Innovative Drug-Device Combination Product Development for Rare Diseases
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Orphan Disease Landscape

- ~ 7,000 orphan diseases
- Individually rare but collectively affect 1 in 10
- 25 million Americans, 25-30 million EU
- 50% Paediatric
- 85% Serious or life-threatening
- > 50% lysosomal storage diseases (LSDs) with significant or severe CNS involvement

Disease Prevalence

1 Meikle et al., JAMA 1999
Biologics Drug Development for Rare Diseases

- **Unmet Medical Need**
  - Rare diseases require chronic treatments
  - Treatments are intended for global markets
  - Fast-to-approval development model for ERT/PRTs vs. fast to clinic/fast-to-proof-of-concept model in Phase II clinical studies:
    - Development timeline is often accelerated
    - Front loading of development work to ensure “right first time” results

**Rare Disease Investigational Programs @ Shire:**
- Dystrophic Epidermolysis Bullosa
- Duchene's Muscular Dystrophy
- Retinopathy of Prematurity
- Hunter Syndrome
- Sanfilippo A
- Metachromatic Leukodystrophy
- Hereditary Angioedema
- Gaucher Disease
Expedited Development and Approval of Therapies for Rare Diseases – Regulatory Expectations

- The decision to expedite a development program is exclusively a clinical decision, based on seriousness of the disease, unmet medical need and therapy availability.
- All aspects of a program should be developed at a more rapid pace, including the CMC.
- Balancing speed to clinic with speed to developing capable and robust commercial process and methods.
- Assurance of uninterrupted, high quality product supply to the patients.

Adapted from Emanuela Lacana, CDER, FDA, CMC Strategy Forum – Jan2014
Begin with Critical Quality Attributes

- Enzyme activity
  - Sulfatases require conversion of an active site cysteine to formylglycine (FG) for activity; FG Content
- Enzyme must get to target organ, cell, or organelle
  - Mannose-6-phosphate (M6P) content
- Product must stay in circulation long enough
  - Sialic acid content
- Product must be stable
  - Significance of sequence liabilities; sites prone to deamidation, oxidation, fragmentation, C-terminal clipping, etc.
Expedited Development and Approval of Therapies for Rare Diseases – Regulatory Expectations for the Product and the Manufacturing Process

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Drug Substance</th>
<th>Drug Product</th>
</tr>
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<tbody>
<tr>
<td>Characterization</td>
<td>●</td>
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<tr>
<td>CQAs</td>
<td>●</td>
<td>●</td>
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<tr>
<td>Process control strategies/plans</td>
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<td>●</td>
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<tr>
<td>Dosage form</td>
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<td>●</td>
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<tr>
<td>Admin instructions, final packaging and delivery systems</td>
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<td>●</td>
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<tr>
<td>Proposed shelf life and stability studies</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

- Development plan: Formulation changes, manufacturing changes, scale-up and comparison to clinical process
- Physico-chemical comparability of lots used in clinical studies and commercial lots or a plan to establish analytical comparability, bridging information / plan
- Manufacturing and testing sites information and readiness
- Process and Analytical Method Validation timelines and activities
Intrathecal Drug Delivery Device (IDDD)

- To circumvent the Blood Brain Barrier, recombinant enzymes are administered into the subarachnoid space, via a transcutaneously accessible indwelling intrathecal drug delivery device (IDDD)

- SOPH-A-PORT® Mini S is an implantable access system designed to provide repeated access to the intrathecal space for drug delivery

- It is CE marked in Europe and approved for investigational use in the US

- It is currently being used in Shire’s Hunter-IT, Sanfilippo A and MLD clinical development programs
Hunter Syndrome (Mucopolysaccharidosis II)

