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Advanced Medical Technology Association

# AdvaMed Combination Workshop Case Study - AdvaMed Combination Products Workshop Case Study-- Antibacterial Orthopedic and Neurological Devices

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BRINGING INNOVATION TO PATIENT CARE WORLDWIDE

October 2012
AHWP Combination Products Workshop

# Agenda

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- General Framework US FDA Regulations
- Case Study of Two Combination Products
  - Antibiotic Impregnated Devices for Drainage of Cerebrospinal Fluid
  - Antibiotic Bone Cement for Orthopedic Indications
- Product Introductions
- FDA Classifications
- Primary Mode of Actions and Indications
- Regulatory Histories
- Quality Systems Controls

# US FDA Regulation of Combination Products – General Framework

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- In the United States, FDA Center for Devices and Radiological Health will seek a consulting opinion from the Center for Drug Evaluation and Research
- No requirement for prior drug approval
- **US FDA's guidance allows a medical device combination product to be approved with a drug that has not been previously approved for another use**
- **In addition to device requirements;**
  - FDA guidance calls for an evaluation of the preclinical information, which may include conventional pharmacology and toxicology studies to establish a basic understanding of safety issues of the drug component itself
  - Such studies are used to establish the safety and efficacy of the dosing regimen and indications proposed for the combination product
- See www.fda.gov/oc/combination/innovative.html

# Bactiseal Product Introduction

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- Bactiseal™ Catheters incorporate an Antimicrobial Impregnation Process (AIP) patented technology
  - BACTISEAL EVD Catheters
  - BACTISEAL Ventricular Catheters
- The catheters are impregnated with two antibiotics (Rifampicin & Clindamycin HCL) into the silicone matrix


Reduces colonization of gram positive bacteria

# Bactiseal Impregnation

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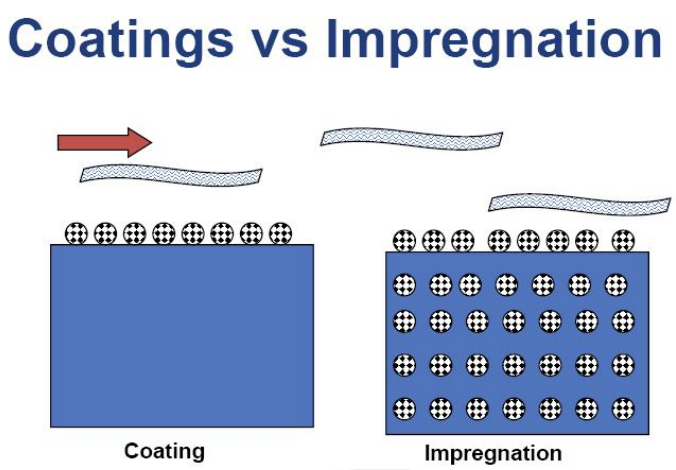
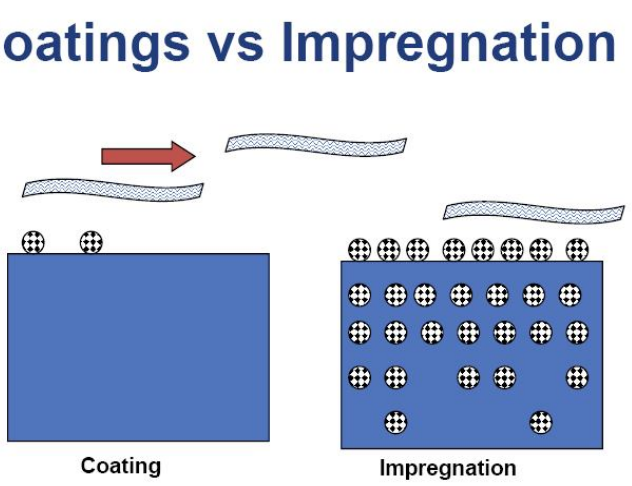
BACTISEAL catheters have been shown in laboratory studies to reduce the colonization of gram-positive bacteria on the tubing surfaces for 28 days.




Day 0




Day 28

# Bactiseal

- The quantities of rifampin and clindamycin hydrochloride used to impregnate the catheters are only a small fraction of a therapeutic dose of these two antibiotics, and have no potential for any systemic therapeutic effect.
  - The drug concentrations impregnated in the catheters are so low, there is no chance of resistance

# US FDA Classification for BACTISEAL EVD Catheter Products

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New Search | Back To Search Results

| | |
|---|---|
| **Device** | Shunt, Central Nervous System And Components |
| **Regulation Description** | Central nervous system fluid shunt and components. |
| **Regulation Medical Specialty** | Neurology |
| **Review Panel** | Neurology |
| **Product Code** | JXG |
| **Submission Type** | 510(k) |
| **Regulation Number** | 882.5550 |
| **Device Class** | 2 |
| **Total Product Life Cycle (TPLC)** | TPLC Product Code Report |
| **GMP Exempt?** | No |

**Recognized Consensus Standards**

- ISO 7197:2006 Neurosurgical Implants - Sterile, single-use hydrocephalus shunts and components
- ASTM F647-94 (Reapproved 2006) Standard Practice for Evaluating and Specifying Implantable Shunt Assemblies for Neurosurgical Application
- ISO 7197:2006 Technical Corrigendum1:2007 Neurological implants - Sterile, single-use hydrocephalus shunts and components

**Third Party Review**

- Eligible for *Accredited Persons Expansion Pilot Program*

**Accredited Persons**

- Dekra Certification B.v.
- Intertek Testing Services
- Regulatory Technology Services, Llc
- Tuv Sud America Inc.
- Underwriters Laboratories, Inc.

