

Guidance for Industry

Efficacy Studies to Support Marketing of Fibrin Sealant Products Manufactured for Commercial Use

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Guidance for Industry¹: Efficacy Studies to Support Marketing of Fibrin Sealant Products Manufactured For Commercial Use

I. INTRODUCTION

This document pertains to commercially-produced fibrin sealants composed of purified, virus-inactivated/removed human fibrinogen and human or bovine thrombin, with or without added components such as virus-inactivated/removed human factor XIII and/or aprotinin. A number of such products are currently available in Europe and Canada as hemostasis agents. Although manufacturers and clinicians in the United States have been actively engaged in the development and testing of fibrin sealants, only one fibrin sealant product has been licensed in this country. This document outlines the agency's current position with regard to clinical data used to support licensure of safe and effective commercially-produced fibrin sealants in the United States.

In the Federal Register of January 26, 1998 (63 FR 3750), the Food and Drug Administration (FDA) announced the availability of a draft guidance for industry entitled "Efficacy Studies to Support Marketing of Fibrin Sealant Products Manufactured for Commercial Use." In response to a 90 day comment period, only one comment was received. The comment expressed concern that the wording of the draft guidance document was too restrictive with regard to the term "specific indications". The comment suggested that the FDA would approve fibrin sealants only for the specific indications that were studied in the clinical trials. The comment stated that the guidance document should recognize the use of data from representative surgical procedures in support of a range of indications, such as arterial-venous access procedures representing vascular surgical procedures. The FDA agrees with this recommendation and has revised this guidance document accordingly in section III. Guidance.

II. BACKGROUND

As early as 1909, surgeons were reporting the hemostatic properties of fibrin powder used in the operative field. In the 1940s, combinations of fibrinogen and thrombin were first utilized. The development of Cohn fractionation in the 1940s, and a method for cryoprecipitation of fibrinogen in the 1960s, led to the development of fibrin sealants in the 1970s. However, fibrinogen concentrates were found to transmit hepatitis and thus all U.S. licenses for Fibrinogen (Human) were revoked on December 7, 1977. Since that time, a number of manufacturers have

¹ This guidance document represents the FDA's current thinking on efficacy studies to support marketing of fibrin sealant products manufactured for commercial use. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

been evaluating a new generation of virus-inactivated/removed fibrin sealants.

In 1994, the FDA co-sponsored a conference on the characteristics and clinical uses of fibrin sealants, held at the Uniformed Services University of the Health Sciences, Bethesda, Maryland (summarized in *Transfusion* 35:783-790, 1995). A number of academic investigators presented data from clinical trials in which fibrin sealants either reduced blood loss or reduced the time to achieve hemostasis. However, based on the available data, FDA representatives were of the opinion that a direct clinical benefit to patients treated with fibrin sealant should be demonstrated in a well-controlled clinical trial to support product licensure for a narrow indication.

Despite FDA's requests for well-controlled clinical trials with patient outcomes as endpoints, many clinicians have been reluctant to conduct placebo-controlled trials in settings where they view the standard of care to be the use of fibrin sealant prepared on site from commercial bovine thrombin and various sources of fibrinogen. These clinicians consider the use of locally-prepared fibrin sealant to be of such benefit in controlling bleeding in confined or nearly inaccessible areas that a placebo-controlled trial would put the control patients at significant and unnecessary risk. However, locally-prepared fibrin sealants are not standardized or consistent, and the available sources of fibrinogen are not treated to inactivate or remove viruses.

III. GUIDANCE

Based on clinical trial experience since 1994, FDA's Center for Biologics Evaluation and Research (CBER) intends to consider, for licensure of commercially-produced fibrin sealants, data from pivotal studies in which the primary endpoint is hemostasis effectiveness. This review standard is similar to that used by the Center for Devices and Radiological Health, in clearing a number of devices as adjuncts to hemostasis on the basis of clinical studies in which the primary endpoint was control of hemostasis within a specific time in a variety of clinical settings. CBER intends that time to hemostasis could also serve as a primary endpoint for pivotal studies of fibrin sealants.

As in the past, CBER also encourages manufacturers to conduct well-controlled clinical trials using a variety of other endpoints, including blood loss, transfusion requirements, tissue sealing, and wound healing. Endpoints for such trials will be reviewed on a case-by-case basis. Manufacturers who demonstrate the safety and efficacy of their fibrin sealant preparations for specific indications may, upon FDA licensure, label and promote their products for these indications. FDA licensure for a given indication will denote that the specific formulation of fibrin sealant is safe and effective for that specific indication. The indication may be a group of surgical procedures if the clinical trial data are considered to be representative of surgeries of that type. Further, manufacturers who demonstrate the safety and efficacy of their fibrin sealant preparations in a variety of clinical settings may, upon FDA licensure, label and promote their products as general adjuncts to hemostasis. The number and types of procedures required to support a broad labeling claim should be discussed with the agency.

For fibrin sealant products containing multiple biologic components, the contribution of each component may be demonstrated in a non-clinical setting appropriate to the indication(s) sought, although the overall efficacy of multiple-component fibrin sealant products should be

demonstrated in clinical trials. Proposals to utilize in vitro and/or animal studies to support the inclusion of multiple biologic components into a fibrin sealant product should be discussed with CBER.

The following points are to be considered when designing and executing pivotal clinical trials for fibrin sealant products:

- 1) Fibrin sealant products should be tested in settings and under conditions where they would normally be expected to be used in clinical practice.
- 2) Fibrin sealant products may be tested against a placebo, a cleared hemostatic device, or other control, as appropriate.
- 3) Efficacy of fibrin sealant products may be tested by using either hemostasis endpoints or other measures of clinical benefit, depending on the indications sought.