Disease Overview

- Extremely rare X-linked lysosomal storage disease
- Incidence ~ 1 in 170,000 male births
- Absence or deficient activity of the lysosomal enzyme iduronate-2-sulfatase (I2S)
- Diagnosis typically at 2-6 years, prompted by typical appearance (coarse facial features), organomegaly or developmental delays
- Multiple physical issues caused by deposits of glycosaminoglycans in the soft tissues of upper respiratory tract, joints, heart, liver and spleen
- 2/3 of patients experience progressive developmental delay and cognitive decline, usually leading to death in the teenage years
- Idursulfase (ELAPRASE) is an intravenous enzyme replacement therapy which addresses some of the somatic issues but does not address the cognitive issues

Muenzer et al., Pediatrics 2009; Martin et al., 2008

A series of photographs showing the progression of the characteristic facial features of Hunter syndrome.
The ages of the boy from left to right are 6 months and 5, 9 and 30 years.
I2S-IT Product Development

- I2S-IT is based on a legacy process that requires a different formulation and delivery method.

- New clinical trials and new filing offer the opportunity for retrospective Quality by Design studies:
  - Follow the typical QbD workflow for a late phase product
  - Leverage existing knowledge and data (including knowledge from other sulfatases like rhASA and Heparan-N-Sulfatase)
  - Identify and remediate gaps in understanding and control
  - Update analytical methods

- Challenge: aggregating and analyzing data, reports, and filings generated over >10 years is time and labor intensive
SANFILIPPO A (MPSIIIA) Disease Overview

- Autosomal recessive lysosomal storage disease: mutations in \(SGSH\), encoding heparan N sulfatase (HNS)
- Live birth incidence ~ 1 in 100,000
- Enzyme defect causes accumulation of heparan sulfate
- Clinical features are overwhelmingly neurological
  - Normal early infancy
  - Developmental delays often first manifestations
  - Severe behavioral disturbances are a prominent feature of middle childhood
  - Progressive dementia leads to a “quiet phase” of withdrawal and developmental regression
  - Survival to late teens / early 20s
- Primary accumulation of the glycosaminoglycan (GAG) heparan sulfate triggers poorly understood pathological cascade with primarily CNS manifestations
Understanding the Product: New Insight (Crystal structure of HNS solved in 2014!)

- 56 kDa glycoprotein comprised of 482 AA (not including a 20 AA leader sequence)
- 5 N-linked glycosylation sites
- 5 cysteines; Cys-70 conversion to Formylglycine (FG) required for activity
- M6P required for uptake and transport to lysosomes
- Dimeric native association state required for activity: domain 2 and C-terminus integrity important

Sidhu et. al. (2014), Acta Cryst. D70, 1321-1335

Metachromatic Leukodystrophy
Disease Overview

Manifestations of MLD

- MLD results from deficiency of the lysosomal enzyme arylsulfatase-A
- Arylsulfatase-A breaks down sulfatides and accumulation causes nerve demyelination

Disease Summary

- An inherited leukodystrophy
- Inheritance is autosomal recessive
- Birth incidence 1 in 100,000
- Three different phenotypic presentations classified by age of onset: late-infantile, juvenile, and adult
- Motor weakness and cognitive loss the most prominent symptoms
- Uniformly fatal; earlier onset correlates with more rapid decline
- Management focused on palliative care
- No treatments currently available
- Significant negative impact on patients & caregiver quality of life
- High economic costs

Distribution & PK of $^{124}$I-labeled rhASA

$^{124}$I-labeled rhASA
IT-L dose = 6 mg
1 hr post-dose

*In vivo* Distribution & PK of $^{124}$I-labeled rhASA (6 mg) at t = 1hr Post-dose in Cynomolgus Monkeys by PET / CT Imaging
What is a Medical Device?

- Medical Device (1)

  - Instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings…

(1) BSI EN ISO 14971: 2009 Medical devices – Application of risk management to medical devices
What is a Combination Product?

