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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
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CITIZEN PETITION

On behalf of King Pharmaceuticals, Inc., pursuant to the Public Health Service Act (PHSA), the Federal Food, Drug, and Cosmetic Act (FFDCA), and 21 CFR 10.30, the undersigned submits this petition to request that the Commissioner of Food and Drugs take the actions requested below regarding topical thrombin products. The issues described herein have become especially relevant due to the recent actions of a recombinant thrombin applicant, ZymoGenetics, Inc.

A. Actions Requested

King respectfully requests that the Commissioner:

(1) refrain from approving a recombinant thrombin biologics license application (BLA) that does not include at least two adequate and well-controlled trials in the absence of a compelling justification for an exception from FDA's long-held statutory interpretation that the scientific and legal requirements of BLA approval require that effectiveness generally be established based on at least two adequate and well-controlled studies,

(2) require that each such adequate and well-controlled study for recombinant thrombin include a clinically meaningful efficacy endpoint,

(3) refrain from approving a recombinant thrombin BLA that relies upon data, clinical experience, or a previous determination of safety, purity, and potency of a non-recombinant thrombin product,

(4) if scientific and legal requirements for approval of recombinant thrombin are eventually met, prohibit labeling that would permit the sponsor to make unsubstantiated comparative superiority claims unless such claims are supported by evidence obtained from adequately powered, properly designed and conducted comparative clinical trials, and

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(5) confirm that FDA will require that sponsors of *all* thrombin products, whenever discussing observed immunological changes associated with product use (e.g., incidence or amount of antibody formation), include a truthful statement that the clinical relevance of such findings remains unknown.

B. Statement of Grounds

I. Background

A. Bovine Thrombin

King is the holder of BLA 977 for Thrombin-JMI® (thrombin, topical USP, bovine origin),[1] the only approved stand-alone bovine thrombin formulation currently marketed. Thrombin-JMI is indicated as an aid to hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible, or in conjunction with an absorbable gelatin sponge. Since its approval in 1995, Thrombin-JMI has been used in an estimated 12 million surgical procedures.

Based on literature case reports that suggested a possible association of topical bovine thrombin and coagulation abnormalities, in 1996 FDA requested manufacturers of bovine thrombin to include a boxed warning regarding the potential for abnormalities in hemostasis. The abnormalities mentioned range from asymptomatic laboratory abnormalities to severe bleeding or thrombosis which rarely have been fatal, and "appear to be related" to the formation of antibodies. This boxed warning was recommended by FDA in an exercise of caution even though a clinically significant coagulopathy has never been reported in a controlled trial of any bovine thrombin product. Correspondingly, despite the lack of an established causal connection between Thrombin-JMI and coagulation abnormalities, the Thrombin-JMI product labeling was nonetheless updated to include the warning information as requested by FDA.

Notably, the bovine thrombin products in the marketplace that led to FDA's decision in 1996 that a possible association may exist between bovine thrombin products and coagulation abnormalities were prior formulations of other brands of bovine thrombin that contained a higher level of extraneous proteins than Thrombin-JMI. Thrombin-JMI was first marketed in 1995, and since that time King has continued to improve the purification process.

B. Recombinant Thrombin

There are currently no recombinant thrombin products approved for marketing in the United States. ZymoGenetics publicly announced the submission of a BLA for recombinant thrombin on December 18, 2006.[2] However, since well before that date, ZymoGenetics and its

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[1] The registered holder of the Thrombin-JMI BLA is Gentrac, Inc., a wholly-owned subsidiary of King Pharmaceuticals, Inc.

[2] ZymoGenetics Press Release, *ZymoGenetics Submits Biologics License Application to the FDA for rhThrombin as an Aid to Controlling Bleeding During Surgery,* Dec. 18, 2006; ZymoGenetics recently reported that the date of its user fee goal was extended by three months due to the submission of a major amendment regarding its manufacturing process. ZymoGenetics Form 8-K, Aug. 22, 2007.

consultants have claimed that unapproved recombinant thrombin is superior to Thrombin-JMI, a claim not supported by any clinical safety or efficacy data.

ZymoGenetics has publicly released the results of its single phase III clinical trial. The trial consisted of a "non-inferiority" design, wherein the stated objective was to establish the safety and efficacy of recombinant thrombin as not worse than Thrombin-JMI. This trial consisted of approximately 400 patients, with half exposed to recombinant thrombin and half exposed to Thrombin-JMI. From this study, ZymoGenetics concluded that there were *no differences observed in the safety or efficacy of recombinant thrombin compared to Thrombin-JMI.*[3]

As a secondary endpoint in its trial, ZymoGenetics measured incidence of antibody formation following administration of the two products. Using different methods to detect antibody response to each product, ZymoGenetics reported that 1.5% of patients in the recombinant thrombin group developed antibodies against its product, compared to 21.5% of patients in the Thrombin-JMI group that developed anti-bovine antibodies.[4] Based on this numerical difference and reference to the boxed warning for Thrombin-JMI, ZymoGenetics has made comparative claims regarding the relative safety of the two products, such as "better safety profile" and "improved safety."[5]

