Material Science In Medical Device Industry

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SABPA Biomedical Forum

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Outline

- Medical Device Basics
- Common Materials
- Polyphosphazenes
  - Embolization Microspheres
  - Coronary Stents

Medical Device Defined

201(h) of FD&C Act defines medical device as:

"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes."

Medical Device Classifications

Increasing Risk

Classification determines extent of regulatory control (Risk Based)

Class I ~ 47%
- General Controls

Class II ~ 43%
- General controls
- Special controls

Class III ~ 10%
- General controls
- Premarket approval (PMA)

General Controls
- Electronic Establishment Registration
- Electronic Device Listing
- Quality Systems
- Labeling
- Medical Device Reporting (MDR)
- Premarket Notification [510(k)] (unless exempt)

Special Controls (addressing Risk)
- Guidelines (e.g., Glove Manual)
- Mandatory Performance Standard
- Performance testing, such as biocompatibility, engineering, animal, etc.
- Special Labeling

Medical Device Regulatory Pathways

- **Exempt Devices**: certain Class I and Class II devices
- **510(k)** (Premarket Notification): certain Class II devices if the intended use and technology are similar to something already classified
- **PMA** (Premarket Approval): Most Class III devices
- **De Novo**: devices that aren't comparable enough to something on the market. This generates a new device classification regulation, and will typically (but not always) be Class II

510(k) Substantial Equivalence

A device is substantially equivalent if, in comparison to a predicate it:

- has the same intended use as the predicate; **and**
- has the same technological characteristics as the predicate;

  or

- has the same intended use as the predicate; **and**
- has different technological characteristics and does not raise different questions of safety and effectiveness; **and**
- the information submitted to FDA demonstrates that the device is at least as safe and effective as the legally marketed device.

PMA (Premarket Approval)

- Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.
- Due to the level of risk associated with Class III devices, FDA has determined that general and special controls alone are insufficient to assure the safety and effectiveness of Class III devices.
- PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s).

De Novo Request

- FDA will review De Novo requests for devices that are not within a device type that has been classified under the criteria at section 513(a)(1) of the FD&C Act.
- This includes devices that do not fall within any existing classification regulation, where the De Novo requester either determines that there is no predicate device or has received an NSE determination on a 510(k) submission.

Combination Products

- 21 CFR 3.2(e): Combination products are therapeutic and diagnostic products that combine drugs, devices, and/or biological products
- Lead center is based on “primary mode of action” (PMOA)

Medical Device Quality
FDA Case for Quality Program

- FDA CDRH has a new initiative: Case For Quality. The program includes FDA/CDRH, MDIC and CMMI organizations.
- After enrolling and passing appraisal, FDA waives routine inspections and fast-track 30-day change reviews

Biocompatibility

- Biocompatibility of a medical device refers to the ability of the device to elicit the desired biological response without causing adverse effects in the body.
- Biocompatibility depends on the body's responses to the device as well as the device's responses to the physiological environment inside the human body.

Biocompatibility Assessment

- Required for all submission types: PMA, HDE, IDE, 510(k), and de novo requests.
- CDRH regulates medical devices, not materials
- CDRH doesn’t clear/approve materials (vs. CDER - e.g., drugs, excipients)
- CDRH recommends biocompatibility assessment on final, sterilized (if applicable) product unless otherwise justified

Nature and Duration of Contact

- **Direct contact**: device or device component that comes into physical contact with body tissue
- **Indirect contact**: device or device component through which a fluid or gas passes, prior to the fluid or gas coming into physical contact with body tissue
- **Transient contact**: device or device component that comes into very brief/transient contact with body tissue.
- **Non-contact**: device or device component that has no direct or indirect contact with the body.
- **Duration**: A: Limited (≤ 24 hours)
  B: Prolonged (> 24 hours to 30 days)
  C: Permanent (> 30 days)

Risk Based Biocompatibility Assessment

ISO 10993-1 includes consideration of:

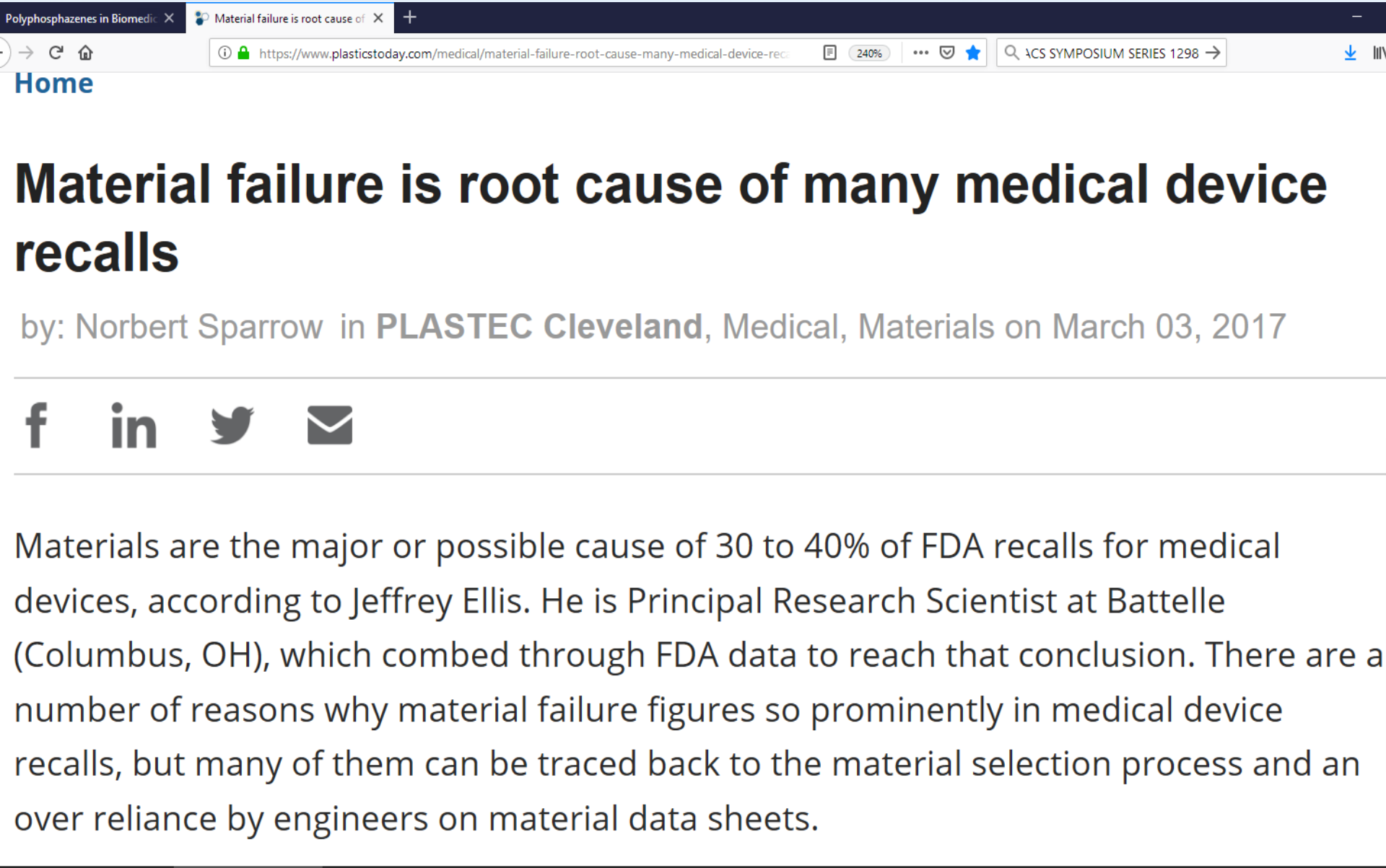
- device design, material components and manufacturing processes;
- clinical use of the device including the intended anatomical location;
- frequency and duration of exposure;
- potential risks from a biocompatibility perspective;
- information available to address the identified risks; and
- information needed to address any remaining knowledge gaps, such as new biocompatibility testing or other evaluations that appropriately address the risks.

Risk Based Biocompatibility Assessment

New biocompatibility testing may NOT be needed if:

- The device is made of materials that:
  - Have been well characterized chemically and physically in the published literature; and
  - Have a long history of safe use;
  - Materials and manufacturing information is provided to demonstrate that no new biocompatibility concerns exist.
- It may be possible to leverage previously conducted biocompatibility information if:
  - The previously tested device has similar indications, type, and duration of contact;
  - An explicit statement is provided regarding any differences in materials or manufacturing between the new and leveraged devices under consideration; and
  - Information is provided to explain why differences aren't expected to impact biocompatibility.

Importance of Material Science in Medical Device Industry



Importance of Material Science in Medical Device Industry

The Bleeding Edge: behind the

https://www.theguardian.com/film/2018/jul/25/the-bleeding-edge-netflix-documentary-medi

