



Hemostatic Products Regulated by CBER

Nisha Jain, M.D.

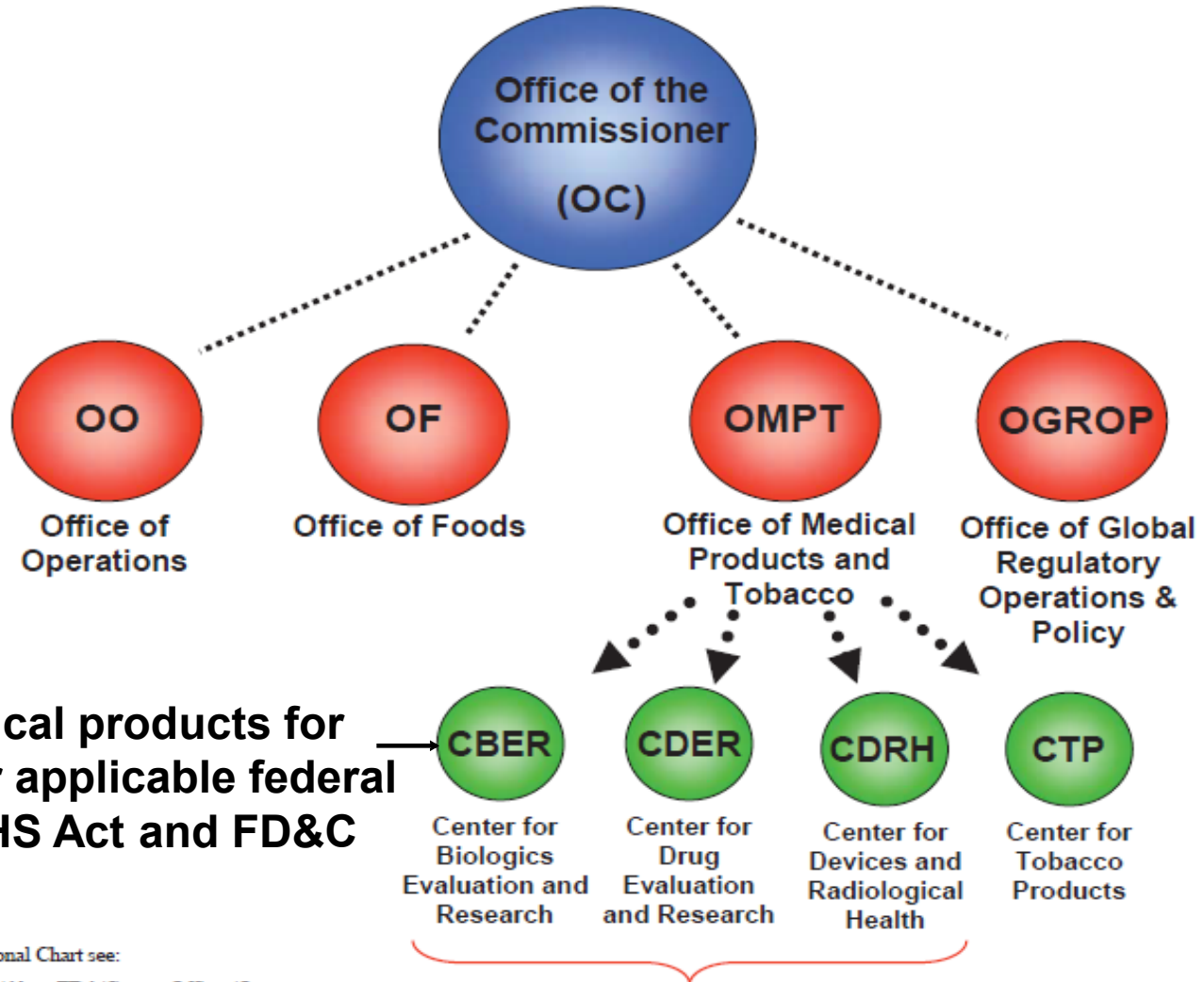
Chief, Clinical Review Branch

Division Of Hematology Clinical Review

OBRR/CBER/FDA

The findings and conclusions in this presentation have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy.

FDA Organization Chart



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

For Complete FDA Organizational Chart see:

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OrganizationCharts/UCM288864.pdf>

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
<http://www.ncbi.nlm.nih.gov/pubmed/23301961>
 - Freeze dried platelets
<http://www.entegron.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

History of Fibrin Sealants



1900
Surgeons report hemostatic properties of fibrin powder used in operative field

1940
Combination of fibrinogen and thrombin first utilized
Development of Cohn fractionation

1960
Cryo-precipitation of fibrinogen

1970
First Fibrin Sealants developed
Licenses of fibrinogen revoked due to Hepatitis

1980
First marketed Fibrin Sealant in Europe

1990
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](http://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 trials¹²