These claims are made despite the fact that in the ZymoGenetics head-to-head study, no differences in the safety or efficacy of the drugs were observed. Further, there is no evidence from the ZymoGenetics development program or in the published literature that differences in antibody formation between these products are correlated to the absolute or relative frequency or severity of adverse events. By reference to Thrombin-JMI's boxed warning, ZymoGenetics' statements may mislead surgeons to believe that the *incidence* of antibody formation is directly correlated with the potential risk described in the Thrombin-JMI boxed warning. In numerous presentations to investors and health professionals, ZymoGenetics further extrapolates this reference to a claim of superior safety for its unapproved recombinant thrombin product. Again, *ZymoGenetics' own trial did not generate data supporting a conclusion that either frequency or amount of antibody formation is correlated with a safety concern for bovine thrombin, let alone a claim of relative difference in product safety based on antibody formation.*

It is on the basis of these recent public statements that King is compelled to submit this petition to ensure that FDA requires ZymoGenetics to fully demonstrate the safety and effectiveness of its recombinant product, and that any recombinant thrombin product approved be accurately labeled so that potentially misleading comparative superiority claims are not permissible post-approval. Approval of an unsafe or ineffective thrombin product that has not met the statutory standards designed to ensure only safe and effective products are marketed may

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[3] Chapman WC, et al., *A Phase 3, Randomized, Double-Blind Comparative Study of the Efficacy and Safety of Topical Recombinant Human Thrombin and Bovine Thrombin in Surgical Hemostasis*, J Am Coll Surg 2007;205:256-265.

[4] Id.

[5] See, e.g., presentation slides, Bruce L.A. Carter, ZymoGenetics President & CEO, Bear Stearns 19th Annual Healthcare Conference, Sept. 2006. The conclusions drawn by observers from presentations by ZymoGenetics are also of note. See, J. Gever, *Recombinant Human Thrombin Provides Better Surgical Haemostasis than Bovine Version: Presented at ACS*, Doctors Guide (DG Dispatch), October 12, 2007.

undermine the confidence surgeons have in all thrombin products, including King's Thrombin-JMI.

II. Data Requirements for FDA Approval of a Recombinant Thrombin BLA

ZymoGenetics announced its decision to move forward with its phase III trial in the absence of reaching a written agreement with FDA (i.e., a Special Protocol Assessment) for its clinical program although the company had been in discussion with FDA to negotiate such an understanding.[6] Nonetheless, ZymoGenetics has also clearly stated that it intends to receive marketing approval of its BLA based on a single phase III trial. The phase III study was designed as a non-inferiority trial using Thrombin-JMI as the comparator. This design followed results from a series of small phase II studies in which the company was not able to show that recombinant thrombin was better than placebo in controlling bleeding at 10 minutes.[7] ZymoGenetics has also recently initiated an uncontrolled clinical exposure trial which it refers to as a "phase 3b safety trial," although it states that this is not a requirement of approval.[8]

Such limited patient exposure to recombinant thrombin raises concerns regarding the approvability of this BLA in the absence of additional clinical data.[9] Such an approval would be contrary to law and agency precedent.

A. Incidence of Hemostasis Within 10 Minutes Is Not Clinically Relevant as the Primary Endpoint in a Single Non-Inferiority Study

ZymoGenetics has reported that its phase II development program did not demonstrate any significant difference from placebo in time to hemostasis, a secondary endpoint.[10] Given these results, it is of concern that FDA would consider approving recombinant thrombin on the basis of a single non-inferiority study against Thrombin-JMI using incidence of hemostasis within 10 minutes as the primary efficacy endpoint.

It is well documented by standardized methods that normal bleeding times are less than six minutes.[11] In fact, recent publications sponsored by ZymoGenetics state that hemostasis

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[6] ZymoGenetics Investor Call, October 27, 2005.

[7] Lockstadt H, et al., *The Safety, Immunogenicity, and Efficacy of Recombinant Human Thrombin as a Topical Surgical Hemostat, Integrated Results for a Multi-Surgery Phase 2 Program*, ZymoGenetics poster.

[8] ZymoGenetics News Release, *ZymoGenetics Reports Second Quarter 2007 Financial Results*, August 1, 2007, available at: http://www.zymogenetics.com/ir/newsItem.php?id=1034693.

[9] The recent approval of Omrix Biopharmaceutical's BLA for Evithrom on August 27, 2007, does not raise the same concerns addressed in this section because human plasma-sourced thrombin has for many years been produced and marketed by Omrix as a component of its fibrin sealant products. In contrast to the ZymoGenetics BLA, this information and experience was available for reference and inclusion by Omrix in the Evithrom BLA, and is supportive of the safety, purity, and potency of stand-alone human plasma-sourced thrombin.

[10] Chapman WC, et al., *A Phase 3, Randomized, Double-Blind Comparative Study of the Efficacy and Safety of Topical Recombinant Human Thrombin and Bovine Thrombin in Surgical Hemostasis*, J Am Coll Surg 2007;205:256-265, at 263; Lockstadt H, et al., *The Safety, Immunogenicity, and Efficacy of Recombinant Human Thrombin as a Topical Surgical Hemostat, Integrated Results for a Multi-Surgery Phase 2 Program*, ZymoGenetics poster.

[11] Manual of Laboratory and Diagnostic Tests, Ivy Method, 2004.