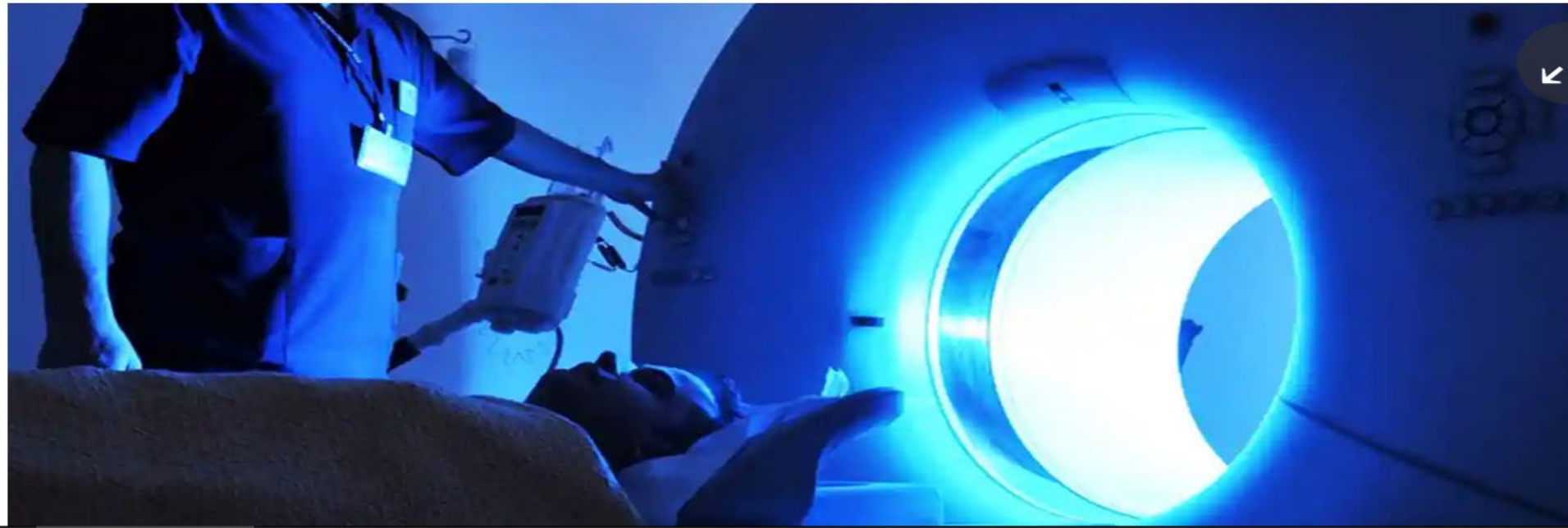
170%

bleeding edge documentary

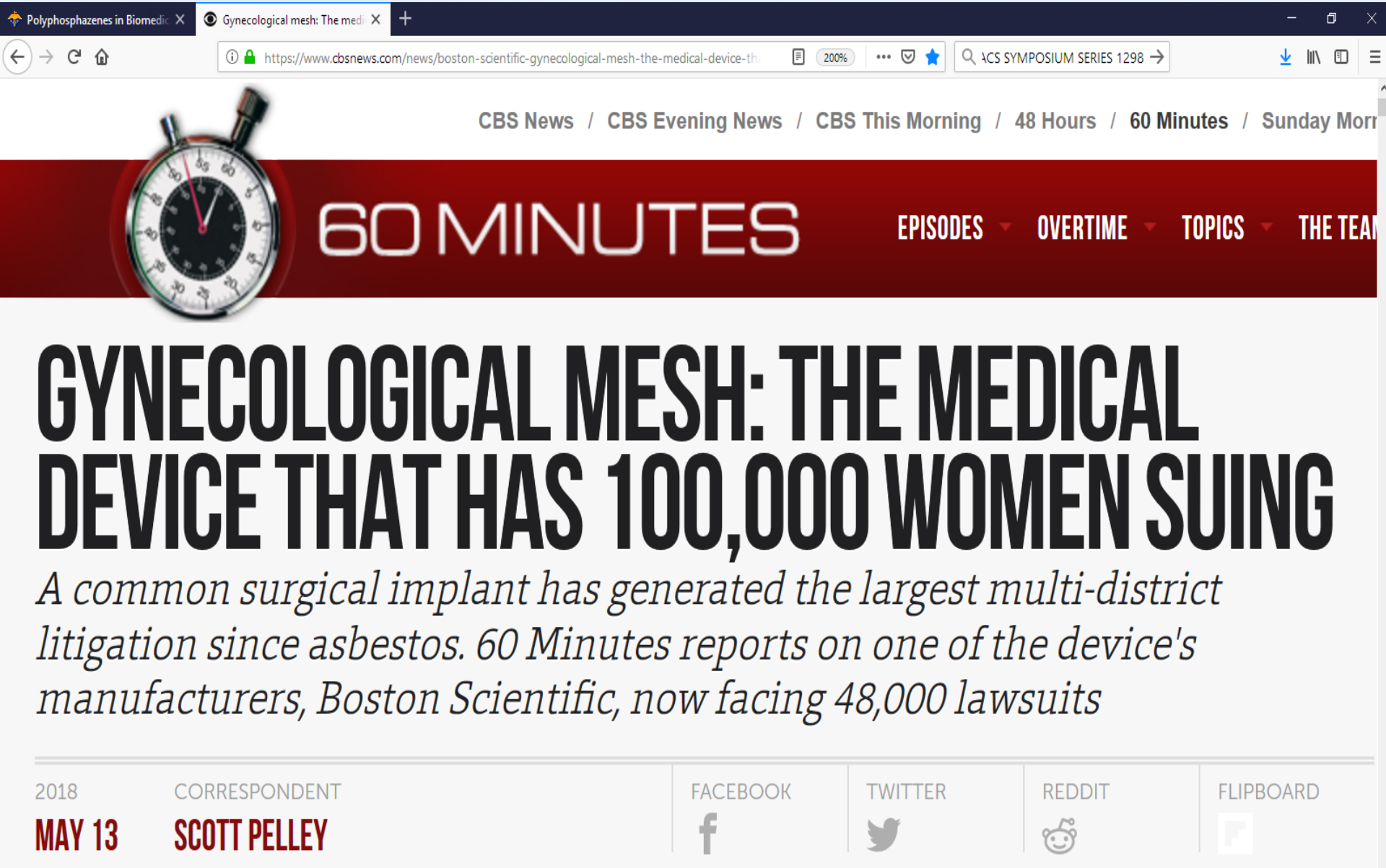
Documentary films

The Bleeding Edge: behind the terrifying new Netflix documentary

The $400bn medical device industry is exposed in a horrifying look at a string of products that have wreaked havoc on patients



Importance of Material Science in Medical Device Industry



Common Materials in Medical Devices

- Metals
- Polymers
- Ceramics
- Composites

Biomaterials

Any substance (other than drugs) or combination of substances synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replaces any tissues, organ, or function of the body

Body's Responses to Biomaterials

- Tissue

Inflammation, Fibrous Tissue Formation, Immune Response, Infection, Necrosis

- Blood

Thrombosis, Lipid or Mineral Deposition, Infection

Biomaterial Responses to the Physiological Environment

- Protein/cell adsorption on the surface - fouling
- Property decay through water interactions - softening, crazing
- Leaching of plasticizer, filler, etc. in bio environment
- Dissolution of component/device
- Materials degradation of device - hydrolysis of esters or amides
- Corrosion - oxidation or reduction
- Calcification - "growing unwanted bone" or Ca deposits
- Catastrophic fibrous encapsulation

Metallic Biomaterials

For a metal to be used as a biomaterial, it needs to be

- **Bioinert/Biotolerant**: having minimal interaction with the surrounding body fluids, soft/hard tissues.
- **Mechanically compatible**: especially for orthopaedic implants, having a similar modulus to the hard tissues.
- **Strong**: expressed in the form of mechanical strength, fatigue resistance (if cyclic loading is required), wear resistance

Metallic Biomaterial Applications

- **Prosthesis**: to replace a portion of the body (e.g. joints).
- **Fixation devices**: to stabilize broken bones during heeling or permanently (e.g. plates, screws, spinal devices, wires).
- **Vascular & urological systems devices**: stents
- **Functional devices**: pacemakers or cochlear implants.

Major Metallic Biomaterials

Material	Major Applications
316L Stainless Steel	cranial plates, orthopedic fracture plates, dental implants, spinal rods, joint replacement prostheses, stents, catheters
Cobalt-Chromium alloys	orbit reconstruction, dental implants, orthopedic fracture plates, heart valves, spinal rods, joint replacement prostheses
Titanium, Nitinol, Titanium alloys (Ti-6Al-4V, Ti-SAL-2.5 Fe, Ti-6Al-7Nb)	cranial plates, orbit reconstruction, maxillofacial reconstruction, dental implants, dental wires, orthopedic fracture plates, joint replacement prostheses, stents, ablation catheters

Technical Considerations for Non-Clinical Assessment of Medical Devices containing Nitinol

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on April 19, 2019.

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written

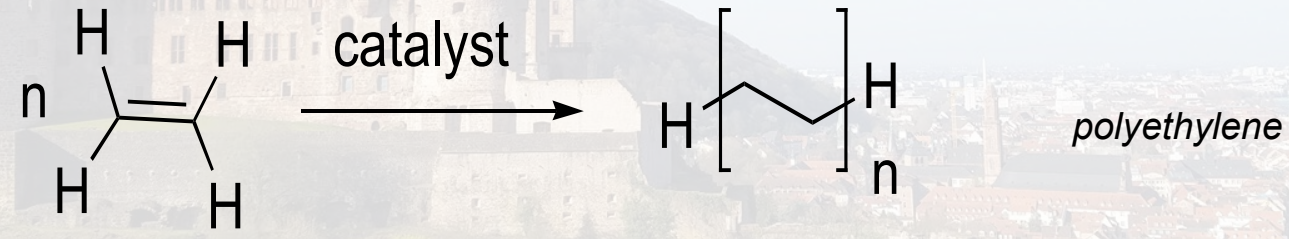
Polymer Biomaterials

- Advantages
  - Easy fabrication
  - Wide range of compositions and properties
  - Many ways to immobilize biomolecules/cells
- Disadvantages
  - Contain leachable compounds (additives, stabilizers, plasticizers, etc.)
  - Surface contamination
  - Chemical/ biochemical degradation

What Are Polymers?

Polymer = many parts

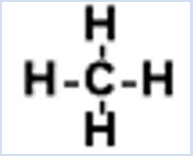
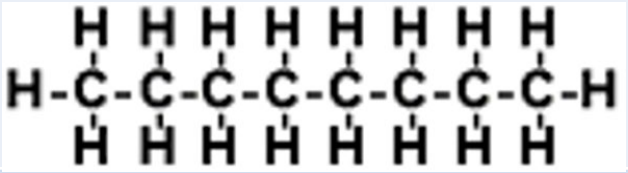
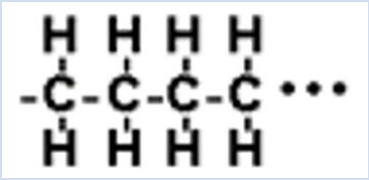
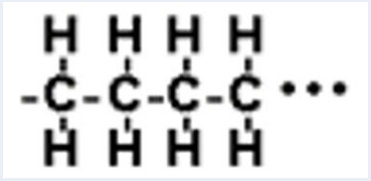
Macromolecule = large molecule



ethylene

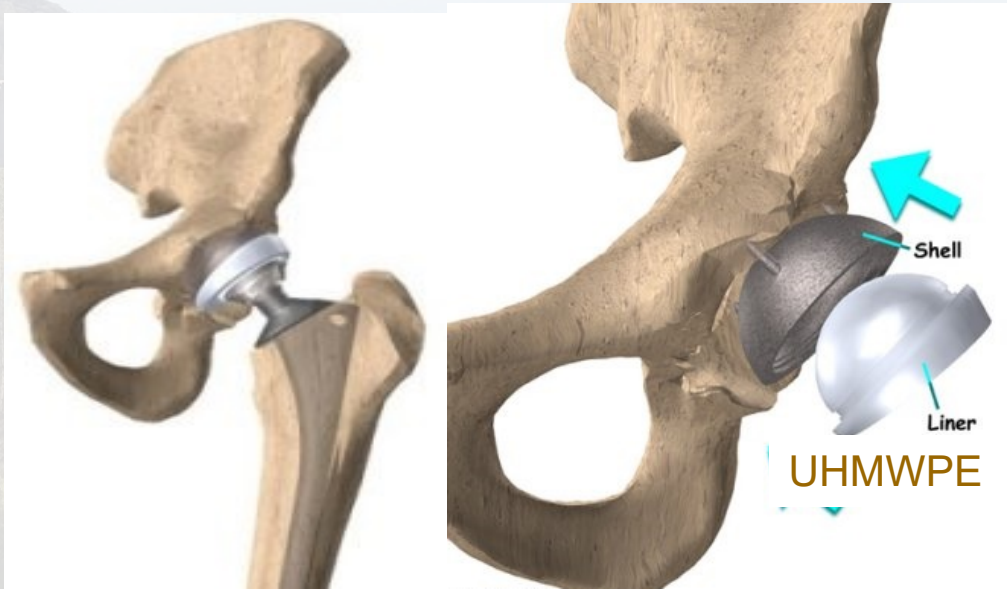
polyethylene

Size of Molecules

Gas	Methane	1 Carbon	
Liquid	Octane (Gasoline)	8 Carbons	
Wax	Paraffin	50 Carbons	
Plastics	Polyethylene	10,000 Carbons	