# Bactiseal EVD Catheter

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- Primary Mode of Action—Device
- Indication- For gaining access to the ventricles of the brain and can be used with dimensionally compatible devices for draining cerebrospinal fluid (CSF) and other fluids of similar characteristics as a means of reducing intracranial pressure (ICP) and CSF volume
- FDA Classification Sec. 882.5550 Central nervous system fluid shunt and components. (a)*Identification.* A central nervous system fluid shunt is a device or combination of devices used to divert fluid from the brain or other part of the central nervous system to an internal delivery site or an external receptacle for the purpose of relieving elevated intracranial pressure or fluid volume (e.g., due to hydrocephalus). Components of a central nervous system shunt include catheters, valved catheters, valves, connectors, and other accessory components intended to facilitate use of the shunt or evaluation of a patient with a shunt.
- (b)*Classification.* Class II (performance standards).

# US FDA Classification
# Bactiseal Ventricular Catheters

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New Search | Back To Search Results

| | |
|---|---|
| **Device** | Catheter, Ventricular |
| **Regulation Description** | Ventricular catheter. |
| **Regulation Medical Specialty** | Neurology |
| **Review Panel** | Neurology |
| **Product Code** | HCA |
| **Submission Type** | 510(k) |
| **Regulation Number** | 882.4100 |
| **Device Class** | 2 |
| **Total Product Life Cycle (TPLC)** | TPLC Product Code Report |
| **GMP Exempt?** | No |

**Recognized Consensus Standards**

- ISO 7197:2006 Neurosurgical Implants - Sterile, single-use hydrocephalus shunts and components
- ASTM F647-94 (Reapproved 2006) Standard Practice for Evaluating and Specifying Implantable Shunt Assemblies for Neurosurgical Application
- ISO 7197:2006 Technical Corrigendum1:2007 Neurological implants - Sterile, single-use hydrocephalus shunts and components

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- Tuv Rheinland Of North America, Inc.
- Tuv Sud America Inc.
- Underwriters Laboratories, Inc.

# Bactiseal Ventricular Catheters

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- Primary Mode of Action—Device
- Indication- For use in the treatment of hydrocephalus as a component of a shunt system when draining or shunting of cerebrospinal (CSF) is indicated
- FDA Classification--Sec. 882.4100 Ventricular catheter. (a)Identification. A ventricular catheter is a device used to gain access to the cavities of the brain for injection of material into, or removal of material from, the brain.
- (b)Classification. Class II (performance standards).

# Regulatory History

- USA
  - First FDA BACTISEAL Clearance received in 2001
  - Four additional FDA Clearances for BACTISEAL technology received with the latest in 2011
    - Since the new Guidance was released

- EU Class III

# Quality Systems Requirements for Bactiseal

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- Includes Drug Quality Controls
- Antibiotics must not be adversely affected by sterilization process
- Antibiotics must be stable over shelf life of device

# Discussion Points

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- Antibiotics impregnated in catheter are part of the raw material of the device
- The drug concentrations impregnated in the catheters are so low, there is no chance of resistance
- Clinical evidence exists in the form of published literature on Bactiseal catheters

# Bone Cement for Orthopedic Indications

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- **USA FDA Class II Medical Device**
- 21 CFR 888.3027
- Sec. 888.3027 Polymethylmethacrylate (PMMA) bone cement. (a)*Identification.* Polymethylmethacrylate (PMMA) bone cement is a device intended to be implanted that is made from methylmethacrylate, polymethylmethacrylate, esters of methacrylic acid, or copolymers containing polymethylmethacrylate and polystyrene. **The device is intended for use in arthroplastic procedures of the hip, knee, and other joints for the fixation of polymer or metallic prosthetic implants to living bone.**
- (b)*Classification.* Class II (special controls). The special control for this device is the FDA guidance document entitled "Class II Special Controls Guidance Document: Polymethylmethacrylate (PMMA) Bone Cement."

