“A Drug-Eluting Stent Case Study: TAXUS™ Express²™ - From Development to Approval”

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Boston Scientific Corporation
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Key Considerations for DES*

Balance Between Individual Components and the Methods of Combining Them

Device

Targeted Biological Response

Active Ingredient (Drug, Biologic)

Carrier Matrix (Polymer, Excipient)

*DES = Drug Eluting Stent

*DES = Drug Eluting Stent
Key Components of DES Combination Products That Can Impact Biocompatibility, Functionality and Manufacturing

**DEVICE**
- Material
  - Polymers
  - Metals
- Design
  - Geometry
  - Mechanical Function
  - Anatomical location

**CARRIER MATRIX**
- Chemistry
  - Manufacturing residuals
  - Compatibility with drug
- **Compatibility with Device**
  - Mechanical Integrity
  - Material stability
  - Maintain device function

**DRUG**
- **Pharmacology**
  - Tissue kinetics
  - Toxicity profile
  - Systemic effects
- **Chemistry**
  - Purity
  - Stability
- **Compatibility with Matrix**
  - Chemical interactions
  - Solid state characterization
  - Manufacturing residuals
  - Degradation products
- **Compatibility with device**
  - Maintain device function
  - Compatible with material
Key Components of DES Combination Products That Can Impact Biocompatibility, Functionality and Manufacturing

**Finished Product Analysis (Drug related)**

- **Label claim for drug**
  - Drug content per device
- **Drug Release Profile**
  - Sustained versus short term
- **Lot uniformity**
  - Manufacturing variability of drug content from unit to unit
- **Drug degradants**
- **Drug-Carrier adduct formation**
- **Residual processing solvents**
- **Endotoxins**
  - bulk to capture process impact
  - surface to capture final product assembly impact
- **Sterility**
- **Stability (ICH)**
- **Pharmacokinetics of drug**
  - Depot formation in tissue
  - Metabolism
Manufacturing Controls for DES Combination Products Ensure Safety and Biocompatibility

<table>
<thead>
<tr>
<th>DEVICE</th>
<th>DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Quality Systems Regulations (QSR)</td>
<td>– cGMP</td>
</tr>
<tr>
<td>– 21 CFR 820</td>
<td>– 21 CFR 210</td>
</tr>
<tr>
<td>– ISO</td>
<td>– 21 CFR 211</td>
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<tr>
<td>– ASTM</td>
<td><strong>Defined Analytical Procedures and Acceptance Criteria</strong></td>
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<td></td>
<td>– International Conference on Harmonization (ICH)</td>
</tr>
<tr>
<td></td>
<td>– FDA CDER or CBER guidances</td>
</tr>
<tr>
<td></td>
<td>– Compendial guidances (U.S. Pharmacopeia)</td>
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</tbody>
</table>
Case Study:
TAXUS ™ Express²™ Paclitaxel Drug-Eluting Stents
The Problem: In-stent Restenosis
A Solution: Drug-Coated Stents

Current Design Components and Functions

- **Stent**
  - Provides a mechanical scaffold to maintain patency of vessel
- **Drug**
  - Pharmacological or biological agent targeting cellular control of restenosis
- **Polymer Carrier**
  - Provides a means to control administration of drug (site, rate and dose)
Drug: Paclitaxel (PTx)

Polymer: poly (styrene-b-isobutylene-b-styrene) (SIBS)

An ABA type triblock thermoplastic elastomer that exhibits phase separation as microdomains
Polymer Carriers

Advantages of Polymer Carriers

- Range of drug loading allows targeting a specific therapeutic response
- Precise control of drug dosage
- Uniform drug distribution on device surfaces
- Prevents loss of drug during handling and deployment
- Versatile
  - One polymer can be used for a portfolio of drugs
  - Can be applied to various device geometries
  - Manufacturing processes are compatible with pharmaceuticals

Regulatory (CMC) issues regarding polymers as excipients

- Residual monomers, catalysts, process solvents in polymer raw materials
- Residual process solvents from stent or device coating process
- Process-induced interactions with drug or device
Examples of Variable Polymer Coating Integrity

Effects of Drug Loading

- 30% Paclitaxel
- 45% Paclitaxel

Coating Process Incompatibility

- Post Sterilization PLA-PCL
- Post-Expansion EVA
Coating Integrity with Translute™ Carrier

- Smooth, Uniform Coverage
- No Cracking, Flaking or Delaminating
- Post sterilization, post expansion
Effect of Animal Model and Implant Site on Compatibility Assessment