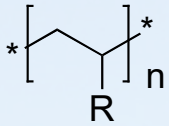
UHMWPE (Ultra-High Molecular Weight PE)

- Orthopaedic Joint Replacement
- UHMWPE $-(CH_2CH_2)_n-$
- Molecular Weight > 1 million
- Good impact strength, low creep, low stress-crack
- Wear debris is a major concern
- Sterilization
  - Gamma irradiation
  - Ethylene Oxide
  - Gas plasma

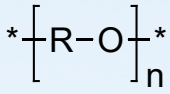


Polymers According to Structure

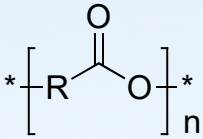
Vinyl Polymers



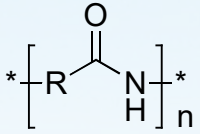
Polyethers



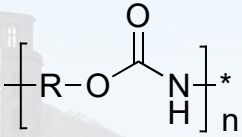
Polyesters



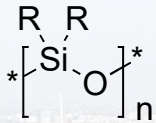
Polyamides



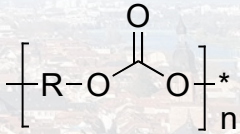
Polyurethanes



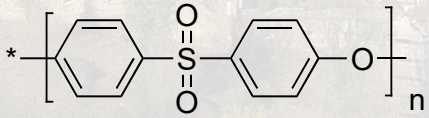
Polysiloxanes



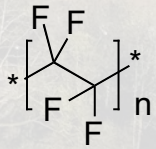
Polycarbonates



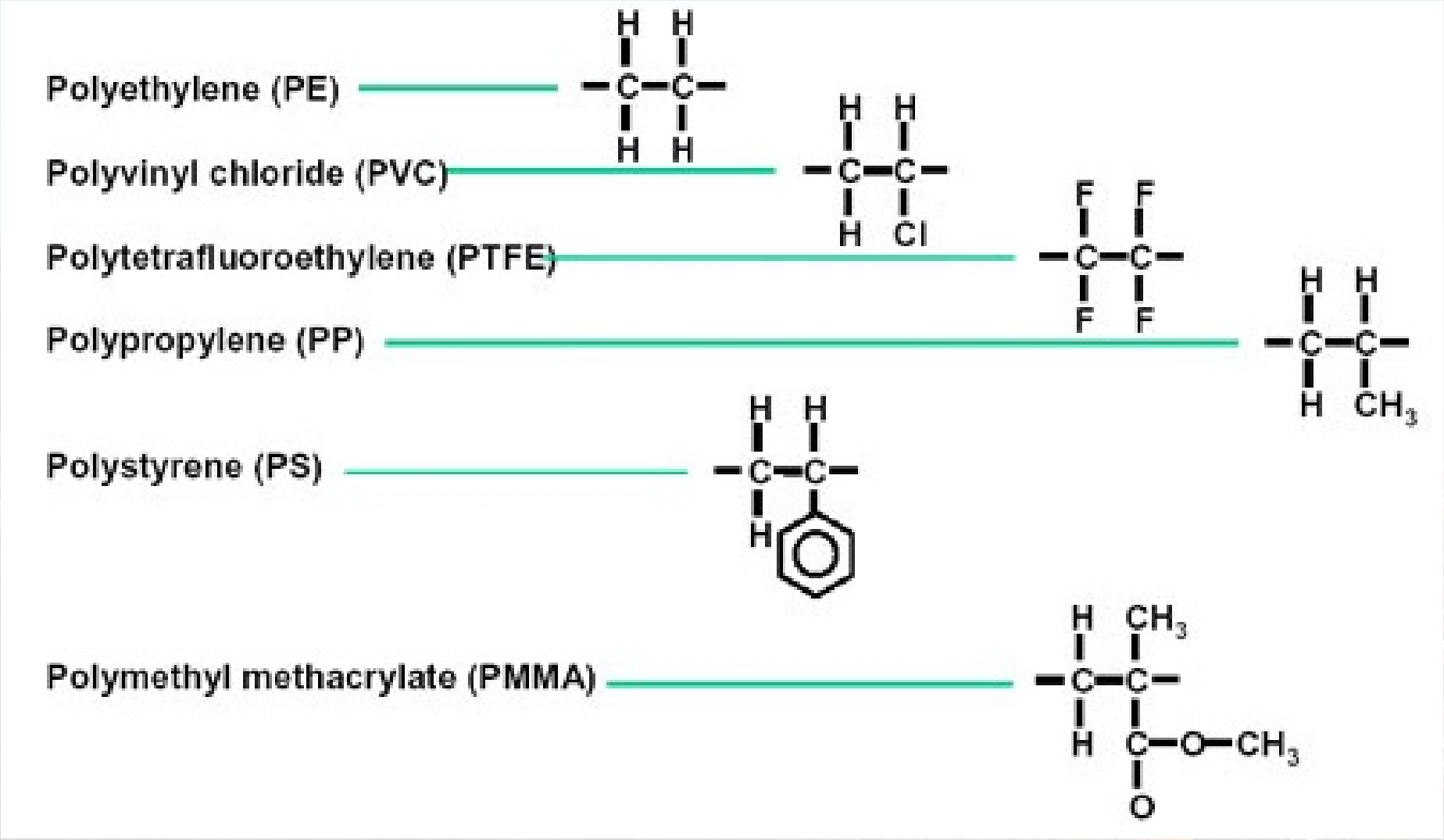
Polysulfones



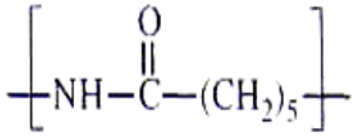
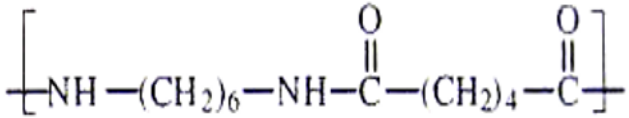
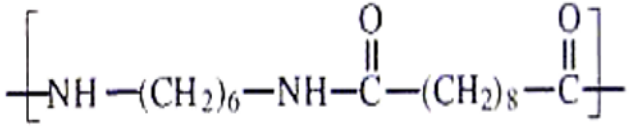
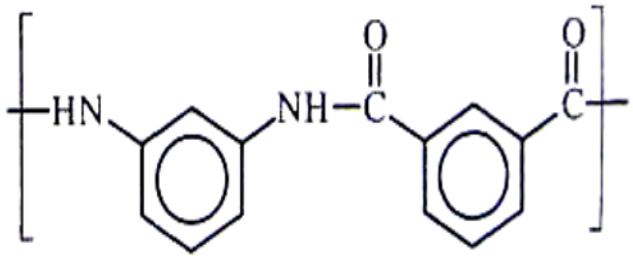
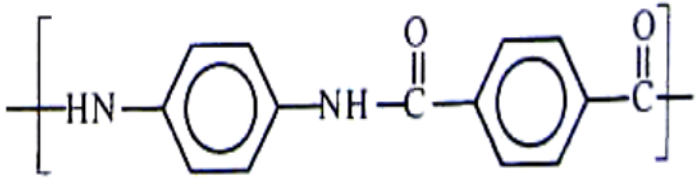
Fluoropolymers



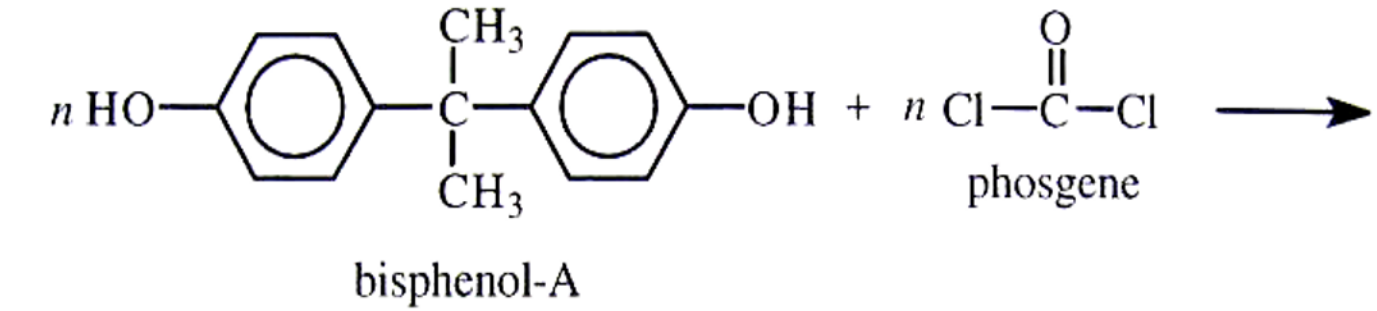
Commodity Vinyl Polymers



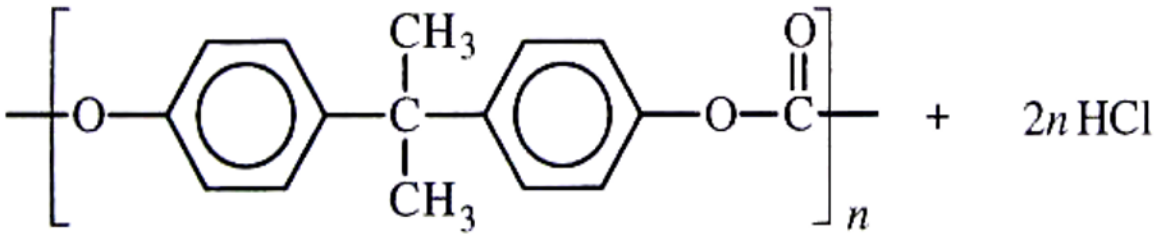
Engineering Polymers - Polyamides

Caprolactam	Poly(ε-caprolactam) (nylon-6)	
Hexamethylene diamine adipic acid	Poly(hexamethylene adipamide) (nylon-6,6)	
Hexamethylene diamine sebacic acid	Poly(hexamethylene sebacamide) (nylon-6,10)	
Isophthaloyl chloride *m*-phenylenediamine	Poly(*m*-phenylene isophthalamide) (Nomex™)	
Terephthaloyl chloride *p*-phenylenediamine	Poly(*p*-phenylene terephthalamide) (Kevlar™)	