# Bone Cement FDA Classification

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CDRH SuperSearch

510(k) | Registration & Listing | Adverse Events | Recalls | PMA | Classification | Standards
CFR Title 21 | Radiation-Emitting Products | X-Ray Assembler | Medsun Reports | CLIA | TPLC

New Search | Back To Search Results

| | |
|---|---|
| **Device** | Bone Cement |
| **Regulation Description** | Polymethylmethacrylate (PMMA) bone cement. |
| **Regulation Medical Specialty** | Orthopedic |
| **Review Panel** | Orthopedic |
| **Product Code** | LOD |
| **Submission Type** | 510(k) |
| **Regulation Number** | 888.3027 |
| **Device Class** | 2 |
| **Total Product Life Cycle (TPLC)** | TPLC Product Code Report |
| **GMP Exempt?** | No |

**Recognized Consensus Standards**

- ASTM F451-08 Standard Specification for Acrylic Bone Cement
- ASTM F 983-86 (Reapproved 2009) Standard Practice for Permanent Marking of Orthopaedic Implant Components
- ASTM F 565-04 (Reapproved 2009)e1 Standard Practice for Care and Handling of Orthopedic Implants and Instruments

**Guidance Documents**

- Class II Special Controls Guidance Document: Polymethylmethacrylate (PMMA) Bone Cement; Guidance for Industry and FDA
- Clinical Trial Considerations: Vertebral Augmentation Devices to Treat Spinal Insufficiency Fractures - Guidance for Industry and FDA Staff

| | |
|---|---|
| **Third Party Review** | Not Third Party Eligible |

# Antibiotic Bone Cement History and Product Information

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- Surgeons were mixing antibiotics into bone cement
- No controls on which antibiotic or quantity of antibiotics added
- Poor mixing
- Potential adverse effects on cement properties and long term stability of joint implants

# Antibiotic Bone Cement

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- USA FDA Class II Medical Device
- Primary Mode of Action is Medical Device
  - Addition of antibiotics to bone cement
- Same Classification 888.3027 as bone cement
- Different Indication:
  - Indicated for use in the second stage of a two-stage revision for total joint arthroplasty after the initial infection has been cleared
- Creates Zone of Inhibition

SmartSet®

# Antibiotic Bone Cement

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## Product Classification

FDA Home ▸ Medical Devices ▸ Databases

CDRH SuperSearch

510(k) | Registration & Listing | Adverse Events | Recalls | PMA | Classification | Standards
CFR Title 21 | Radiation-Emitting Products | X-Ray Assembler | Medsun Reports | CLIA | TPLC

New Search | Back To Search Results

| | |
|---|---|
| Device | Bone Cement, Antibiotic |
| Regulation Description | Polymethylmethacrylate (PMMA) bone cement. |
| Regulation Medical Specialty | Orthopedic |
| Review Panel | Orthopedic |
| Product Code | MBB |
| Submission Type | 510(k) |
| Regulation Number | 888.3027 |
| Device Class | 2 |
| Total Product Life Cycle (TPLC) | TPLC Product Code Report |
| GMP Exempt? | No |
| Recognized Consensus Standards | • ASTM F451-08 Standard Specification for Acrylic Bone Cement<br>• ASTM F 983-86 (Reapproved 2009) Standard Practice for Permanent Marking of Orthopaedic Implant Components<br>• ASTM F 565-04 (Reapproved 2009)e1 Standard Practice for Care and Handling of Orthopedic Implants and Instruments |
| Third Party Review | Not Third Party Eligible |

# Regulatory History

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- USA
  - First DePuy FDA Antibiotic Bone Cement Clearance received in 2003
  - Four additional FDA Clearances for Antibiotic Bone Cement since 2003
- EU Class III

# Quality Systems Requirements for SmartSet

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- Includes Drug Quality Controls
- Antibiotic must not be adversely affected by sterilization process
- Antibiotic must be stable over shelf life of device
- Cement properties must not be affected by addition of antibiotics

# Performance Data – Mechanical Testing Example

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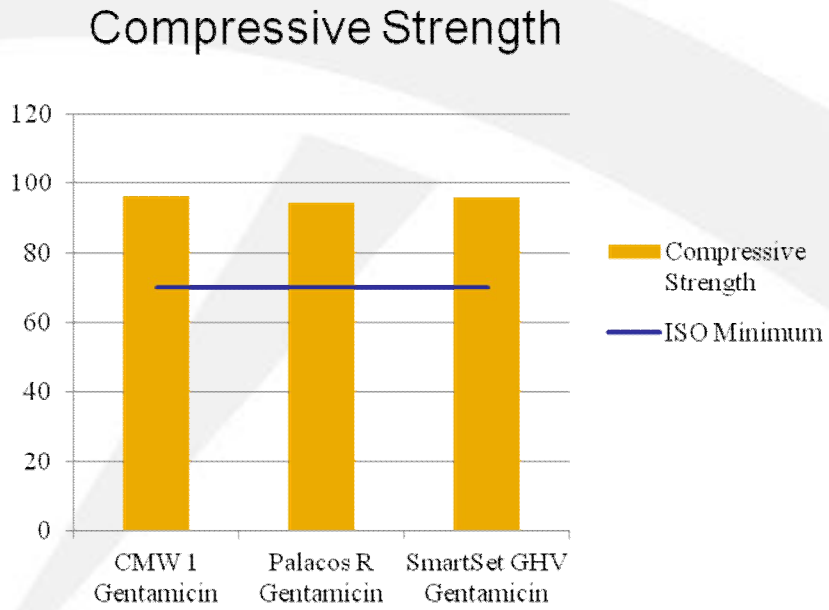
- Mechanical testing (ISO 5833 & ASTM 5833)
  - Static strength tests (compressive, flexural) are used to compare to cements with extensive clinical performance.



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# Thank You