"generally is complete within a few minutes."[12] Since the vast majority of patients will achieve hemostasis within 10 minutes regardless of pharmacologic intervention, the primary efficacy endpoint in the ZymoGenetics pivotal trial is clinically irrelevant. The authors reporting the results of the ZymoGenetics pivotal study themselves conclude that "[t]he current trial had several inherent limitations...This study was designed to evaluate whether bThrombin (Thrombin-JMI) and rhThrombin gave comparable efficacy, and no placebo group was included. No conclusions can be drawn about the efficacy of either treatment relative to placebo in this study."[13]

In contrast, the pivotal study that served as the basis of approval for Thrombin-JMI demonstrated a 70% improvement in time to hemostasis compared to placebo ($p<0.0001$).[14] In this phase III, controlled, double-blinded, investigation comparing the safety and efficacy of Thrombin-JMI to isotonic saline, the average time to hemostasis was 209 seconds (approximately three and a half minutes) for saline compared to 54 seconds (one minute) for Thrombin-JMI. All patients in the placebo group showed hemostasis within six minutes. These findings were again confirmed in the placebo arm of the ZymoGenetics phase II studies where 50% of patients stopped bleeding in less than three minutes, and 80% in less than six minutes.[15] Thus, the fact that a majority of both recombinant thrombin and Thrombin-JMI patients achieved hemostasis within 10 minutes in the ZymoGenetics phase III trial provides no clinically relevant information regarding efficacy of recombinant thrombin.

Importantly, the recent approval of human plasma-sourced thrombin was based on a phase III study that utilized as its primary endpoint hemostasis within 10 minutes, but also contained pre-specified secondary endpoints of hemostasis at 3 and 6 minutes. Other BLA approvals for hemostatic agents containing thrombin have similarly included more clinically relevant endpoints.[16] For example, Tisseel® VH Kit (hemostasis within 5 minutes[17]), Evicel® (hemostasis within 4 minutes[18]), and Crosseal (absolute time to hemostasis (5.3 minutes)).[19] In addition, the Center for Devices and Radiological Health (CDRH) at FDA recommends an endpoint of incidence of hemostasis within 5 minutes for sponsors of absorbable hemostatic medical devices required to perform a clinical study to demonstrate substantial equivalence

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[12] Bishop PD, et al., *Comparison of Recombinant Human Thrombin and Plasma-Derived Hume α-Thrombin*, Semin Thromb Hemost, 2006;32(suppl 1): 86-97; Hedner U. *Mechanism of action of factor VIIa in the treatment of coagulopathies*. Semin Thromb Hemost 2006;32(suppl 1):77-85; Roberts H, et al., *A cell-based model of thrombin generation*. Semin Thromb Hemost 2006;32(suppl 1):32-38.

[13] Chapman WC, et al., *A Phase 3, Randomized, Double-Blind Comparative Study of the Efficacy and Safety of Topical Recombinant Human Thrombin and Bovine Thrombin in Surgical Hemostasis*, J Am Coll Surg 2007;205:256-265

[14] Thrombin-JMI Summary Basis for Approval; Gentrac BLA 92-0153.

[15] Lockstadt H, *The Safety, Immunogenicity, and Efficacy of Recombinant Human Thrombin as a Topical Surgical Hemostat, Integrated Results for a Multi-Surgery Phase 2 Program*, 2004, International Society on Thrombosis and Haemostasis International Society on Thrombosis and Haemostasis. ZymoGenetics poster.

[16] CBER's Guidance setting forth the clinical data necessary for fibrin sealant products that contain a thrombin component recommends time to hemostasis as a primary endpoint, but does not prescribe a specific time. It does, however, reference CDRH's hemostatic device approvals, which, as discussed infra, are recommended to use hemostasis within 5 minutes. *Efficacy Studies to Support Marketing of Fibrin Sealant Products Manufactured for Commercial Use,* May 1999, at 2.

[17] Tisseel, SBA at 13, May 1, 1998.

[18] Evicel BLA supplement approved May 9, 2007.

[19] Crosseal, SBA at 9, March 21, 2003.

under Section 510(k).[20] FDA should therefore require ZymoGenetics to establish effectiveness in a phase III trial with a clinically relevant endpoint.

B. FDA's Guidance Generally Requires a Confirmatory Phase III Trial

Even if the ZymoGenetics non-inferiority trial were adequately conducted to establish effectiveness, a single such trial is typically insufficient for meeting the legal and scientific standards for BLA licensure. The FFDCA requires applicants to demonstrate effectiveness of new drug products through the conduct of "adequate and well-controlled" studies.[21] FDA has interpreted this requirement to apply equally to biological products approved under authority of the PHSA, and has explained the quantity of evidence required for a given product to meet this statutory standard in its Guidance for Industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,* May 1998.

In the Guidance, FDA explains the scientific need for independent substantiation of experimental results and that generally more than one adequate and well-controlled clinical trial is required for approval, as well as the circumstances in which the Secretary may determine that data from one trial plus confirmatory evidence are sufficient to demonstrate effectiveness.