Engineering Polymers - Polycarbonates

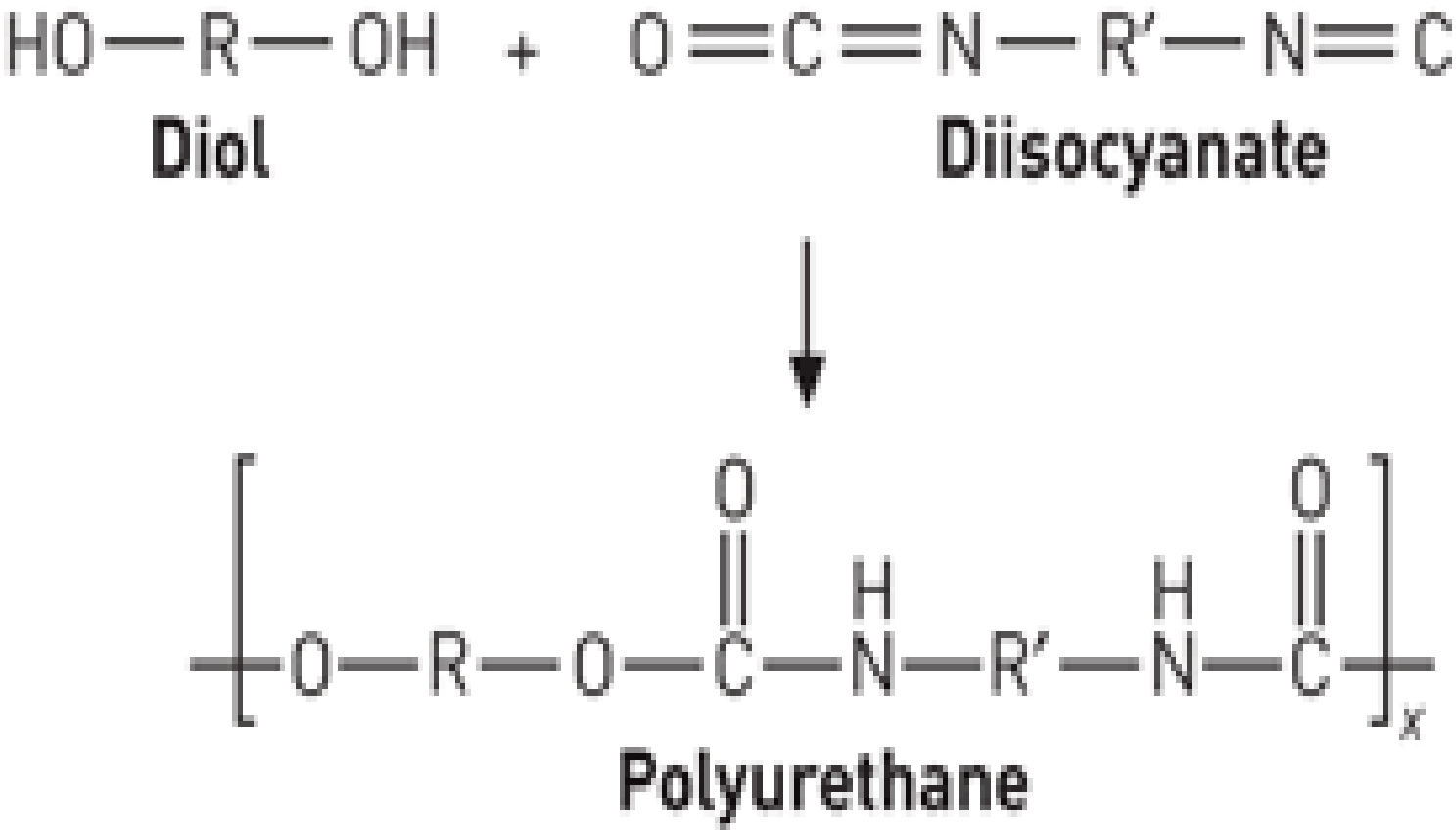


bisphenol-A



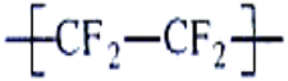
polycarbonate

Engineering Polymers - Polyurethanes

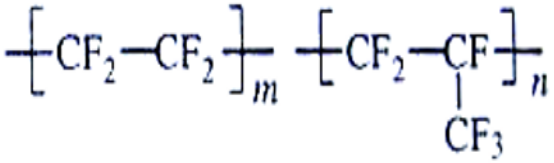


Engineering Polymers – Fluoropolymers

Polytetrafluoroethylene



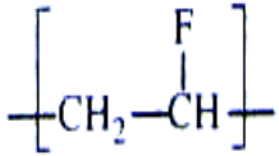
Fluorinated ethylene-propylene copolymer (FEP)



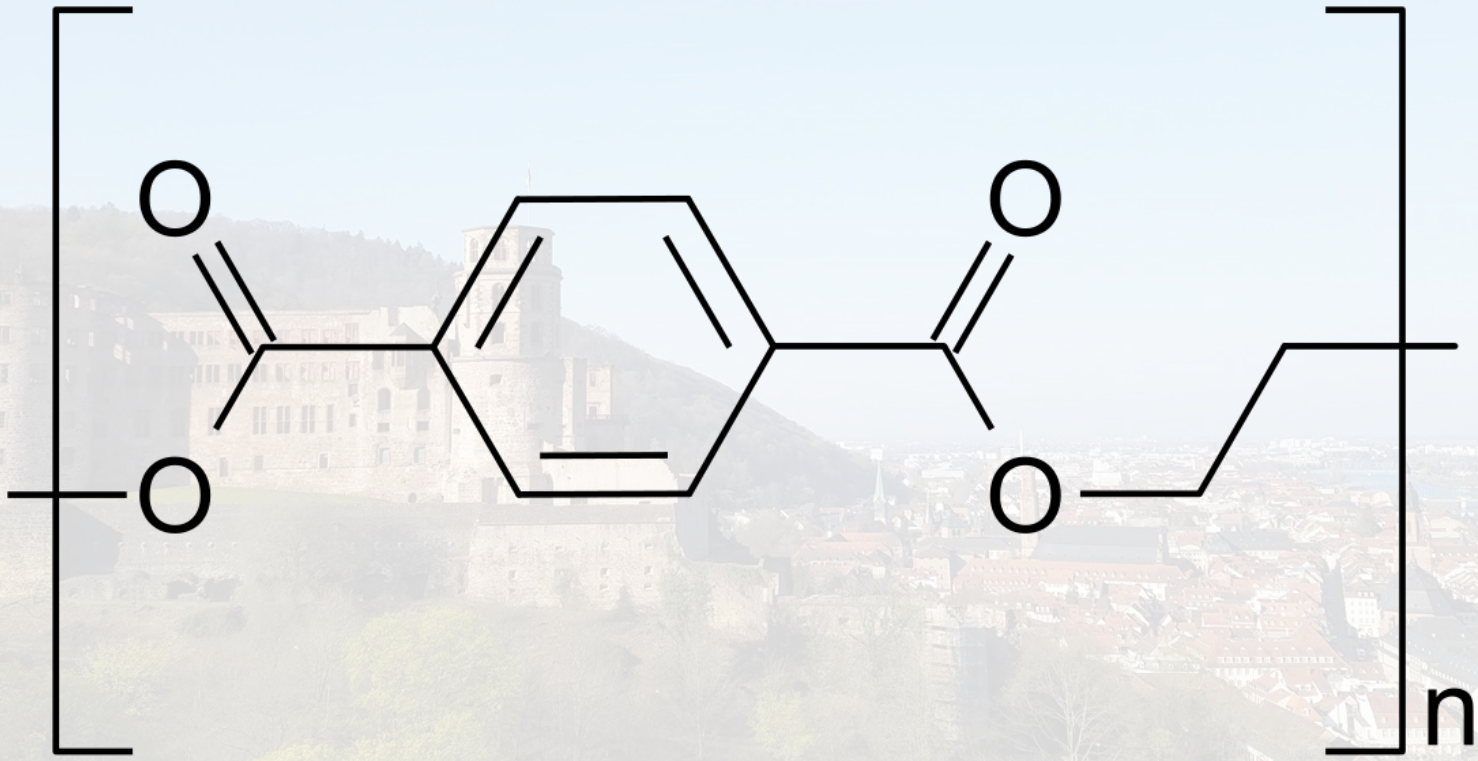
Polychlorotrifluoroethylene (CTFE)

Poly(vinylidene fluoride) (PVDF)