- The combination of a device, drug and/or biological product:
  - Drug – Device
  - Drug – Biologic
  - Device – Biologic
  - Drug – Device - Biologic

- **Not** a drug-drug, device-device or biologic-biologic

21 CFR Part 4 – Final Rule Published January 22, 2013:
Combination Product Categories

- Physically Combined ("single entity")
  - A product comprised of two or more regulated components that are physically, chemically or otherwise combined or mixed as a single entity – 21 CFR 3.2(e)(1)

- Co-Packaged (or Kit)
  - Two or more separate products packaged together (e.g., co-package of a drug and a device) – 21 CFR 3.2(e)(2)

- Cross Labeled
  - Products provided/packaged separately but intended for use together where both are required to achieve the intended use, and where mutually conforming labeling is needed -- 21 CFR 3.2(e)(3) [and (e)(4) for investigational cross labeled products]
Medical Device Development Process

**Design Concept**
- User needs
- Create project teams
- Development plan
- Human factors plan; marketing assessments
- Quality plan
- Risk management plan

**Design Input**
- Design Input Requirements
- Development planning
- Create project teams
- Human factors
- Marketing Assessments
- Container Closure System

**Design Output**
- 2D Drawings
- Non-functioning prototypes
- BOM
- Functioning prototypes
- Human factors plan; heuristic evaluation
- FMEAs

**Design Reviews**

**Design Verification**
- ISO Testing (e.g., dose accuracy, free fall, functionality, biocompatibility)
- ASTM, ISTA-2A
- Aging equivalency / Expiry

**Design Transfer**
- Design Freeze (Commercial)
- Process scale-up; robustness
- Equipment FAT/SAT / Commissioning
- Process Validation

**Design Validation**
- Simulation use studies (e.g., summative usability)
- Clinical evaluation
Medical Device Documentation Practices

- Design Planning
- Design Input
- Design Output
- Design Review
- Design Verification
- Design Validation
- Design Transfer
- Design Changes
- Risk Management

- BOM / Specs
- Processes
- Procedures
- Test Plans

- Batch Record
- Part List
- IPC Data
- Release Data
Medical Device Life Span – Phased Approach

Participant – Stakeholder Relationship

Manufacturer → Vendor → User

Design Concept & Development

Packaging & Labelling

Advertising

Sale

Use

Disposal

Pre-Market

Placing On-Market

Post Market Surveillance / Vigilance

Government Regulations

Manufacturer

Vendor

User

Items or activities regulated

STAGE

CONTROL/MONITOR

PRE-MARKET

PRODUCT

PLACING ON-MARKET

SALE

POST-MARKET

AFTER-SALE/USE

PERSON

MANUFACTURER

VENDOR

VENDOR/USER

Device attributes

• Safety and performance

Establishment registration

• List products available or in use

Surveillance/vigilance

• After-sale obligations

Manufacturing

• Quality systems (see 3.4.4)

Requires vendor to fulfil after-sale obligations

Monitoring of device’s clinical performance

Labelling (representation)

• Accurate description of product

Advertising (representation)

• Prohibits misleading or fraudulent advertisement

• Instructions for use

Problem identification and alerts

Reference: Medical Device Regulations Global Overview and Guiding Principles WHO ©2003
Intrathecal Drug Delivery Device (IDDD)

- **IDDD**
  - Goal is delivery of the drug directly to the CNS (cross the BBB)
  - Performed via lumber puncture into the subarachnoid space of the spinal cord
  - Evolved historically via spinal anesthesia
  - Well established for anesthesia and pain management

- **SOPH-A-PORT Product Line**
  - Manufactured by Sophysa (Orsay, France)
  - CE marked in the European Union (EU) since 1998, and authorized for marketing in Japan since August 2000, and in China since March 1999
  - SOPH-A-PORT Mini S modifications: modification were made to the device more optimal for intrathecal use for target population. CE marked in EU (May 2013) and allowed for investigational use in the US
Overview of Device Partner – Sophysa S.A.

- Headquarters; Orsay, France
- Founded in 1976
- Core competency – neurosurgery specialist, manufacturer, and marketer
- Customer base – HCP and Patients
- Product line - neurosurgical implants and accessories which include:
  - Valves, Catheters, Reservoirs
  - Intracranial Pressure Monitoring System
  - External drainage systems
  - Subcutaneous spinal access ports
- Largest European shunt manufacturer for hydrocephalus treatment
- Three strategic business units
  - Neurosurgery
  - Intensive Care Unit
  - Chemotherapy
History of Sophysa S.A.