Rat Subcutaneous Implant Model

28 day implant - H&E Staining

*Uncoated Metal Stent*

*Polyurethane-coated Stent*

In collaboration with Drs. Anderson and Ziats, CWRU
Effect of Animal Model and Implant Site on Compatibility Assessment

Porcine Coronary Artery Implant Model

28 day implant - H&E Staining

Uncoated Metal Stent

Polyurethane-coated Stent

In collaboration with Drs. Rogers and Edelman, MIT
Effect of Animal Model and Implant Site on Compatibility Assessment

Rabbit Iliac Artery Implant Model

H&E Staining

28 day PLA/PCL coated stent

56 day PLA/PCL coated stent

In collaboration with Drs. Rogers and Edelman, MIT
Vascular Compatibility of Translute™ Polymer
Normal Porcine Coronary Artery

In collaboration with Dr. Rob Schwartz Mayo Clinic
and Dr. Greg Wilson Sick Children’s-Toronto

90D Bare Metal Control
90D polymer coated

180D Bare Metal Control
180D polymer coated
Cumulative % Drug Release Can Be Modified By Solvent Properties

MR PTx: Translute Formulation
Mixed solvent system (100ug drug)

Solvent Ratios:
- 100% A
- 100% B

Percent Paclitaxel Released (% of total PTx loading) vs Time (days)
Range of In vitro release profiles
Release Media: PBS-Tween 20 @ 37°C

Paclitaxel Released (µg/108 µg total loading)

35% PTx / 65% SIBS
25% PTx / 75% SIBS
8.8% PTx / 91.2% SIBS
Vascular Effects of High Dose Paclitaxel over Time

35% Paclitaxel

28 Days
Few Vascular Effects

90 Days
EC absence, medial necrosis, Sub strut fibrin, positive remodeling

In Collaboration w/Drs. Rogers and Edelman, MIT
Wide Dose Range Achievable with Paclitaxel and Translute™ Polymer

Normal Porcine Coronary Artery Response with Increasing Total Loaded Doses with the Moderate 25%PTx Release Formulation.

- Patent lumen (similar across doses)
- Thin neointima covering all struts (similar across doses)
- Preserved media (similar across doses)
- Uniform healing across all doses (similar across doses)
TAXUS™ Express²™ Clinical Trial
Slow Release (SR) Formulation
8.8% Paclitaxel : 91.2% Translute™
$1\mu g/mm^2$
Range of In vitro release profiles
Release Media: PBS-Tween 20 @ 37°C

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>35% PTx / 65% SIBS</th>
<th>25% PTx / 75% SIBS</th>
<th>8.8% PTx / 91.2% SIBS</th>
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<tbody>
<tr>
<td>0-4</td>
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<tr>
<td>4-8</td>
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<td>8-12</td>
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<tr>
<td>12-16</td>
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</table>
Transmission Electron Microscopy
Paclitaxel-SIBS Solvent Cast Films

SIBS - 50,000X - RuO₄ stain

25% PTx / 75% SIBS
14,000X - RuO₄ stain

Paclitaxel
Atomic Force Microscopy: Paclitaxel-SIBS Coating Surface

AFM Phase Images. Paclitaxel appears as discrete white particles.

- SIBS (1µm)
- 8.8% PTx – 91.2% SIBS (5µm)
- 35% PTx – 65% SIBS (5µm)
Changes in Surface Morphology of Stent Coating Post Drug Elution

Holes, previously occupied by PTx, appear on surface after 25 hrs of \textit{in vitro} extraction in PBS / Tween 20. Topography images.
Range of In vitro release profiles
Release Media: PBS-Tween 20 @ 37°C

- 35% PTx / 65% SIBS
- 25% PTx / 75% SIBS
- 8.8% PTx / 91.2% SIBS

Paclitaxel Released (µg/108 µg total loading)
Sub-surface Morphology Changes of Coated Stents Pre and Post Drug Elution

After 2 days of elution w/PBS-Tween 20
AFM shows that the frequency and size of paclitaxel-containing domains increases with increasing paclitaxel content in the matrix.
Chemistry, Manufacturing and Controls (CMC)
Drug Evaluation

Drug Substance
- Structure, physicochemical properties, manufacturing information
- Equivalent to NDA, IND, NCE

Drug Product
- Chemical characterization
- Manufacturing process
- Controls
  - Drug content / Impurities / degradants / residuals / kinetic drug release
  - Stability
  - Toxicity threshold
  - Pharmacokinetics, Pharmacodynamics (MOA)
Product Release Testing:
Drug Content Analysis (Assay)
Typical HPLC Chromatogram for Sample

WSB-Ck (2,1)