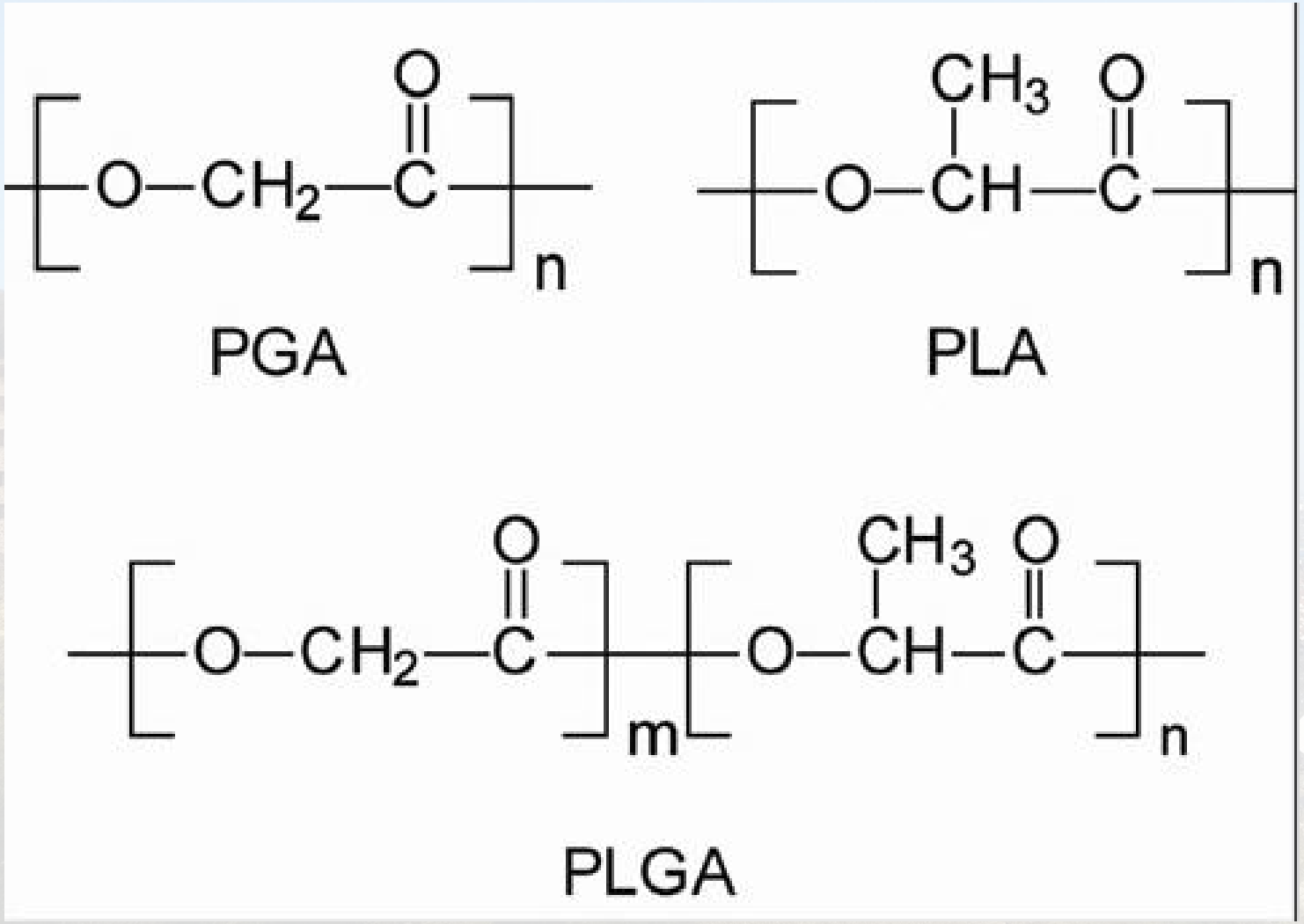
Poly(vinyl fluoride) (PVF)



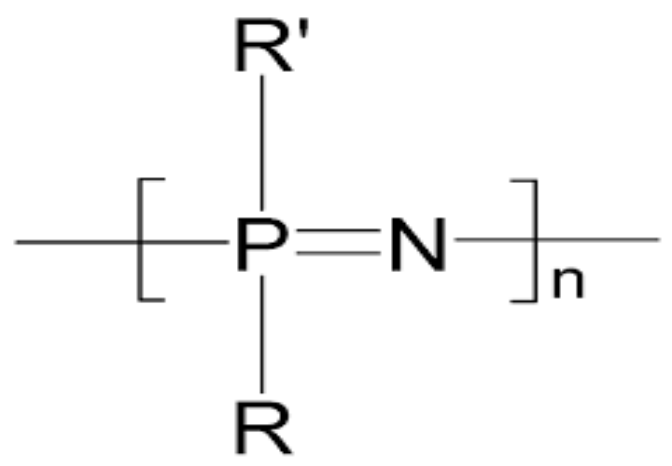
PET (Polyethylene Terephthalate)



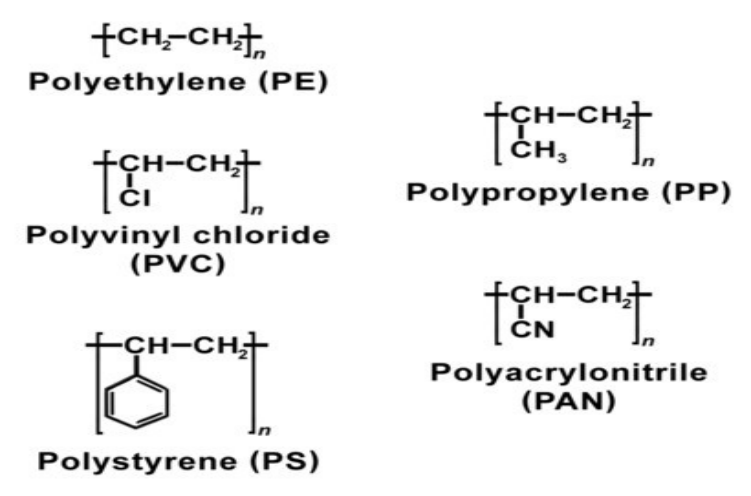
Polyglycolic Acid, Polylactic Acid

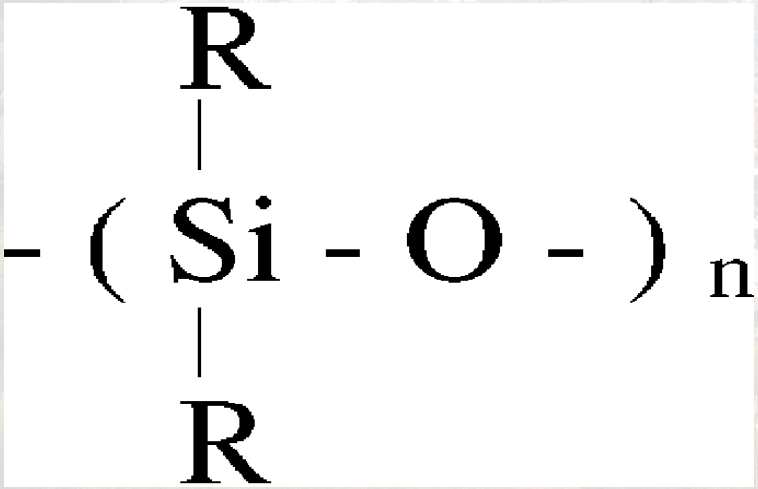


Polyphosphazenes

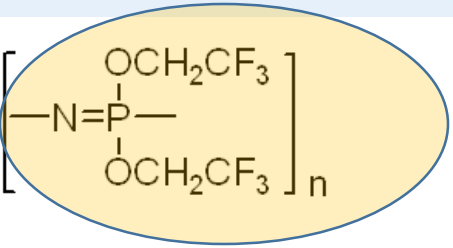


Comparison to Vinyl Polymers and Silicones

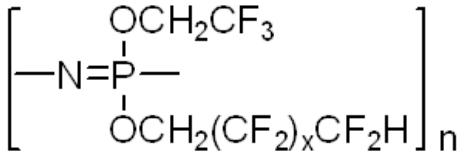




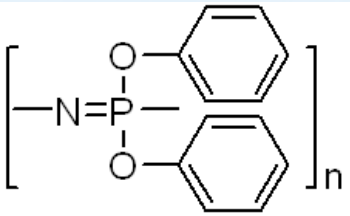
Polyphosphazene Structure Variations



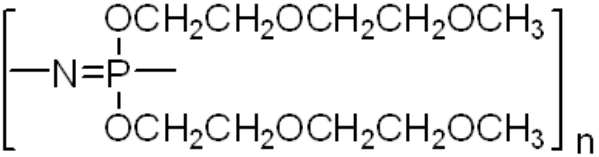
Hydrophobic film-, fiber-, and membrane-forming material



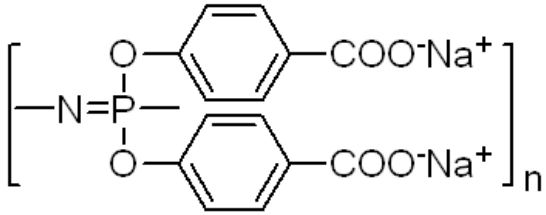
Hydrophobic elastomer



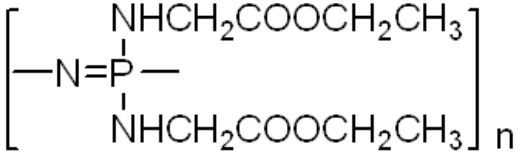
Hydrophobic film- and fiber-forming material



Water soluble polymer and solid polymer electrolyte



Water soluble polymer



Bioerodible polymer

Polyphosphozene Applications

1. Embolization Microspheres

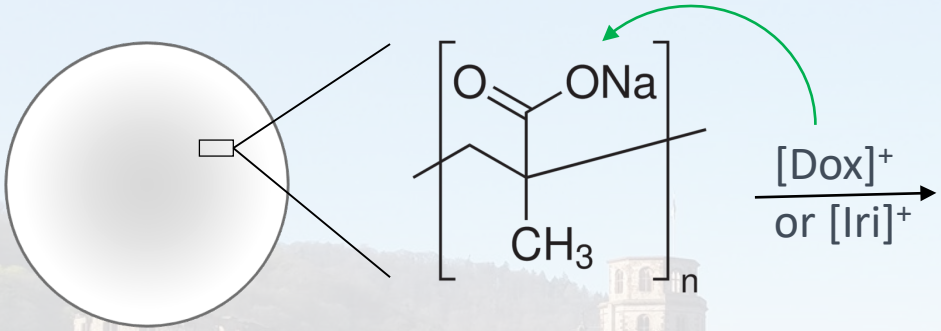
Animation of Embolization Microspheres in TACE procedure

https://www.youtube.com/watch?v=um-Gg4E4u1I&feature=youtu.be

Non-Drug-Loading Microspheres

- Size ranges from 40 μm to 1300 μm
- Precise size calibration
- Structural integrity and compressibility
- Stable suspension
- Biocompatibility

