Drug /Device Combinations:
The Convergence of Pharmaceutical and Biomaterial Science

Are We Just Raising the Stakes for Industry, Regulators, and Decision Makers?

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Director, Health Economics and Emerging Technologies
Johnson & Johnson Medical Products
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Convergence of Therapeutics and Devices

**Device**
An instrument, apparatus, implement, machine contrivance, implant, *in vitro* reagent, or component that provides a diagnosis, cure, mitigation, treatment, or prevention of a disease or condition, which does not achieve its intended use by being metabolized or through a chemical reaction.

**Therapeutics**
Drug: A small-molecule, chemically synthesized product that provides a diagnosis, cure, mitigation, treatment, or prevention of a disease or condition, which achieves its intended use by being metabolized or through a chemical reaction.

Biologic: A therapeutic agent or analog; most consisting of proteins, monoclonal antibodies, or hormones; derived from living organisms that provides a diagnosis, cure, mitigation, treatment, or prevention of a disease or condition, which achieves its intended use by being metabolized or through a chemical reaction. Although recombinant human insulin and human growth hormone are biologics, they are regulated as drugs under the Food, Drug, and Cosmetics Act.
Background

- 1980’s implantable pacemaker electrode with steroid (reduce tissue scarring)

- Science marched on, but regulatory was out of step (lack of experience and expertise with multiple technologies)

- FDA established the Office of Combination Products to accelerate approval process (2003)

- Health Canada reviewing issue
Examples of Combination Products

Antibiotic Bone Cement Beads

Dermal Collagen Implants
The New Paradigm … Drug Eluting Stents
Marketshare by Product Classification

DESs will continue to hold the greatest share of the combination products market through 2009. Driven by strong demand, bio-artificial pancreases and closed loop glucose monitor/insulin pump combinations that are slated to enter the field by 2009 will account for 5% of the total marketshare.

2004E Total Market = $5.92B

2009E Total Market = $9.54B
Product Class Market Growth

- **Strong**
  - Antimicrobial Orthopedic Sleeve
  - Bone Fusion System
  - Hemostatic Sealant

- **Moderate**
  - Antibiotic Bone Cement
  - Bone Graft with Peptide
  - Drug Eluting Stent
  - Hernia Repair
  - Steroid-Eluting Electrode

- **Low**
  - Cartilage Replacement
  - Wound Covering

- Drug Eluting Stent
- Steroid-Eluting Electrode
- Wound Covering
- Hernia Repair
- Antibiotic Bone Cement
- Cartilage Replacement
- Bone Fusion System with Growth Factor
- Hemostatic Sealant
- Antimicrobial Orthopedic Sleeve
### Possible Future Combinations

<table>
<thead>
<tr>
<th>Medical Devices</th>
<th>Drugs and Biologics</th>
<th>Antibiotics</th>
<th>Antibodies</th>
<th>Biomimetic Peptides</th>
<th>Biopolymers</th>
<th>Cells</th>
<th>Nucleotides</th>
<th>Growth Factors</th>
<th>Steroids</th>
<th>Other Therapeutics</th>
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<tbody>
<tr>
<td>Heart Valve</td>
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<td>Heart Pump</td>
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<tr>
<td>Water-jet Device</td>
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<td>Catheter</td>
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<td>Stent</td>
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<td>Electrode</td>
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<tr>
<td>Deep Brain Stimulation</td>
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<tr>
<td>Neural Prosthesis</td>
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</tbody>
</table>

● = Low Need  
○ = Moderate Need  
● = Strong Need
What’s around the corner

1. AngioJet System with Tenecteplase: rapid achievement of revascularization of limbs
2. CIRCE’S HEPATASSIST 2000: hollow fiber bioreactor containing primary porcine hepatocytes, two charcoal filters, a membrane oxygenator, and a pump.
3. Islet Sheet Bio – Artificial Pancreas: releases insulin into the bloodstream
4. Stem Cell Coated Porcine Valves: much more biocompatible; may aid in the integration process
## Overview: Combination Products Market

### WW Market Size and Growth

<table>
<thead>
<tr>
<th>Year</th>
<th>Value</th>
<th>CAGR 2004-2009</th>
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<tbody>
<tr>
<td>2004E</td>
<td>$5.92 Billion</td>
<td>10%</td>
</tr>
<tr>
<td>2009E</td>
<td>$9.54 Billion</td>
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### Current Therapeutic Areas

- Cardiovascular
- Wound Management
- Orthopedic
- Diabetes

### Potential Future Products

- AngioJet system with TNK
- Antibody coated stent
- Anti-microbial urinary catheter
- Biodegradable bone screw and BMP
- Deep brain stimulator with steroid
- Gene-coated stent
- Injectable biopolymers with growth factors
- Liver assist device
- Thin sheet bio-artificial pancreas
- Closed-loop glucose monitor and insulin pump
Combination Product Trends, Challenges, and Strategic Options

**Trends, Challenges and Strategic Options**

**Trends**
- Faster Approval Process
- Further Development of Cardiovascular Related Products
- Product Displacement by New Combination Products