> *A conclusion based on two persuasive studies will always be more secure than a conclusion based on a single, comparably persuasive study. For this reason, reliance on a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.*[22]

None of these conditions for relying on a single trial exist here. Indeed, by demonstrating noninferiority, ZymoGenetics has confirmed in its study that there is no "clinically meaningful" safety or efficacy benefit to using recombinant thrombin over available therapy.[23] In fact, FDA has also clearly indicated that a single-trial approval is only appropriate when the trial results are statistically strong and when there is no contradictory or nonsupportive information.[24] As discussed herein, ZymoGenetics' phase II results for recombinant thrombin do not support a conclusion that recombinant thrombin is a more effective hemostatic agent than placebo, and the use of hemostasis at 10 minutes as the primary endpoint for a phase III noninferiority trial is inappropriate to adequately demonstrate product performance. Although FDA has approved

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[20] *Class II Special Controls Guidance Document: Absorbable Hemostatic* Device, Draft Guidance, October 31, 2006.

[21] 21 USC 355(d).

[22] Guidance for Industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,* May 1998, at 6; *Statement Regarding the Demonstrations of Effectiveness of Human Drug Products and Devices*, 60 Fed. Reg. 39180, 39181 (Aug. 1, 1995).

[23] The August 27, 2007, approval of another topical thrombin product, Omrix Biopharmaceutical's Evithrom® (thrombin topical, human) provides an additional option for surgeons requiring a topical thrombin product. This makes an exception to the confirmatory trial requirement for recombinant thrombin even less compelling.

[24] Guidance for Industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,* May 1998, at 6; *Statement Regarding the Demonstrations of Effectiveness of Human Drug Products and Devices*, 60 Fed. Reg. 39180, 39181 (Aug. 1, 1995).

biologic products based on a single phase III trial in the past, these have been instances where confirmatory information was available to the sponsor or the factors enumerated in the Guidance were present.

In the Guidance, FDA specifically mentions replacement of a coagulation factor as an example of when the agency may consider a single trial of effectiveness *with independent substantiation from related study data.* FDA states that whether related adequate and well-controlled studies are capable of substantiating a single study is a matter of judgment. However, there are no adequate and well-controlled studies of recombinant thrombin to substantiate the recombinant thrombin BLA study. Furthermore, as set forth below, BLA product applications, unlike 505(b)(2) new drug product applications, may not rely upon data or a previous FDA determination that another product has demonstrated effectiveness. Therefore, there is no study data available which may be relied upon to independently substantiate a single phase III recombinant thrombin study.[25]

If FDA intends to permit reliance on a single phase III trial with a clinically insignificant efficacy endpoint and no confirmatory evidence, King respectfully requests that the adequacy of safety and efficacy data be assessed by the Blood Products Advisory Committee.

C. The ZymoGenetics BLA Cannot Rely Upon Data, Clinical Experience, or a Previous Determination That Non-Recombinant Thrombin Products are Safe, Pure, and Potent

The rationale for the existence of different statutory standards of approval between drug and biologic products has been recognized by both Congress and FDA as relating generally to the importance of the manufacturing process of a biological product and the resultant implications on patient safety.[26] Applications submitted for licensure of biological products under Section 351 of the Public Health Service Act must independently demonstrate that the product meets standards designed to ensure the safety, purity, and potency of the product.

The ZymoGenetics clinical program has resulted in only a limited number of patients exposed to recombinant thrombin, a situation exacerbated by the wide range of patient demographics and overall size of the population expected to be exposed to the product following approval. Thus, based on its statements that it is expecting approval on its current data package, ZymoGenetics must be relying upon data or a previous demonstration that another thrombin product is safe, pure, and potent. Such an abbreviated approval pathway would be contrary to law.

1. BLA's Must Independently Establish Safety, Purity, and Potency

FDA has categorized the different pathways available for obtaining approval of drug products regulated pursuant to the FFDCA into those submitted under Section 505(b) of the

[25] Again, this is in stark contrast to the recent Evithrom approval. Omrix and J&J have many years of experience both manufacturing and marketing human plasma-sourced thrombin.

[26] On August 22, 2007, ZymoGenetics reported an extension of its user fee date due to the submission of a major amendment regarding its manufacturing process.

FFDCA ("stand-alone NDA" and "505(b)(2) application") and those submitted under Section 505(j) of the FFDCA ("ANDA" and "petitioned ANDA").[27] For drugs, only 505(b)(2) and 505(j) applications allow applicants to submit a less than complete data package and to rely to a certain extent on other data. However, for biologic products regulated under the PHSA, FDA has consistently maintained that,

> *there is no abbreviated approval pathway analogous to 505(b)(2) or 505(j) of the Act for protein products licensed under Section 351 of the PHSA.*[28]

This is confirmed by the plain language of the relevant statutory provisions and their legislative histories, FDA's implementing regulations, and agency precedent.[29] The lack of statutory authority for abbreviated BLA approvals is further confirmed by current Congressional proposals to create such an abbreviated pathway for biological products.