Drug-Loading Microspheres



$[Dox]^+$
or $[Iri]^+$

Doxo-rubicin

or

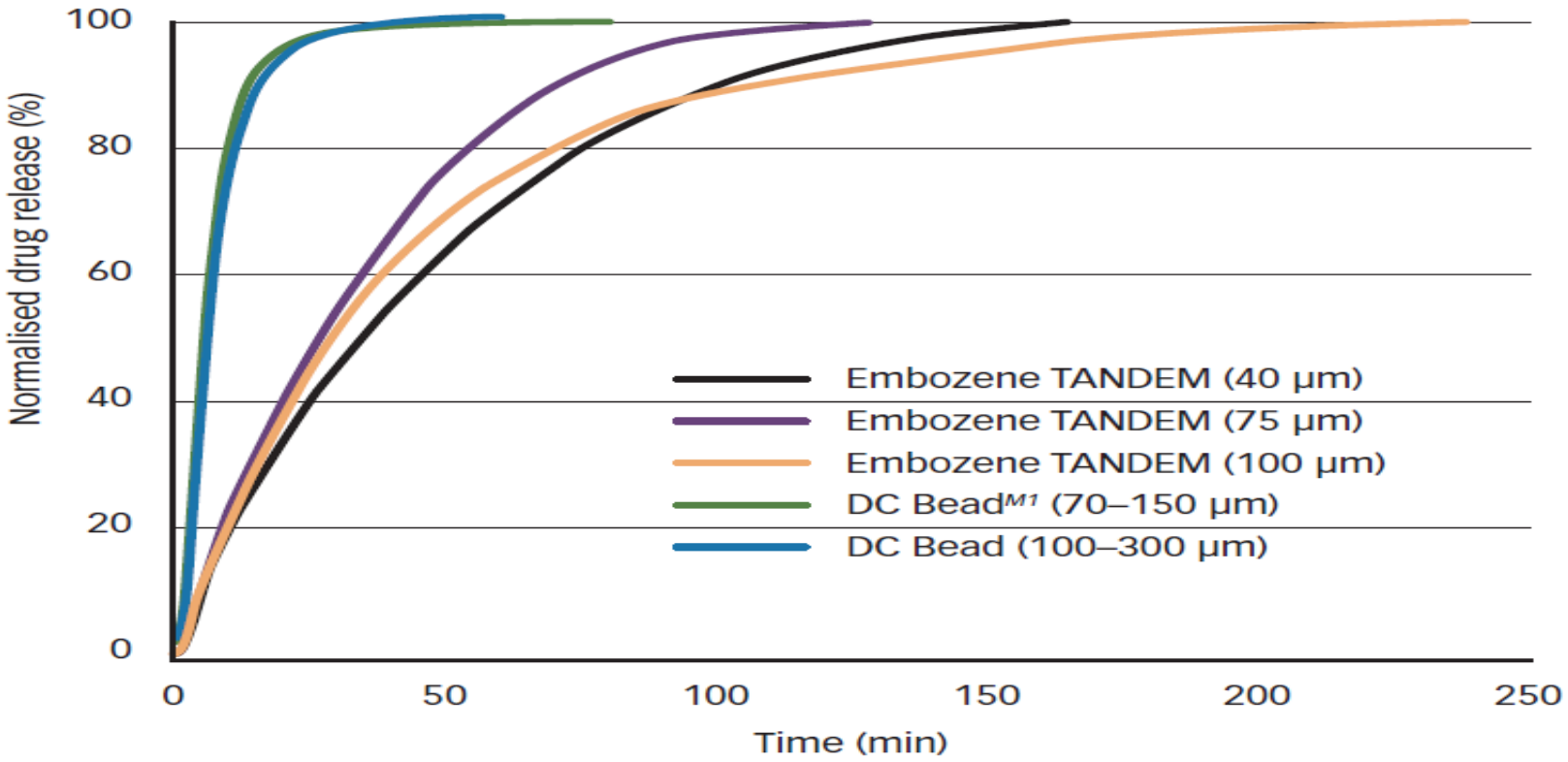
Irino-tecan

DEB-TACE
non-ionic CA

drug releasing via ion exchange

Drug-Release Times

Figure 2: Release Profiles of Different Irinotecan-loaded Drug-eluting Beads (50 mg/ml Microspheres)

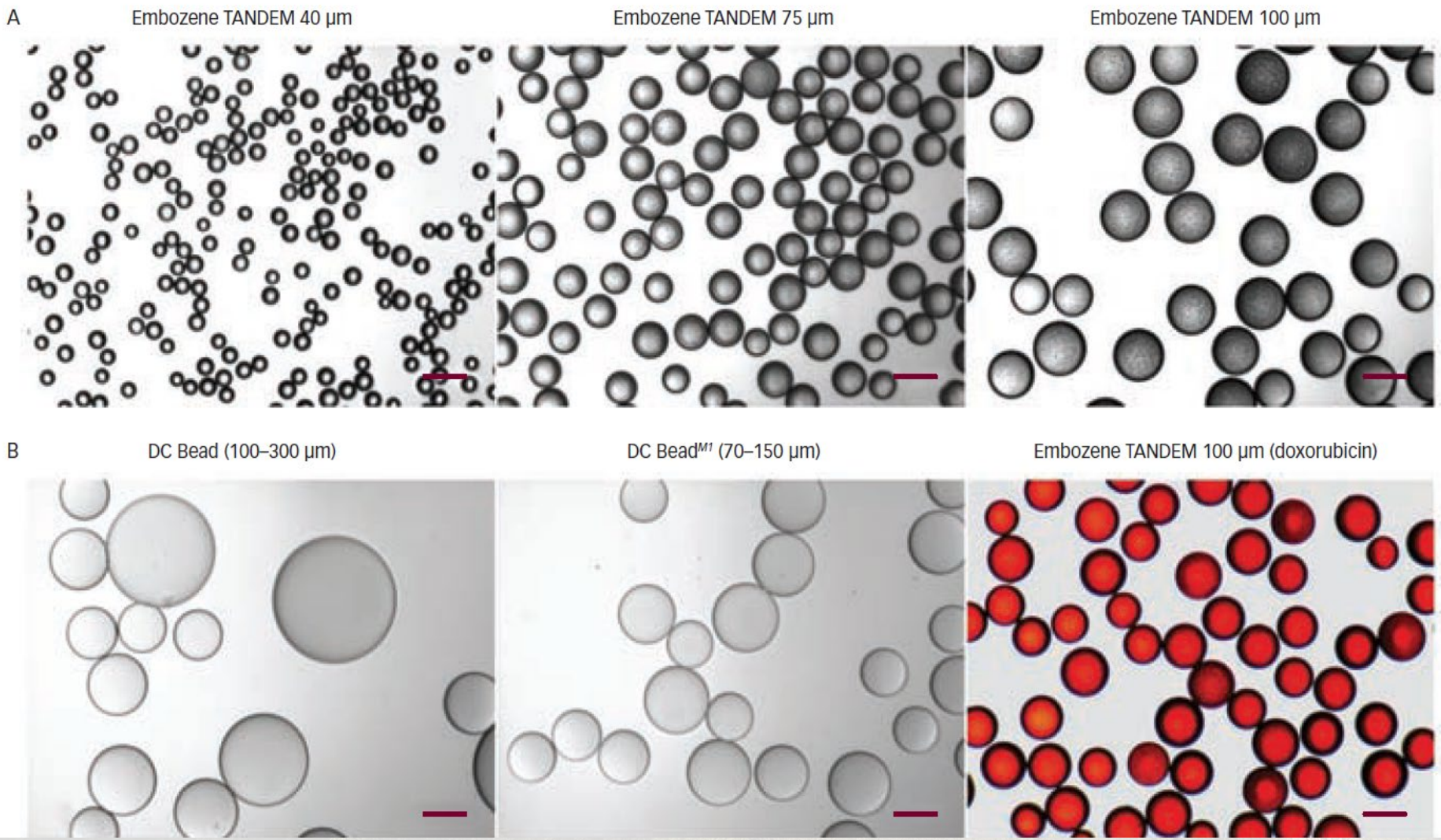


Release monitored in process via ultraviolet-visible spectroscopy in SOTAX CE 1 elution system at 37 °C using isotonic medium, 5 ml/min flow rate.

Figures represent typical measured values, not specifications

Microsphere Size Uniformity

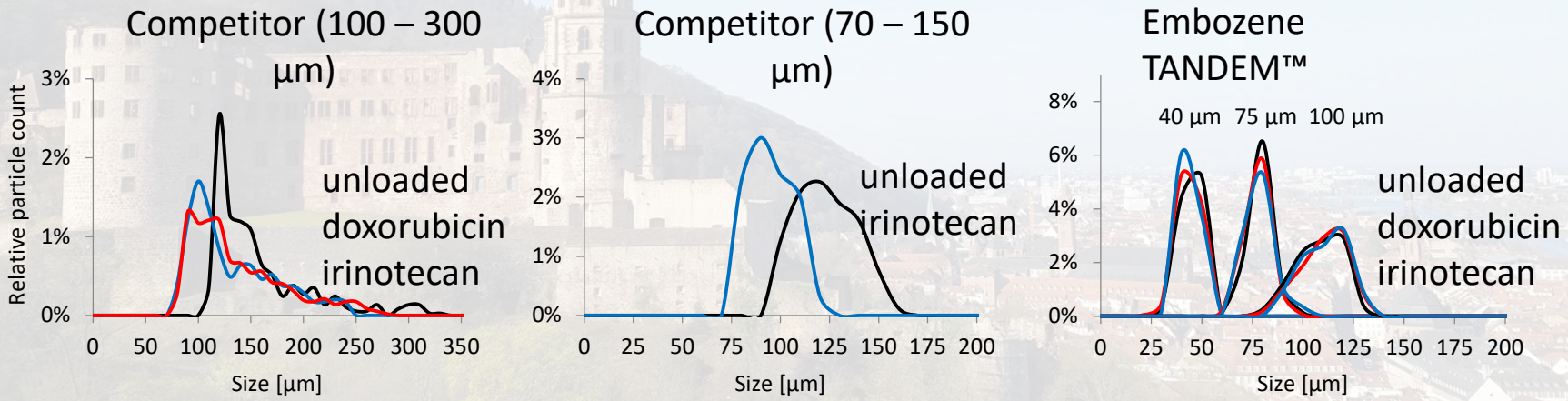
Figure 1: Optical Micrographs and Size Distribution of Embozene TANDEM™, DC Bead® and DC Bead®M1



Figures represent typical measured values, not specifications

Microsphere Size Stability

Microsphere	Doxorubicin [mg/ml microspheres]	Irinotecan [mg/ml microspheres]
Embozene TANDEM™	50	50
Competitor (100-300 µm)	37.5	50
Competitor (70-150 µm)	-	50

