Hemostatic Products Regulated by CBER

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Regulates biological products for human use under applicable federal laws including PHS Act and FD&C Act

For Complete FDA Organizational Chart see:
Hemostatic Products Regulated by CBER

• Combination products: Biologic and device:
  – Adjuncts to hemostasis: Fibrin Sealants

• Biological Products
  – Plasma: lyophilized, freeze dried, spray dried
    • Clinicaltrials.gov # NCT00968487,
  – Platelet derived hemostatic agents
    • Thrombosomes Clinicaltrials.gov # NCT02223117
    • Freeze dried platelets
      http://www.entegrion.com/products/stasix/
What are Adjuncts to Hemostasis?

• Adjuncts to hemostasis are Fibrin Sealants indicated for use in patients undergoing surgery, when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.

• For topical use only on the surface of the organ or tissue.
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1900</td>
<td>Surgeons report hemostatic properties of fibrin powder used in operative field</td>
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<tr>
<td>1940</td>
<td>Combination of fibrinogen and thrombin first utilized</td>
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<tr>
<td>1960</td>
<td>Development of Cohn fractionation</td>
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<tr>
<td>1970</td>
<td>Cryo-precipitation of fibrinogen</td>
</tr>
<tr>
<td>1980</td>
<td>First Fibrin Sealants developed</td>
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<tr>
<td>1990</td>
<td>Licenses of fibrinogen revoked due to Hepatitis</td>
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**1994:** FDA and uniformed services held conference

**1998:** First commercially available Fibrin Sealant in US
Types of Fibrin Sealants

Source: Package inserts of the US approved products

- Thrombin (human, bovine, and recombinant) with calcium chloride: May be used in conjunction with absorbable gelatin sponge
  - Evithrom (human)
  - Recothrom (recombinant)
  - Thrombin JMI (bovine)
Types of Fibrin Sealants
Source: Package inserts of US approved products

- Fibrinogen and thrombin with or without added components such as Factor XIII
  - Supplied in separate vials as frozen solution, lyophilized powder, and spray dried powder, or as absorbable patch
  - Two components admixed at site of application
  - Administered by spraying, dripping, or patch left in situ

EVICEL, TISSEEL, Tachosil, EVARREST
Efficacy Studies to Support Marketing of Fibrin Sealants

www.fda.gov/.../GuidanceComplianceRegulatoryInformation/Guidances

• In a pivotal clinical trial, Fibrin Sealants should be tested
  – in settings and under conditions where they would normally be expected to be used in clinical practice
  – against a placebo, a cleared hemostatic device, or other control, as appropriate
  – by using either hemostasis endpoints or other measures of clinical benefit, depending on the indications sought
Primary Endpoint(s) are Reviewed on a Case-by-Case Basis

- Time to hemostasis primary endpoint for the currently licensed Fibrin Sealants
- Other endpoints to consider:
  - blood loss, transfusion requirements, tissue sealing, and wound healing
Fibrin Sealants with Multiple Biologic Components

• The contribution of each component may be demonstrated in a non-clinical setting appropriate to the indication(s) sought

• The overall efficacy of multiple-component Fibrin Sealants should be demonstrated in clinical trials
Fibrin Sealant Safety Information

Source: Package Inserts of US licensed Fibrin Sealants

• CONTRAINDICATIONS:
  – Do not inject directly into the circulatory system
  – Do not use for the treatment of severe or brisk arterial bleeding

• WARNINGS AND PRECAUTIONS:
  – Air or gas embolism: use of spray devices employing a pressure regulator
Summary

• Number of Fibrin Sealant products licensed in the US

• Safety and efficacy demonstrated in adequate and well-controlled clinical trials

• Indicated as adjuncts to hemostasis to control bleeding and oozing from capillaries and small venules

• Use of Fibrin Sealants to control other types of bleeding has not been studied in adequate and well-controlled clinical trials

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