In 1974, in its final regulations implementing the Freedom of Information Act (FOIA), FDA explained that safety and effectiveness data for a biologic product regulated under the PHSA may not be withheld from the public because each sponsor of a BLA must develop and submit its own data.[30] As FDA has recognized, the PHSA has not been substantively amended to alter the licensing requirements for biologic products; in fact, when Congress amended the FFDCA in 1984 to allow for more streamlined abbreviated approvals of drugs, it declined to apply similar abbreviated approval pathways for biologics.[31] Thus, FDA's articulation of its interpretation over 30 years ago is still accurate and applicable today:

> *Unlike the regulation of human and animal drugs, all biological products are required to undergo clinical testing in order to demonstrate safety, purity, potency, and effectiveness prior to licensing, regardless whether other versions of the same product are already marketed or standards for the product have been adopted by rule making. Indeed, many of the existing standards require specific clinical testing before approval will be granted. This is required because all biological products are to some extent different and thus each must be separately proved safe, pure, potent, and effective. Although, like an approved NDA, a license to manufacture a particular biologic is a private license that is applicable only to a single manufacturer, a biologics license is under no circumstances granted by the Food and Drug Administration to a second manufacturer based upon published or otherwise publicly available data and information on another*

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[27] See, Aug. 12, 2005, petition response to Nancy L. Buc and Carmen M. Shepard re: Docket No. 2004P-0015/CP1.

[28] See, e.g., Woodcock J, et al., *The FDA's assessment of follow-on protein products: a historical perspective,* Nature Reviews Drug Discovery, Vol. 6, June 2007; May 30, 2006, consolidated response to Kathleen M. Sanzo, Stephan E. Lawton, and Stephen G. Juelsgaard re Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC 1, 2004P-0171/CP1, and 2004N-0355.

[29] Consistent with its statutory authority to permit abbreviated approvals of products regulated under Section 505 of the FFDCA, FDA has approved abbreviated applications for biologic products that are regulated as drugs under Section 505(b)(2). See, e.g., hyaluronidase, human growth hormone. These approvals are inapposite here as all thrombin products are regulated under authority of the PHSA, and accordingly ZymoGenetics has submitted a BLA for recombinant thrombin, not an application under Section 505(b)(2).

[30] 39 Fed. Reg. 44602, 44641 (Dec. 24, 1974).

[31] In promulgating its regulations implementing the Hatch-Waxman amendments, FDA confirmed that the abbreviated process for generic drugs is "inapplicable to ...biological drug products licensed under [Section 351 of the PHSA]." 57 Fed. Reg. 17950, 17951 (April 28, 1992).

manufacturer's version of the same product. Under section 351 of the Public Health Service Act, biologics never become "old drugs" and cannot be marketed solely on the basis of an existing product standard published in the Federal Register. There is no such thing as a "me-too" biologic.

Thus, the regulatory scheme for biologics is quite different from the methods by which new drugs and antibiotic drugs are controlled under sections 505 and 507 of the Federal Food Drug, and Cosmetic Act (21 U.S.C. 355 and 357).

Accordingly, the Commissioner concludes that the safety and effectiveness data for a biologic regulated under section 351 of the Public Health Service Act is not properly classified as a trade secret. Such data afford no competitive advantage because, unlike the situation with new drugs, no competitor can utilize it to gain approval for his product.[32]

Thus, a BLA submitted under the PHSA for a protein product such as recombinant thrombin must contain in the application the data necessary for approval without reliance on data, clinical experience, or a previous determination for a different product not included in the application.

2. Even When the Law Permits a Drug Applicant to Rely on Information Not Included in an Application, FDA May Only Consider Submitted Publications or a Previous Determination that FDA Has Been Statutorily Authorized to Make

FDA's broad interpretation regarding reliance on information in drug product applications regulated under Section 505(b)(2) set forth in its Draft Guidance, *Applications Covered by Section 505(b)(2),* and various FDA Citizen Petition responses is instructive of the limitations on its ability to rely upon data and conclusions not contained within a BLA. For 505(b)(2) applications, an applicant is limited to reliance on either (1) submitted published literature, or, (2) the Agency's finding of safety and effectiveness for an approved drug.[33]

Thus, even for 505(b)(2) applications where FDA has been granted statutory authority to permit reliance on data not included in an application, sponsors are limited to relying on either published literature which has been submitted for consideration, or a formal Agency action that FDA has been statutorily authorized to make (i.e., the review and approval of a drug product pursuant to Section 505 of the FFDCA[34]). Nowhere is there any statutory authority for FDA to rely upon any other conclusions or information not submitted for agency consideration.[35]

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[32] 39 Fed. Reg. at 44641.

[33] Draft Guidance, *Applications Covered by Section 505(b)(2)*, October 1999, at 2-3.

[34] The extent of the reliance on a previous determination permitted under the 505(b)(2) pathway is the same as under 505(j), and thus requires an agency *approval* of a previous product. See 54 Fed. Reg. 28872 at 28892 ("The [505(b)(2)] applicant will thus be relying on the approval of the listed drug only to the extent such reliance would be allowed under 505(j) of the act.").

[35] Nor is there any case law to support FDA's reliance on information not submitted in a BLA. In *Berlex v. FDA*, 942 F.Supp at 25, discussed infra, in agreeing with FDA's application of biologic product comparability, the court specifically recognized that, "[n]either the PHSA itself nor FDA's regulations issued under the PHSA provide that

3. The Comparability Guidance Approach is Not Applicable to a Recombinant Thrombin BLA

FDA has approved a BLA for a new biologic product based on an extensive showing that data obtained with the sponsor's predecessor product could support the newer product BLA. This approach, however, does not support the reliance of a different product (recombinant thrombin) from a different manufacturer (ZymoGenetics) on data, experience, and conclusions gained with other licensed products (bovine or human-plasma sourced thrombin).