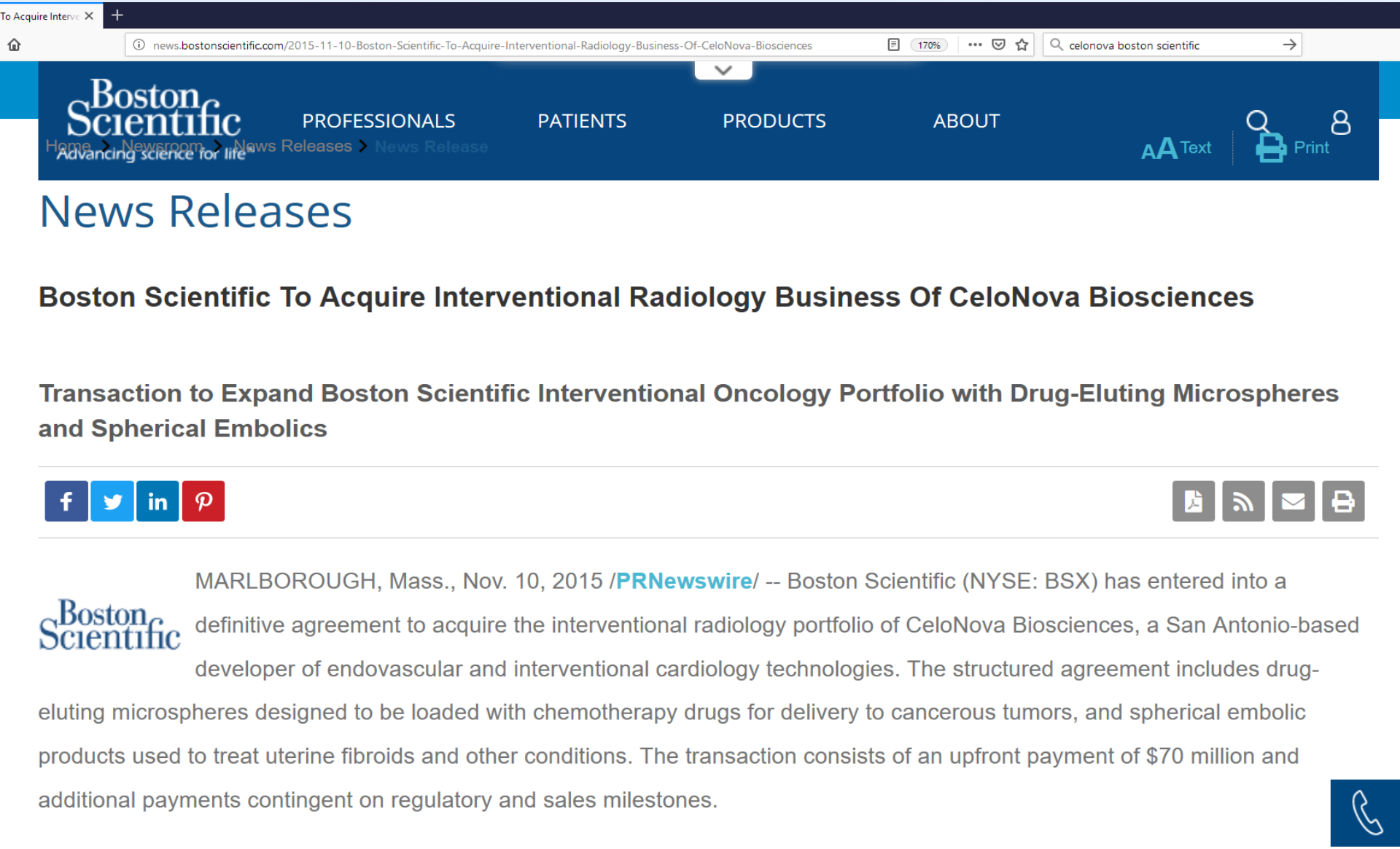


Figures represent typical measured values, not specifications

Product Benefits

- Can load doxorubicin and irinotecan faster and easier
  - Save time for the pharmacy
- Can load more drugs: up to 50 mg/ml microspheres
  - Load 150 mg of drug in one 3 ml syringe
- Drugs release slower
  - May reduce systemic side effects
- Microspheres do not change in size after drug loading
  - Easy passage through microcatheters
  - Ideal for targeted drug delivery near the tumor site

Embolization Microsphere Product Line Was Acquired by Boston Scientific



Polyphosphozene Applications

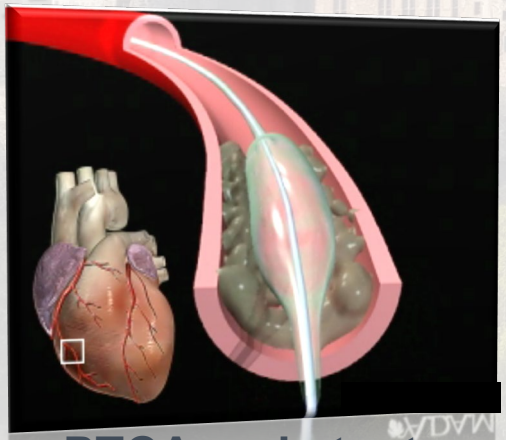
2. Coronary Stents

Evolution of Stent Technology
Matter of Scale

80s and 90s
Mechanical solutions to visible problems

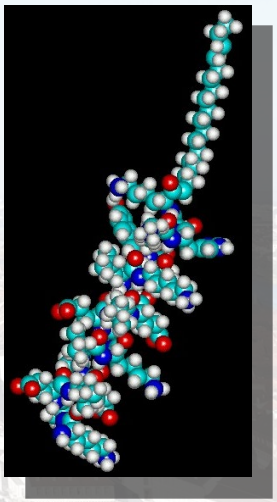
2000 to 2010
Pharmacologic response to cellular reactions

Future
Molecular level



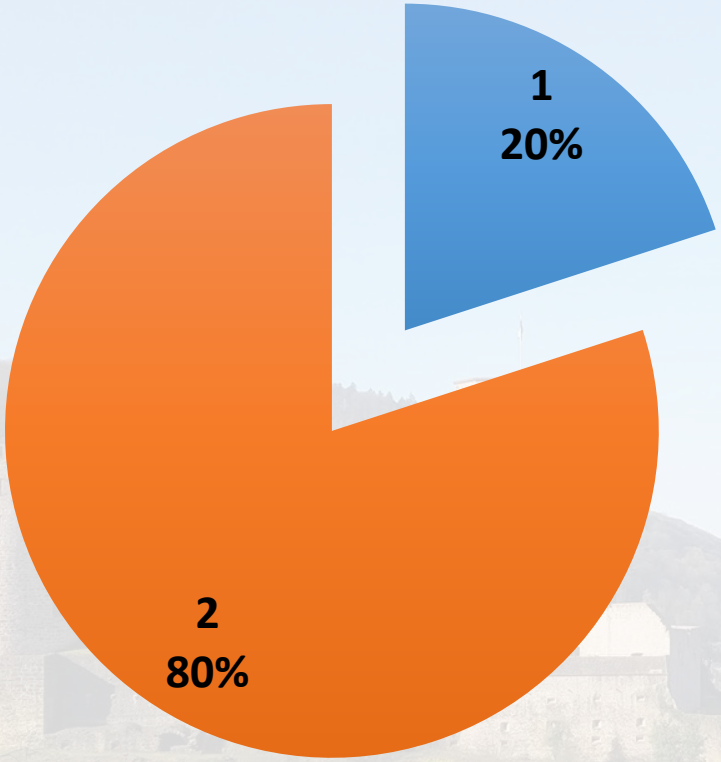
PTCA and stent

DES



Surface Modifications & Bioabsorbable

High Bleeding Risk (HBR) Population At Risk With Prolonged DAPT



- Age ≥ 75 yrs
- Oral Anticoagulation after PCI
- Planned major surgery < 12 months
- History of bleeding/stroke
- Severe Anemia
- Chronic Kidney Disease (CKD)
- Cancer
- Other (DAPT intolerance, non-compliance, platelet count < 100k, etc…)

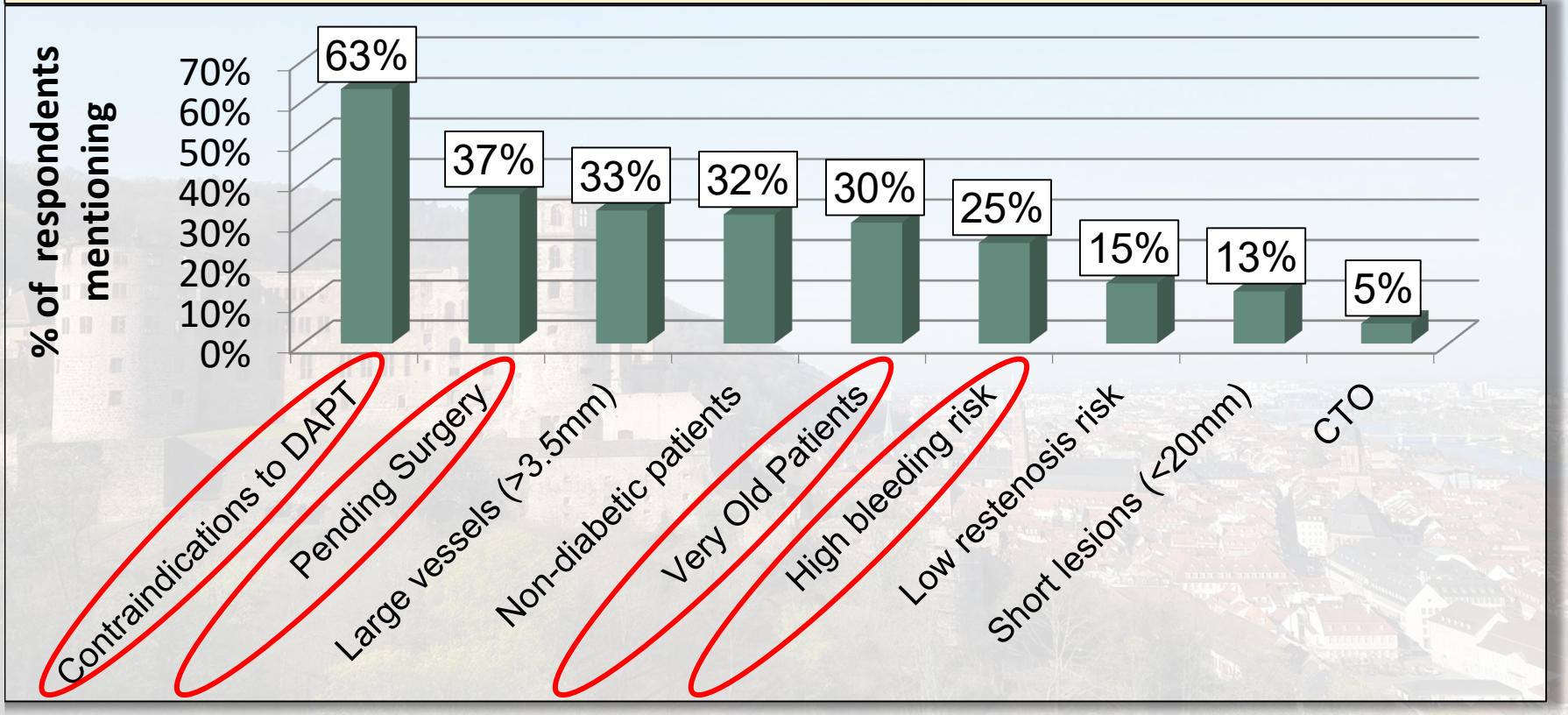
At least 20% of PCI patients are High Bleeding Risk (HBR)

Unmet Clinical Need

Low Restenosis Rates with Short DAPT

When are you NOT selecting DES? In which patient population?