Paclitaxel

Kathleen M. Miller, Ph.D.
Product Release Testing: Degradant Analysis
HPLC Chromatogram 13-Taxane Mixed Degradant Standard

1. 10-Deacetylbaccatin III
2. Baccatin III
3. 7-xylosyl-10-deacetyl cephalomannine
4. 7-xylosyl-10-deacetyl paclitaxel
5. Taxinine
6. 7-xylosyl-10-deacetyl paclitaxel C
7/8. 10-deacetylpaclitaxel / 7-xylosylpaclitaxel
8. 10-deacetylpaclitaxel / 7-xylosylpaclitaxel
9. Cephalomannine
10. 7-epi-10-deacetyl paclitaxel
11. Paclitaxel
12. Paclitaxel C
13. 7-epi-paclitaxel

7, 8 = co-eluting degradants
Product Release Testing: In-process SR Coating Solution

Paclitaxel: 99.83 % area

7-epi-10-deacetylpaclitaxel: 0.17 % area
Example of Acceptable Paclitaxel Degradant Profile
No individual degradant is > 1.0%, and total degradants < 2.0% (ICH guidances)
Product Release Testing: Kinetic Drug Release (KDR)

- KDR required for each lot (n=12)
- 10 Day Assay
- Manufacturing Control
- Uniform % Cumulative Paclitaxel Release from Express™ over full range of stent lengths (8mm to 32mm)
- Translute™ polymer carrier
- 1.0 ug/mm² Slow Release (SR) dose
Drug Release Profile of 8.8% Paclitaxel : 91.2% SIBS
90 Day In Vitro Release Assay, PBS-Tween 20 Medium

Evidence for pseudo steady-state, diffusion controlled release behavior, based on Higuchi’s planar slab matrix diffusion model.

\[ M = kt^{1/2} \]

\[ R^2 = 0.9904 \]
Paclitaxel Concentration in Stented Artery Tissue
Bilateral Rabbit Iliac Model

- Paclitaxel concentration over time in stented artery tissue.
- Maximum concentration ($t_{max}$) is 30 days.
- 8.8% Paclitaxel present.

Graph shows:
- Blue line for Paclitaxel ng per total stented artery tissue.
- Red line for Paclitaxel per mg stented artery tissue.
Multi-functional approach to developing the DES combination product has demonstrated:

- Translute™ carrier in combination with Paclitaxel is compatible and safe
- Formulation selected for clinical trials (SR 1μg/mm²) is safe
- The product complies with drug product manufacturing controls to support product safety
# TAXUS Clinical Trial Summaries

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>PATIENT ENROLLMENT</th>
<th>IN-STENT RESTENOSIS RATE</th>
<th>THROMBOSIS</th>
<th>TIME AT FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAXUS I (S/E) 3 sites</td>
<td>61</td>
<td>10%</td>
<td>0%</td>
<td>12 months</td>
</tr>
<tr>
<td>TAXUS II (de novo lesions)</td>
<td>536</td>
<td>19% 15.5%</td>
<td>2.3% 5.5%, 3.9%</td>
<td>12 months 24 months</td>
</tr>
<tr>
<td>TAXUS III (non-de novo, up to 2 stents)</td>
<td>29</td>
<td>N/A 4%</td>
<td>0%</td>
<td>12 months</td>
</tr>
<tr>
<td>TAXUS IV (Pivotal I Trial, S/E, de novo)</td>
<td>1,326</td>
<td>11.3% 14.7%</td>
<td>3.0% 4.2%</td>
<td>9 months (8/2003) 12 months (11/2003)</td>
</tr>
<tr>
<td>TAXUS V (Pivotal II Trial, Complex)</td>
<td>1,108</td>
<td>14.7% 4.2%</td>
<td>0%</td>
<td>30 day (9/2003) 9 month (5/2004)</td>
</tr>
<tr>
<td>TAXUS VI (MR, Complex)</td>
<td>448</td>
<td>18.9% 6.8%</td>
<td>0%</td>
<td>30 day (5/2003) 9 month (1/2004)</td>
</tr>
<tr>
<td>Total Patient Enrollment</td>
<td>3,479</td>
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Combination drug-device products offer a unique challenge to product development and manufacturing.

Successful designs and applications are based on the integration of many disciplines:

- Materials Sciences
- Engineering Fields (Mechanical, Chemical, Bioengineering)
- Pharmaceutical Sciences
- Pre-clinical and Clinical evaluation of both drugs and devices
- Pilot and Scale-up manufacturing for both drugs and devices
- Regulatory appreciation for both devices and drugs, with the ability to
  - recognize the novel
  - rely on the standard
  - blend the two seamlessly