In April 1996, FDA issued "*FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products*." The Guidance "describes those steps that manufacturers may perform and which FDA may evaluate to allow manufacturers to make manufacturing changes without performing additional clinical studies to demonstrate safety and efficacy." Thus, by its very terms, this Guidance is intended to permit manufacturers of an *approved* BLA to demonstrate through specified non-clinical methods that certain changes in its *approved* manufacturing process result in a "comparable" product expected to have the same identity, safety, purity, and potency.

Approximately three weeks after issuance of the Guidance, FDA, for the first time, approved a new biological product, Biogen's Avonex® (interferon-beta), on the basis of a clinical study of a "comparable" product.[36] There are, however, dramatic differences between the approval of Avonex and the potential approval of a recombinant thrombin as being comparable to any previous thrombin product.[37]

Importantly, Biogen was a partner in the joint venture that developed the predecessor product to Avonex, and with which the clinical trial at issue was performed. Thus, Biogen submitted data on the predecessor product in a drug master file and had important knowledge regarding the manufacturing process regarding the predecessor product, just as a manufacturer of an approved biologic making a manufacturing change to a marketed product would as contemplated in the Comparability Guidance. Of significance, Biogen's first attempt to develop a new interferon-beta product which could rely on the joint venture data failed to establish comparability, and Biogen was thus prohibited by FDA from utilizing that data for approval.[38]

On a subsequent interferon-beta cell line that became Avonex, Biogen was required to perform extensive biological, biochemical, and biophysical analyses to demonstrate comparability. For example, in addition to a double-blind, randomized pharmacokinetic comparability study, comparability testing consisted of: peptide mapping, N-terminal amino acid

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the clinical study offered to demonstrate the safety, purity and potency of a new biological product have been conducted on that very product." This decision was limited to consideration of whether the biologic product used in a *sponsor's submitted study* is required to be the same as that for which approval is sought.

[36] *Berlex v. FDA*, 942 F.Supp 19, 22 (D.D.C. 1996).

[37] The Avonex approval is itself an example of a single-trial BLA approval. Consistent with FDA's guidance, the phase III trial supporting the Avonex BLA demonstrated a clinically meaningful effect on irreversible morbidity (decreased progression of disability) and was stopped early. Additionally, the integrated summary of safety contained supportive safety data on 290 patients in addition to the pivotal phase III trial.

[38] Avonex SBA at 2.

sequencing, carbohydrate analysis, immunoblotting analyses, reverse phase HPLC, receptor binding and other functional assays.[39] These data resulted in an FDA determination of comparability that permitted Biogen to rely upon data for the predecessor interferon-beta product *for which it had participated in generating and had a right to reference and submit for FDA consideration in its BLA.*[40]

Because recombinant thrombin is different from previously marketed thrombin products and because ZymoGenetics has no previous experience manufacturing or marketing recombinant thrombin, there is no basis upon which ZymoGenetics could claim comparability of recombinant thrombin to previously marketed or tested thrombin products.

4. Based on the Broad Indication Pursued by ZymoGenetics, the Safety Database for Recombinant Thrombin Is Inadequate

ZymoGenetics has claimed that recombinant thrombin will rapidly "replace bovine thrombin" and has estimated more than 500,000 patient exposures in its first year of marketing. The approximately 300 patient exposures to recombinant thrombin from the phase II and III studies combined offer very little information on the safety of recombinant thrombin, and stand in stark contrast to recent biologic blood product approvals.

For example, the recent approval of Omrix's human plasma-sourced thrombin involved a clinical development program that is supported by extensive use of the product in combination with fibrin sealants in Omrix's Evicel® and Crosseal®. The safety database for Evithrom builds upon the previous Omrix BLA approvals. For example, when Crosseal was approved it was supported by three years of safety data in 7,000 patients.

Furthermore, recent events regarding recombinant human erythropoietin (EPO) proteins underscore that recombinant human proteins are not inherently safe. FDA recently requested the addition of a boxed warning for EPO products relating to increased risk of cardiovascular and tumor progression effects not observed in pre-marketing studies. Additionally, Johnson & Johnson's EPO product, Eprex®, has demonstrated that a subtle manufacturing change in a recombinant protein may have the potential to cause unforeseen significant patient safety risks. When J&J changed the product stabilizer in Eprex, approved routine analytical studies did not detect any potential safety problem. However, this change resulted in a forty-fold increase in the incidence of pure red cell aplasia (PRCA) since 1998.[41] PRCA, a severe and life-threatening form of anemia, was triggered by antibodies to the patients' own erythropoietin after treatment with the recombinant human EPO product. This is a notable example of a serious, unexpected, autoimmune disorder that is manifested in a high proportion of patients who produce antibodies to a recombinant product even though the frequency of a product specific antibody response is reported to be lower than 1%. The EPO experience suggests that adequate patient experience in

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[39] Id. at 2-4.