(Top 3 Responses per MD; 60 MDs surveyed)

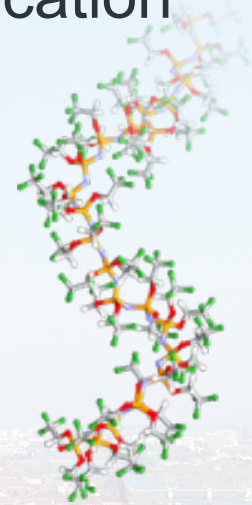


DAPT concern is top reason when DES is not selected

COBRA PzF™ Stent

Cobra Coronary Stent System

Polyzene™-F Surface Modification



COBRA PzF™ Coronary Stent System

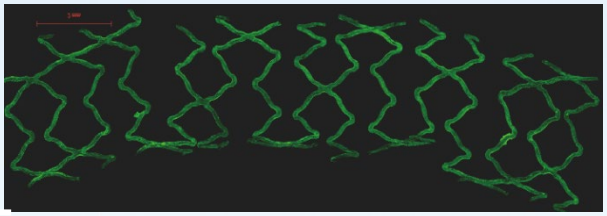
COBRA PzF™ Stent Solves the Unmet Clinical Need
Short DAPT with Low Restenosis

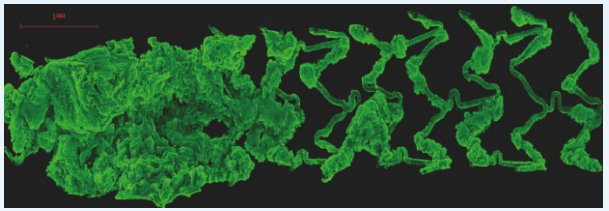
Thrombo-resistance[1]

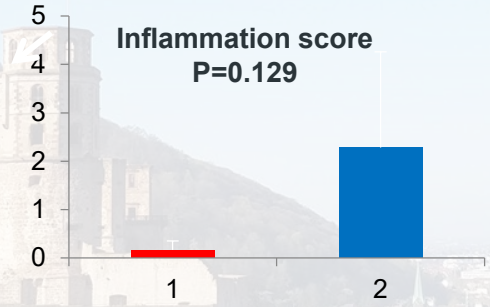
Reduced Inflammation[2]

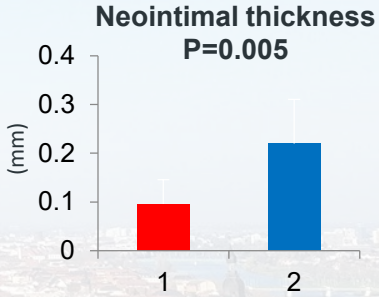
Rapid and More Natural Healing[3]

Cobra PzF™	MULTI-LINK Vision™





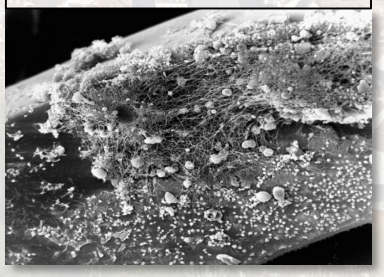




PzF Nano-Coated Stent

Healthy Proteinaceous Layer

Uncoated Stent



Fibrous Tissue

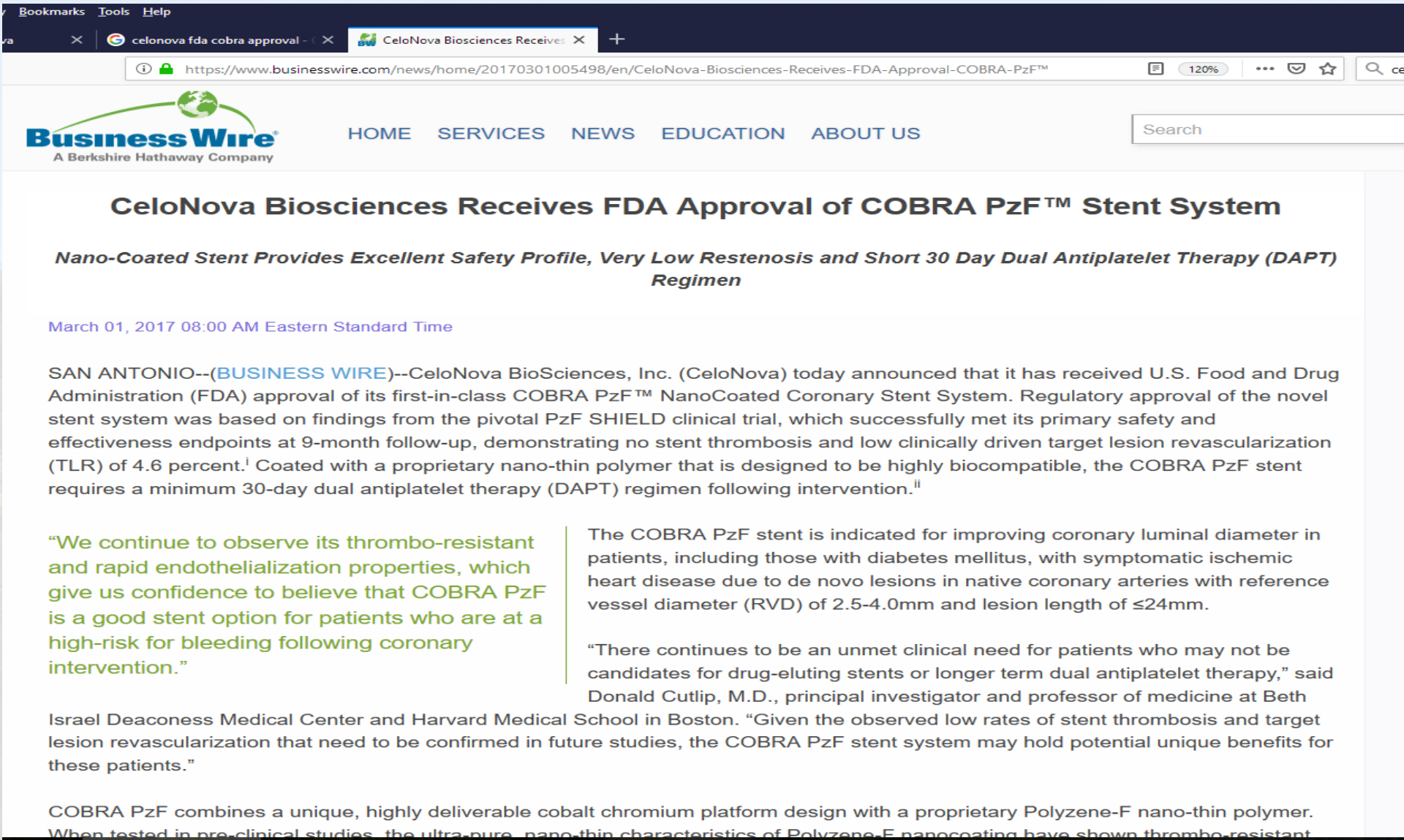
COBRA PzF™ Stent Clinical Data

Twelve-months Clinical Outcomes of published Data

Study Name	Stent used	MACE %	Cardiac Death %	Spontaneous MI %	TLR %	Late Stent Thrombosis %
eCOBRA	COBRA PzF N=940	8.6	3.7	3.7	4.3	0.3
PzF SHEILD	COBRA PzF N=296	10.1	0.36	0.7	4.6	0
Maillard's	COBRA PzF N=100	7	2	0	5	0
Anderson's	COBRA PzF N=103	-	-	0	3.9	0
ATLANT FIM 2009	Catania PzF n=55	10.9	0	0	3.6	0
ATLANTA II	Catania PzF n=300	8.8%	2.5	0.7	6.5	0
ATLANTA FR	Catania PzF n=379	7	2.2	0.8	4.3	0

Regenerative Engineering and Translational Medicine
https://doi.org/10.1007/s40883-019-00097-3

Cobra PzF™ Coronary Stent Received FDA PMA Approval



CeloNova Biosciences Receives FDA Approval of COBRA PzF™ Stent System

Nano-Coated Stent Provides Excellent Safety Profile, Very Low Restenosis and Short 30 Day Dual Antiplatelet Therapy (DAPT) Regimen

March 01, 2017 08:00 AM Eastern Standard Time

SAN ANTONIO--(BUSINESS WIRE)--CeloNova BioSciences, Inc. (CeloNova) today announced that it has received U.S. Food and Drug Administration (FDA) approval of its first-in-class COBRA PzF™ NanoCoated Coronary Stent System. Regulatory approval of the novel stent system was based on findings from the pivotal PzF SHIELD clinical trial, which successfully met its primary safety and effectiveness endpoints at 9-month follow-up, demonstrating no stent thrombosis and low clinically driven target lesion revascularization (TLR) of 4.6 percent.[i] Coated with a proprietary nano-thin polymer that is designed to be highly biocompatible, the COBRA PzF stent requires a minimum 30-day dual antiplatelet therapy (DAPT) regimen following intervention.[ii]

"We continue to observe its thrombo-resistant and rapid endothelialization properties, which give us confidence to believe that COBRA PzF is a good stent option for patients who are at a high-risk for bleeding following coronary intervention."

The COBRA PzF stent is indicated for improving coronary luminal diameter in patients, including those with diabetes mellitus, with symptomatic ischemic heart disease due to de novo lesions in native coronary arteries with reference vessel diameter (RVD) of 2.5-4.0mm and lesion length of ≤24mm.

"There continues to be an unmet clinical need for patients who may not be candidates for drug-eluting stents or longer term dual antiplatelet therapy," said Donald Cutlip, M.D., principal investigator and professor of medicine at Beth Israel Deaconess Medical Center and Harvard Medical School in Boston. "Given the observed low rates of stent thrombosis and target lesion revascularization that need to be confirmed in future studies, the COBRA PzF stent system may hold potential unique benefits for these patients."

COBRA PzF combines a unique, highly deliverable cobalt chromium platform design with a proprietary Polyzene-F nano-thin polymer. When tested in pre-clinical studies, the ultra-pure, nano-thin characteristics of Polyzene-F nanocoating have shown thrombo-resistant


Thank you!