Design Perspectives on Implantable Devices for Targeted Drug/Biologic Delivery

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The following presentation includes the personal views of the presenters and do not necessarily represent the official views of Medtronic.
Presentation Outline

• Introduction to Medtronic Neuromodulation and SynchroMed® Implantable Infusion System

• Implantable Device Design Considerations
  – Total Life Cycle Quality System
  – Biocompatibility/Biostability
  – Risk Analysis
  – Evaluating Changes

• Drug/Biologic/Device Compatibility Requirements
  – Characterizing Impact of Drug/Biologic on Device
    • Material, Component and System Testing
  – Characterizing Impact of Device on Drug/Biologic:
    • Stability Characterization
    • Leachables Characterization

• Special Considerations for CNS Delivery

• Key Takeaways
INTRODUCTION TO MEDTRONIC NEUROMODULATION AND SYNCHROMed® IMPLANTABLE INFUSION SYSTEM
Medtronic Neuromodulation–SynchroMed® Implantable Infusion System

- Programmable, refillable system for precise infusion into central nervous system (CNS) and vascular spaces.
- Device platform approved under PMA and cross-labeled with specific drugs.
- 1988 first US approval; over 200,000 implanted (US).
- New drugs/biologics and delivery targets under development in collaboration with pharma and biotech partners.
IMPLANTABLE DEVICE DESIGN CONSIDERATIONS
Implantable Device Design Considerations: Total Life Cycle Quality System

“Design in” quality per 21 CFR 820 and ISO 13485

Highlighted QS Elements

- Risk Management System
- Design Controls
- Design Verification
- Design Validation
- System Testing
- Human Factors
- Labeling
- Supply Chain Management
- Change Control
- Post-market surveillance
- CAPA

Feigal, D. CDRH Vision – Total Product Lifecycle, 2/07/02
Implantable Device Design Considerations: Biocompatibility and Biostability

**Biocompatibility**
The ability of the device to perform its intended function, with the desired degree of incorporation in the host, without eliciting any undesirable local or systemic effects in that host.¹

**Considerations for biocompatibility:**
- ISO 10993 – framework for biological evaluation and testing of medical devices within a risk management process; accepted in part by FDA [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm)
- Nature and duration of tissue contact
- Clinical experience with device materials in similar applications
- Evolving requirements for neural tissue biocompatibility

**Biostability**
Chemical and physical stability of the device materials adequate for the device to perform its intended function during implantation in a biological environment.

**Considerations for biostability**
- Clinical history of use of material in similar applications, in-vitro studies, analysis of explanted devices, and in-vivo studies as necessary.

¹ D Williams, Medical Device Technology 14(8) October 2003.
Implantable Device Design Considerations: Risk Assessment

- Assess potential risks by understanding potential effects of drug/biologic on device and potential effects of device on drug/biologic in light of physico-chemical interactions.
- Common risk management tools such as FMEA, Fault Tree Analysis and hazard analysis are used to identify and rank risks and mitigations.
- Cross functional input: e.g., Analytical Chemistry, CMC, Development, Human Factors Engineering, Medical Safety, Quality, Regulatory, Reliability, Systems Engineering, Toxicology, etc.
- Assess risks at all levels: material, component, system, and therapy.
- Testing needed is driven by the criticality of the risk and understanding the physics of potential failure modes. May require testing at material, component and system levels.
Evaluating Changes

• Evaluate changes to drug/biologic or device to determine if additional studies are needed. Examples of potential changes:
  – Formulation changes (materials, process changes, CQA, etc.)
  – Device changes (material, process change, etc.)
  – Infusion paradigm changes (concentration, flow rate, etc.)

• Assess potential risks posed by changes by understanding potential effects on device and drug/biologic in light of physico-chemical interactions.

• Testing needed is driven by the criticality of the risk and understanding the physics of potential failure modes.
Drug/Biologic Device Compatibility Requirements

Characterizing Impact of Drug/Biologic on Device Material Performance
Characterize Impact of Drug/Biologic on Device

- Identify materials in direct or indirect contact with infusion path and duration of contact.

<table>
<thead>
<tr>
<th></th>
<th>Drug/Biologic &amp; Device Material Interaction in Fluid Path</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drug &amp; Metal Reservoir</td>
</tr>
<tr>
<td>2</td>
<td>Drug &amp; Pump Bacterial Filter</td>
</tr>
<tr>
<td>3</td>
<td>Drug &amp; Pump Tube</td>
</tr>
<tr>
<td>4</td>
<td>Drug &amp; Catheter</td>
</tr>
<tr>
<td>5</td>
<td>Drug, Catheter, &amp; CSF</td>
</tr>
</tbody>
</table>

![Diagram of infuson path with numbered interactions](image-url)
Characterize Impact of Drug/Biologic on Device

Consider functionality and potential failure modes at material, component and system level. Testing needed is driven by the criticality of the risk and understanding the physics of potential failure mode.