[40] This is consistent with other instances where manufacturers have demonstrated comparability to a previous version of their own product. See, e.g., Iplex®, Enbrel®.

[41] Casadevall N, et al., Pure Red-Cell Aplasia and Antierythropoietin Antibodies in Patients Treated with Recombinant Erythropoietin, NEJM 346:469-475, Feb. 2004.

controlled clinical trials is essential for evaluating the safety of a recombinant biologic product prior to approval.

Indeed, there are safety signals in ZymoGenetics reported data that should be explored in additional clinical investigation. For example, the ZymoGenetics phase III study resulted in three myocardial infarctions (heart attacks) in the recombinant thrombin group, while none were observed in the comparator Thrombin-JMI group.[42] While this difference was not statistically significant because ZymoGenetics studied so few patients, this is the type of safety issue that a larger patient exposure database may elucidate prior to approval.

Similarly, ZymoGenetics has no available data regarding reexposure to recombinant thrombin. Reexposure is specifically mentioned in the Thrombin-JMI boxed warning as a potential risk factor to be considered in use of the product. ZymoGenetics has repeatedly referred to this statement in its claims of product superiority yet presents no data showing the impact of multiple exposures to recombinant thrombin on clinical outcome or immunological changes including levels of antibody formation. ZymoGenetics should be required to conduct a reexposure study, or, at a minimum, explicitly state in its product labeling in the Precautions and Warnings sections that no data are available regarding patients who have been reexposed until such time as appropriate studies have been completed.

III. ZymoGenetics' Recombinant Thrombin Labeling Should Accurately Reflect the Clinical Significance of Immunogenicity Data Should Its BLA Ultimately Become Approvable

Through its pre-approval promotional statements, ZymoGenetics has clearly demonstrated its intent to market recombinant thrombin based on a suggested safety benefit over Thrombin-JMI which has not been demonstrated through clinical studies of the products. Should ZymoGenetics acquire the data necessary for recombinant thrombin BLA approval, FDA should be vigilant in labeling discussions to prevent label claims that would allow the dissemination of misleading claims based on immunological endpoints including antibody formation.

A. Incidence of Anti-Product Antibody Formation Has Never Been Correlated to Adverse Event Frequency or Severity

ZymoGenetics' reported anti-product antibody formation rates from its phase III trial of 21.5% for Thrombin-JMI and 1.5% for its recombinant thrombin is precisely the type of simplistic comparison of apples to oranges that the FDA comparative promotional restrictions are intended to prohibit. The claims that recombinant thrombin is safer than Thrombin-JMI are not supported by the available data because antibody incidence or levels of antibody formation have never been correlated to frequency or severity of adverse events.

It is clear that the various methodologies used to measure antibody formation to the thrombin products in the ZymoGenetics phase III study were not sufficiently similar with respect to sensitivity, specificity, and accuracy to allow for a meaningful comparison of antibody formation between the study populations. Even assuming that the reported incidence numbers

[42] ZymoGenetics Analyst Briefing, Sept. 18, 2006.

are accurate, the same single phase III clinical trial from which Zymogenetics makes its claims of superior safety showed no clinical differences in product safety between patients receiving either recombinant thrombin or Thrombin-JMI. Thus, Zymogenetics seeks to assert immunological endpoint data to establish a clinically significant safety difference between the products when these data were generated from a trial where there was no observable difference in clinical safety.

Furthermore, the potential association between antibody formation to Thrombin-JMI and certain coagulation abnormalities does not provide any information regarding the potential for antibody formation following exposure to recombinant thrombin. Knowing the incidence of antibody formation to either thrombin product does not provide meaningful insight as to the frequency or severity of adverse events that may result from an immunogenic reaction to recombinant thrombin. ZymoGenetics has claimed that its recombinant thrombin is identical to endogenous human thrombin. As such, the potential for a severe immunogenic reaction may in fact be even greater for this product than for Thrombin-JMI based on possible autoimmune dysfunction associated with exposure in susceptible individuals.

B. Discussion of the Relative Incidence of Antibody Formation Should Always Be Accompanied By an Accurate Statement Regarding Clinical Significance

Because of the inherently misleading nature of claims regarding the incidence of antibody formation, FDA should make clear that whenever sponsors discuss comparative immunological data an accurate statement regarding the clinical significance of those comparisons must be included. This is consistent with the views of FDA labeling guidance, an FDA Advisory Committee which specifically considered this topic, as well as labeling included in the immunogenicity section of many approved biological products.

FDA's recent labeling Guidance regarding the Adverse Reactions section of labeling for biological products states the following regarding comparative safety claims:

> *Care should be taken to avoid inclusion of comparator rates that would imply a comparative safety claim that is unsubstantiated or otherwise misleading (e.g., if an excessive dose of an active comparator was used). If the requirement that claims be based on adequate and well-controlled studies is waived to permit inclusion of comparative rates (e.g., because the identity and rates of adverse reactions for the active comparator are important to understanding the significance of the information), the comparator rates should be qualified by a disclaimer indicating that the data are not an adequate basis for comparison of rates between the study drug and the active control.*[43]

Similarly, in 1999, CBER's Biological Response Modifiers Advisory Committee[44] specifically addressed questions regarding antibody detection assays and the propriety of making product label claims based on those data. The committee first discussed the inherent difficulties

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[43] Guidance for Industry, *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*, January 2006, at 9.