Tokibo Co., Ltd.

Established (1976)

Purchased by tkb Group (1998)

Marketed Sophy Valve (1984)

Marketed Polaris Valve (2004)

FDA Inspected (510K) (2006)


Shire Collaboration (2012)

Marketed Pressio (2005)
Sophysa is a Manufacturer of Neurological Shunts
ICP Monitoring, External CSF Drainage

• designed to bypass or redirect cerebrospinal fluids from one location in the body to a different location

• micro-sensor-tipped catheters
• implanted in ventricle or parenchyma

• allow aseptic shunting of CSF from the ventricular cavities or lumbar subarachnoid spaces

Access Port (Standard) ➔

Access Port (Mini) ➔

• arterial access
• venous access
• peritoneal access
• spinal access

Mini S (used for Shire Product) – both ports manufactured in Besançon, France
# Assessment of Clinically Relevant Forces

<table>
<thead>
<tr>
<th>Force</th>
<th>Possible Failure Modes</th>
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</thead>
<tbody>
<tr>
<td><strong>Body Movement</strong></td>
<td>Port Body/Septum Damage; Catheter Damage; Port-Catheter Disconnection; Catheter Kinking/Blockage; Catheter Migration; Port Pin Breakage</td>
</tr>
<tr>
<td><strong>External Trauma</strong></td>
<td>Port Body/Septum Damage; Septum Failure; Catheter Damage; Port-Catheter Disconnection; Port Pin Breakage</td>
</tr>
<tr>
<td><strong>Device Palpation</strong></td>
<td>Port Body/Septum Damage; Septum Failure; Catheter Damage; Port-Catheter Disconnection; Port Pin Breakage</td>
</tr>
<tr>
<td><strong>CSF Pressure</strong></td>
<td>Catheter Damage; Catheter Migration</td>
</tr>
<tr>
<td><strong>Injection Forces</strong></td>
<td>Port Body/Septum Damage; Septum Failure; Catheter Damage; Port-Catheter Disconnection; Port Pin Breakage</td>
</tr>
</tbody>
</table>
1. The polysulfone implantable port
   a. Integrated suture holes and an engraved serial number in the base with self-sealing silicone septum
   b. A titanium mobile pin connector
   c. A patented self-locking screw-lock system

2. Intrathecal port closed-tip catheter made of radiopaque silicone (with markers on distal end)

3. PTFE-coated guidewire (packaged in cannula)

4. Two suture wings

5. Tuohy needle

6. Huber needle

7. Metal Luer lock connector
IDDD Implantation and Drug Product Administration

**Implantation**

- Slack
- Non-absorbable sutures (x3)
- Sheath
- Catheter
- Wings

**Administration**

- 90°
- Pierce septum (90° angle)
- Non-corning needle
Assessment of Clinically Relevant Forces – Mechanical Verification

Port Pin – Resistance to Fatigue

Catheter Retention

Bench-top models and test plans are developed to perform mechanical verification
### In-use Studies on Intrathecal Drug Delivery Device

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Parameters Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single injection at different concentration of <strong>Phase I/II</strong> drug product.</td>
<td>A280, pH, SDS-PAGE, SEC, specific activity, appearance, SbVPs, and protein recovery</td>
</tr>
<tr>
<td>Repeat injection at different concentration of <strong>Phase I/II</strong> drug product.</td>
<td>Protein recovery, SEC, activity (by IEX).</td>
</tr>
<tr>
<td>Single injection at different concentration of <strong>Phase II/III</strong> drug product</td>
<td>A280, pH, SDS-PAGE, SEC, specific activity, appearance, SbVPs, and protein recovery</td>
</tr>
<tr>
<td>Single injection, at different doses (concentration kept constant) with <strong>Phase II/III</strong> drug product</td>
<td>Protein recovery, SbVPs</td>
</tr>
</tbody>
</table>

