzyme thanks the FDA for the opportunity to provide these comments. Please feel free to call me or Naseem Kabir (617/374-7238) if you have questions or would like clarification on our comments. I look forward to working with the agency to finalize this guidance document.

Sincerely,

A handwritten signature in black ink, appearing to read "James W. Burns". The signature is fluid and cursive, with a large initial "J" and "B".

James W. Burns, Ph.D.
Vice President, Biomaterials and Surgical Products Research

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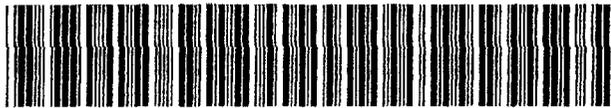
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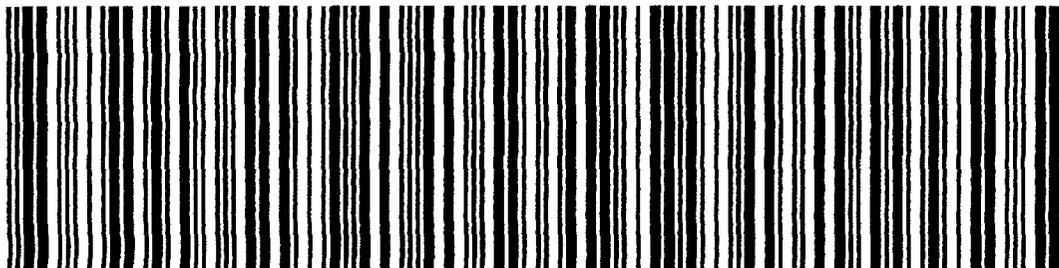
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