<table>
<thead>
<tr>
<th>Level</th>
<th>Functionality</th>
<th>Potential Failure Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material (Polymer)</td>
<td>Seal</td>
<td>Formulation permeates polymer resulting in seal failure and leak</td>
</tr>
<tr>
<td>Component (Pump)</td>
<td>Accurate delivery of programmed amount of medication</td>
<td>Formulation adversely affects pump mechanism, which results in inaccurate delivery of medication</td>
</tr>
<tr>
<td>System (Infusion System)</td>
<td>Accurate delivery of programmed amount of medication</td>
<td>Interaction between formulation and a pump component results in drug precipitation, which obstructs catheter tip and prevents medication delivery</td>
</tr>
</tbody>
</table>
DRUG/BIOLOGIC DEVICE COMPATIBILITY REQUIREMENTS

CHARACTERIZING IMPACT OF DEVICE ON DRUG/BIOLOGIC STABILITY
Characterizing Impact of Device on Drug/Biologic: Potential Interactions and Effects

Potential Drug/Biologic-Device Interactions
- Physicochemical interactions with device surface/environment
- Absorption (permeation)/adsorption (particularly important for peptide/protein/RNA/DNA formulations)
- Aggregate formation
- Formulation excipients interactions with device

Potential Effects on Drug/Biologic
Changes to:
- Drug/biologic delivery concentration profile
- Impurity/degradant profile
- Leachables profile
- Bioactivity
- Toxicity/immunogenicity
Medtronic performs a dynamic simulated “in use” characterization study to evaluate real-time interaction of drug/biologic with the Implantable Drug Delivery System and potential changes to the drug/biologic attribute profiles:

- Provides complete exposure to the drug fluid path
- Provides contact time representative of in-use conditions
- Evaluates drug/biologic content/potency/bioactivity and degradation products over time (profile)

Medtronic also may study a new drug/biologic under “static” (no flow) conditions if needed to understand fundamental properties that may affect interactions, e.g., permeation studies.
Characterizing Impact of Device on Drug/Biologic: Simulated In-Use Stability Characterization Study

| Purpose | • Characterize drug/biological attributes profiles under simulated in-use conditions  
|         | • Characterize pump refill duration |
| Set up conditions and data analysis | • In-vitro temperature under simulated environmental conditions  
| | • Study length and refill cycles determined by shelf stability and therapeutic application  
| | • Drug/biologic select critical quality attributes (e.g., stability profile) are characterized and trended  
| | • Pump refill duration determined by stability profile |
| Analytical methodology | • Analytical methodology based on ICH requirement (Q2), as appropriate to drug/biologic developmental phase  
| | • Stability-indicating methods |
Drug/Biologic Device Compatibility Requirements

Characterizing Impact of Device on Drug/Biologic Leachables
Leachables-Drug\Biologic Interactions


Cross reactivity: Direct chemical interaction between drug and leachables. Secondary effects: Leachable impacts property of drug product (e.g., pH, appearance, particulate matter) which directly or indirectly affects efficacy.
Characterizing Impact of Device on Drug/Biologic: Dynamic Leachables Characterization Study

- Medtronic performs a dynamic leachables characterization study to evaluate real-time interaction of drug/biologic with the Implantable Drug Delivery System and potential changes to the leachables profile:
  - Provides complete exposure to the drug fluid path
  - Provides contact time representative of in-use conditions
  - Evaluates substances that may leach from device into drug/biologic product over time (profile)
### Characterizing Impact of Device on Drug/Biologic: Dynamic Leachables Characterization Study

| Purpose | • Characterize leachables profile  
|         | • Enable toxicological risk assessment of leachables |
| Set up conditions and data analysis | • Consult relevant guidances on leachables\(^1\)  
| | • Perform leachables study using drug/biologic product or simulant as the contact solutions, as justified in analytical method development.  
| | • Identify and quantify leachables based on the capability of instrumentation.  
| | • Report leachables profile (amount and release time course of leachables) for toxicological risk assessment |
| Analytical methodology | • Perform “controlled extraction study” to develop analytical methods and assess extractables as potential leachables. Identification of extractables is optional, only as needed to develop analytical methods for leachables.  
| | • Validate analytical methods based on ICH Q2(R1) standard, taking relevance into consideration. |

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\(^1\) See e.g., ICH Q8(R2) *Pharmaceutical Development* (Aug 2009); ICH Q9 *Quality Risk Management* (Nov 2005); FDA Guidance to Industry, *Container Closure Systems for Packaging Human Drugs and Biologics* (May 1999); PQRI Recommendation (draft), *Safety Thresholds and Best Practices for E/L in Orally Inhaled and Nasal Drug Products* (September 2006).
DRUG/BIOLOGIC DEVICE COMPATIBILITY REQUIREMENTS

SPECIAL CONSIDERATIONS FOR IMPLANTABLE DEVICE
Special Considerations for CNS Delivery

- Drug/biologic formulation must be compatible with neural tissue/CSF
  - Preservative-free & qualified excipients (neurotoxicity)
  - pH ideal ~7 due to
    - Sensitivity of CNS/meningeal innervations
    - Buffering capacity of CSF < blood
  - Osmolality (ideally isotonic)
  - Limits for quality attributes such as endotoxin and impurities are lower for CNS delivery
- Optimized formulation pH, buffer, and drug solubility/ionization for stability and minimal interfacial interactions
- Formulation as well as infusion parameters can affect drug/biologic distribution within CNS
Key Takeaways

- Implantable device design need to consider risks relating to total product life cycle, including those relating to:
  - Effect of device on body (biocompatibility)
  - Effect of body on device (biostability and biomechanical loads)
  - Effect of device on drug/biologic (in-use stability and leachables)
  - Changes to device or drug/biologic, or clinical infusion paradigm

- No “standard” testing methods exist
  - Requires “custom” test system development (e.g., equipment, methods, data analysis)

- Leverage clinical/field experience
Combining All Elements For Therapy Success

Drug/Biologic

Therapy Success

Device

Delivery Principles

\[ \frac{\partial c}{\partial t} + \nabla \cdot (cv - D \nabla c) = R_c \]
Partnering for Innovation – New Partnerships

Welcome

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