**Challenges**
- Determining the Unmet Need
- Determining Regulatory Classification
- Lack of Funding of Early Stage Companies
- Risk of Patent Infringement

**Strategic Options**
- Determine a Market Positioning and Development Strategy
- Work with Contract Research Organizations (Cross)
- Establish Collaborative Relationships
## Overview of Trends in the Combination Market

<table>
<thead>
<tr>
<th>Trend</th>
<th>Description</th>
<th>Benefits</th>
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<tbody>
<tr>
<td>Faster Approval Process</td>
<td>A new office of Combination Products (OCP) was established within the FDA, and this will significantly shorten product approval time.</td>
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<tr>
<td>Further Development of Cardiovascular Related Products</td>
<td>The increasing cardiovascular patient population has heightened the demand for improved combination products utilized in cardiovascular surgeries.</td>
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<tr>
<td>Product Displacement by New Combination Products</td>
<td>A next-generation combination product can make the single-component medical device outdated or obsolete.</td>
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</table>
Historical Perspective

Milestones in Combination Product Development and Regulatory Changes

1820
The U.S. Pharmacopeia, the first compendium of standard drugs for the United States is established by eleven founding physicians.

1902
The Biologics Control Act is passed to ensure the purity and safety of serums and vaccines, and similar products used to prevent or treat disease.

1976
Medical Devices Amendments were passed to ensure safety and effectiveness of devices.

1990

1995

2000

2003

April 2003
Cordis Corporation received FDA Approval for its drug-eluting stent, Cypher, the first to be marketed in the United States.

December 2002
The FDA established an Office of Combination Products in preparation for the imminent approval of the drug-eluting stent and other combination products.

June 2003
Certain biologic compounds such as monoclonal antibodies for in vivo use and cytokines were shifted from the CBER’s jurisdiction to that of CDER.

July 2003
The Food and Drug Administration (FDA) cleared the first device for diabetics which integrates into one devices a glucose meter and an insulin pump with a dose calculator.

1976
The Medical Devices Amendments were passed to ensure safety and effectiveness of devices.

1997
The Food and Drug Administration Modernization Act, which mandates the most wide-ranging reforms in agency practices since 1938, was passed. It accelerates review of devices, regulates advertising of unapproved drug and device usages, and restricts health claims for foods.

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# Overview of Challenges in the Combination Market

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<tr>
<th>Challenge</th>
<th>Description</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine the Unmet Need</td>
<td>Before investing money and effort into developing a combination product, the unmet need must be present. Patient population, current risk, cost of development, and potential revenues must be considered when evaluating need.</td>
<td>![arrow]</td>
</tr>
<tr>
<td>Determining Regulatory Classification</td>
<td>A combination product must be classified as a drug, device, or biologic for regulatory purposes, determined by the primary mode of action of the product.</td>
<td>![arrow]</td>
</tr>
<tr>
<td>Lack of Funding for Early Stage Companies</td>
<td>The current economic landscape has led to diminished funding available for early stage biotechnology companies, leading to a longer product development timeline.</td>
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</tr>
<tr>
<td>Risk of Patent Infringement</td>
<td>Johnson &amp; Johnson holds several key stent patents. Therefore, DES players must have strong legal expertise and sufficient resources to fund costly litigation battles.</td>
<td>![arrow]</td>
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</tbody>
</table>
## Overview of Strategic Options in the Combination Market

<table>
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<th>Strategy</th>
<th>Description</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine a Market Positioning and Development Strategy</td>
<td>By analyzing the market potential and investigating top therapeutic candidates, a company can position its combination product for success.</td>
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<tr>
<td>Work with contract Research Organizations (CROs)</td>
<td>Contract research organizations can help with product development and make the transition to a combination product quicker and smoother when companies do not have surface modification expertise in-house.</td>
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<tr>
<td>Establish Collaborative Relationships</td>
<td>Combination product developers need to collaborate with the FDA, physicians, and third-party payers during the product development phase. This will ensure that all regulatory and reimbursement issues will be settled prior to submission for approval.</td>
<td></td>
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</table>
“Is it Worth the Risk?”

Industry
- Drug development costs but device returns
- Patent protection is minimal
- Shortened product life cycles

Regulatory
- Is it a drug or a device?

Assessment Agencies
- Most will behave like a device

So What!
Medical Devices Differ from Drugs

- Short life cycles (18-months)
- Limited patent protection
- Rapid competitive entry
- Need for quick return on investment (CYPHER - $600MM USD)
- Drug/Device is new paradigm
Further Complicated By

- Outcomes dependant upon clinician competency
- Evidence limited to safety and efficacy at time of market introduction (RCT’s rare, large trials cost prohibitive)
- Effectiveness clinical trials conducted following product introduction (usually 2-5 years)
Drug Pricing Example

Effectiveness and Economic Trials Conducted Early in Life Cycle
BMS Versus DES Price Comparison

BMS (Bare Metal Stent)
DES (Drug Eluting Stent)
Are We Just Raising the Stakes?

• Moderate growth for the next 5-years

• Significant challenges to industry, regulatory and payers

• Promises of patient benefits