[44] CBER, Meeting of the Biological Response Modifiers Advisory Committee, July 15, 1999. Transcript available at: http://www.fda.gov/ohrms/dockets/ac/cber99.htm.

in comparisons based on antibody detection assays, and described that the sensitivity and specificity is not always known and may differ widely between products. Additionally, the committee recognized that assays are so variable that the results are easily manipulated.[45]

The committee also addressed the appropriate content of immunogenicity labeling and how that labeling should or should not be used to make comparative claims to other products. After detailed discussion, a fair summary of the committee's conclusions was given by Dr. Jay P. Siegel, then CBER's Director of the Office of Therapeutics Research and Review:

> *There are two types [of disclaimers] that we might be thinking of here, one that the clinical implications are unknown, but a disclaimer about that these data should not be used for comparisons actually sends a message other than to physicians because it sends a message to sponsors that is up front in case they haven't heard it elsewhere or could claim not to have heard it, that any claims they might make have been determined by the agency not to be appropriate claims.*
>
> * * *
>
> *And importantly, what's in the label forms the basis -- that was the point I was making -- of what is or isn't considered acceptable promotional information.*
>
> * * *
>
> *Before we leave this topic, let me just make sure I understand. It sounds like there's support in this committee that the notion of just giving numerical rates that do not have clinical implications and could be misused, the committee recognizes problems with that and supports it sounds like either of two approaches which might be either not to include those rates or to use a semi-quantitative approach with rates with perhaps some, if not disclaimer, information about what implications of those rates are or are not appropriate.*[46]

The uncertainty and misleading nature of comparative claims based on incidence of antibody formation described by the Advisory Committee has led to what has essentially become class labeling for biological products regarding immunogenicity. This labeling, which appears in the "immunogenicity" section of a number of biologic products,[47] informs practitioners that comparison of the incidence of antibodies between products may be misleading. For example, human plasma-sourced thrombin was recently approved with the following labeling:

> *The detection of antibody formation is highly dependent upon the sensitivity and specificity of the assay. The observed incidence of a positive signal in an assay may be influenced by several factors including timing of sampling, sample handling, concomitant medications, or underlying disease. Therefore, direct comparison of incidence of*

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[45] See, e.g., discussion at transcript p. 242, "Dr. Siegel: There are not only an unlimited number of different ways to do [assays], but for every one of them, you can choose your cut-point of positivity along what is usually a continuum so as to modify the sensitivity and specificity to your liking. Unfortunately, these claims – and this really is at the heart of question number 4 – have induced some sponsors, we believe, to intentionally choose insensitive assays so they can promote low rates."

[46] Transcript at 259-261.

[47] See, e.g., approved labeling for: Neumega® (oprelvekin), Remicade® (infliximab), Zenapax® (daclizumab), Avonex® (interferon beta-1a), Procrit® (epoetin alfa), Raptiva® (efalizumab), Neulasta® (pegfilgrastim), Aranesp® (darbepoetin alfa), Humira® (adalimumab).

antibody development to human or bovine thrombin or Factor V/Va following administration of EVITHROM with incidence of antibody development following administration of other products may be misleading and the clinical significance of these findings is unknown.[48]

This type of labeling statement is especially appropriate for a recombinant thrombin product where the sponsor has made clear its intention to distinguish its product on this basis alone.

In the absence of data that establishes the clinical significance of antibody formation, FDA should confirm in advance that this labeling would prohibit any post-approval claims comparing thrombin products based on antibody formation as recommended by the Advisory Committee. FDA should also clarify that this type of product labeling precludes a discussion of immunological data in the absence of fairly-balanced statements regarding clinical significance of such information.

IV. Conclusion

Based on statements and information made public by ZymoGenetics regarding the limited patient exposure to recombinant thrombin and the lack of supportive data for its single phase III trial which used an efficacy endpoint of uncertain clinical relevance, ZymoGenetics is pursuing an abbreviated pathway to approval of recombinant thrombin in contravention to the law regarding BLA approvals. Under governing law, ZymoGenetics is required to demonstrate the safety, purity, and potency of its product without reliance on data, clinical experience, or a previous determination that another thrombin product is safe, pure, and potent. At a minimum, a well-controlled phase III study, including clinically relevant safety and efficacy endpoints and patients reexposed to recombinant thrombin, is required prior to approval of recombinant thrombin.

If ZymoGenetics acquires the data necessary to meet the legal and scientific requirements for approval, FDA should prohibit labeling that would permit ZymoGenetics to continue to claim product superiority in the absence of scientific evidence that supports such a conclusion. FDA should require, consistent with product labeling, that all sponsors of thrombin products must include a statement regarding clinical significance when discussing immunological data including the incidence of antibody formation in light of the well-documented misperceptions that such data may create.

C. Environmental Impact

The actions requested in this petition are subject to categorical exclusions under 21 CFR § 25.31.

D. Economic Impact

Pursuant to 21 CFR § 10.30(b), an economic impact statement will be submitted upon request of the Commissioner.

[48] Evithrom approved labeling, 9/2007.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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