1 SbVP: sub-visible particles
### IDDD Biocompatibility Studies

#### Biocompatibility Studies on Intrathecal Drug Delivery Device

<table>
<thead>
<tr>
<th>Biocompatibility Study</th>
<th>Study Type</th>
<th>ISO Standard</th>
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</thead>
<tbody>
<tr>
<td>Cytotoxicity</td>
<td>In vitro cytotoxicity</td>
<td>ISO 10993-5</td>
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<tr>
<td>Sensitization</td>
<td>Guinea pig maximization test</td>
<td>ISO 10993-10</td>
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<tr>
<td>Irritation/intracutaneous reactivity</td>
<td>Intracutaneous reactivity test in rabbits</td>
<td>ISO 10993-10</td>
</tr>
<tr>
<td>Acute toxicity including pyrogen test</td>
<td>Acute systemic toxicity study in mice and Rabbit pyrogen test</td>
<td>ISO 10993-11</td>
</tr>
<tr>
<td>Genotoxicity</td>
<td>Bacterial reverse mutation study, Mouse lymphoma assay, In vitro mouse PBM assay</td>
<td>ISO 10993-3</td>
</tr>
<tr>
<td>Haemolysis / Haemocompatibility</td>
<td>In vitro ASTM hemolysis test</td>
<td>ISO 10993-4</td>
</tr>
<tr>
<td>Toxicity Studies</td>
<td>Sub-chronic and chronic toxicity studies</td>
<td>ISO 10993-11</td>
</tr>
<tr>
<td>Implantation Studies</td>
<td>Studies of different duration and different implantation sites</td>
<td>ISO 10993-6</td>
</tr>
<tr>
<td>Supplemental Device Testing</td>
<td>Device/Drug Compatibility (Combination Device) Testing</td>
<td>Device Packaging Design</td>
</tr>
<tr>
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<tr>
<td>Mechanical Biocompatibility (ISO 10993)</td>
<td>In-Use Compatibility</td>
<td>Kit Tray</td>
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<tr>
<td>Design Validation (HF)</td>
<td>Leachable</td>
<td>Kit Carton</td>
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<td></td>
<td>Extractable</td>
<td>Catheter Passer</td>
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<tr>
<td>Other focus area:</td>
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<tr>
<td>• Device risk reduction activities</td>
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<tr>
<td>• Alternative drug delivery devices/systems</td>
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Future Organizational Structure Considerations

Global Medical Device/Combination Product Development “View”
Medical Device Technical Teams

Sustaining Engineering
(commercial focus)

New Product Development
(design control focus)
Product Development Technical Focus Areas

- Design Control
- User Needs identification/design Inputs
- Project Leadership & Cross Functional Deliverable
- Global Regulatory Requirements
- Specifications and CAD Drawing Development
- Materials - Polymer & processing
- Test Development
- Biocompatibility (ISO 10993)
- CRO and CMO Relationship Management
- Device
- Leachable and Extractable
- Drug/Device Compatibility
- Device and Packaging Stability
- Device Clinician Expertise and Interface
- Device Standards (ISO, AMMI, HF etc..)
- Device Competitive Analysis
Focus, Innovation, and Collaboration are Key

• **Place the patient and the product in the center and identify:**
  • **New solutions to old problems:**
    • No payoff without delivery – device allows delivery of the drug products to the site of action
    • Combination product device testing: device- drug product compatibility
    • Supplemental device testing: biocompatibility, mechanical, human factor
  • **Ways to connect the dots and leverage knowledge from:**
    • Treat the device collaborator as an integral part of the team
    • The entire company from Research to Manufacturing (collaboration between disciplines and businesses!)
    • All product development disciplines and functions
    • Other Products
    • Knowledge management

• **Advanced process and product development capabilities are key Enablers:**
  • End-to-end product development and lifecycle management for the benefit of the patient and to achieve the full potential of the combination products