WEBINAR – June 25, 2009

Shoot for Share!
From Vial to Pre-filled Syringe

SPEAKER: Raul Soikes
Senior Director, Program Management
Baxter BioPharma Solutions
Today we will address:

**Why?** Value proposition of moving to a pre-filled syringe

**What?** Regulatory plan to enable move

**How?** Process to move from vial (liquid or lyophilized) to syringe

**Who?** CMO qualifications
WHY?

VALUE PROPOSITION
Why?

Market driven
Line extension – Life cycle management
  • New presentation
  • New administration route
Latest Technology / Market edge
  • Competition
  • Pharmacoeconomics

Customer driven
Safety- fewer manipulations
Accuracy- Dose delivered
Quality of life- self administered

Product driven
Manufacturing
  Less API waste → increased units filled → increased revenue
Why? - Strategies to Improve the Value of a Biologic Molecule

Due to the inherent challenges of biologics, enhancements are difficult yet the market rewards improvements.

<table>
<thead>
<tr>
<th>Short-Term Strategy (6-18 Months)</th>
<th>Mid-Term Strategy (18-36 Months)</th>
<th>Long-Term Strategy (&gt;36 Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attach a safety device to a pre-filled syringe</td>
<td>Move from a vial or syringe into an autoinjector or cartridge</td>
<td>Develop sustained release formulation</td>
</tr>
<tr>
<td>Kit vials with a ready to use diluent syringe</td>
<td>Reformulate lyophilized vials into a liquid vial or pre-filled syringe</td>
<td>Develop alternate route formulation</td>
</tr>
<tr>
<td>Move from a stable liquid vial to a pre-filled syringe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Short and Mid-Term strategies can help to differentiate a biologic molecule.
Teva Pharmaceutical Industries Ltd changes the presentation of Copaxone® from a dry vial preparation to a pre-filled syringe.

Copaxone PFS achieved rapid uptake in the US, with 64% of patients switching within the first three months from the dry vial formulation to the new formulation, and the remainder had switched within six months of launch.

Dry vial to Syringe – rapid uptake 64% switched in 3 months, remainder in 6 months after launch

Source: IMS Health
The Copaxone® reformulation was priced at a premium as compared to the original formulation. In 2002 the premium started at 5%, however, by 2005 the price premium was 48.6%.

For patients, the switch reduced average preparation time from 235 seconds (reconstituted Copaxone) to 38 seconds, saving more than 20 hours over the course of a year.

Premium pricing - from 5% in 2002 to 49% by 2005.
Preparation time reduced from 4 minutes to 38 seconds.
Amgen, Inc. changed the presentation of Enbrel from a dry vial preparation to a pre-filled syringe. To further differentiate and add value, in 2006 Enbrel launched in an auto injector.

Overall Enbrel unit sales have remained stable, however revenue has increased due to the price premium the PFS and SureClick™ format.

Revenue increased due to price premium; unit sales stable
Doctors’ top factors: minimal side effects, patients ease of use, satisfaction, convenience, comfort. Three of five factors (underlined) impacted by product presentation.

Question:
In order of importance, please select the top 5 factors that you consider when selecting a drug delivery type? (1= most important, 2=2nd most important, 3=3rd most important, etc.)
Ease of self administering is the top reason for selecting a device type.

### Top 5 Factors Influencing Prescription Decision

<table>
<thead>
<tr>
<th>Factor</th>
<th>Rank 1</th>
<th>Rank 2</th>
<th>Rank 3</th>
<th>Rank 4</th>
<th>Rank 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy to self administer</td>
<td>46%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost to patient</td>
<td>16%</td>
<td>20%</td>
<td>16%</td>
<td>20%</td>
<td>16%</td>
</tr>
<tr>
<td>Formulary Tiering of Product</td>
<td>10%</td>
<td>13%</td>
<td>17%</td>
<td>20%</td>
<td>16%</td>
</tr>
<tr>
<td>Complexity of device</td>
<td>14%</td>
<td>17%</td>
<td>11%</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Does not require power source</td>
<td>8%</td>
<td>5%</td>
<td>4%</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Published Clinical Data</td>
<td>9%</td>
<td>9%</td>
<td>11%</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Has Reusable Component</td>
<td>7%</td>
<td>6%</td>
<td>6%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Requested by patient</td>
<td>13%</td>
<td>10%</td>
<td>10%</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Specific adverse side effects to device</td>
<td>12%</td>
<td>14%</td>
<td>10%</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Size of device</td>
<td>6%</td>
<td>9%</td>
<td>7%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Appealing appearance of device</td>
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**Question:**
For Device Driven Drug Delivery (Examples: Inhaler, Autoinjector), please select the top 5 factors that most influence your decision to prescribe the product to your patients?

**US Drug Delivery - Frost & Sullivan 2008**

Question:
For Device Driven Drug Delivery what are the top 5 factors that you consider? (1=most important, 2=2nd most important, 3=3rd most important, etc.)
Why? Device Drug Delivery Method – Patient

Ease of self administering is the most important factor for selecting drug delivery type followed by convenience.

Question:
In order of importance, please select the top 5 factors that you consider when selecting a drug delivery type? (1= most important, 2=2nd most important, 3=3rd most important, etc.)

US Drug Delivery - Frost & Sullivan 2008
WHAT?

REGULATORY STRATEGY
### Define Regulatory Strategy

<p>| | | |</p>
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**Regulatory considerations – Major change to regulatory market approval . . . Manageable**
What?

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<td>Evaluate &amp; compare the proposed syringe system to approved materials</td>
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<tr>
<td>✓ Protects the drug product?</td>
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<tr>
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Regulatory considerations – Major change to regulatory market approval . . . Manageable
## Define Regulatory Strategy

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<th>Need supporting clinical data?</th>
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<td>✓ Safety or efficacy effect?</td>
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<td>✓ New indication?</td>
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<tr>
<td>✓ New route of administration?</td>
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**Regulatory considerations – Major change to regulatory market approval . . . Manageable**
### Define Regulatory Strategy

<table>
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<th>Evaluate &amp; compare the proposed syringe system to approved materials</th>
<th>Need supporting clinical data?</th>
<th>Perform Stability protocol - New Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Protects the drug product?</td>
<td>✓ Safety or efficacy effect?</td>
<td>✓ Define stability requirements</td>
</tr>
<tr>
<td>✓ Introduce a new material?</td>
<td>✓ New indication?</td>
<td>✓ Execute stability protocol</td>
</tr>
<tr>
<td>✓ Need drug product formulation changes?</td>
<td>✓ New route of administration?</td>
<td>✓ Analyze stability data</td>
</tr>
</tbody>
</table>

**Regulatory considerations – Major change to regulatory market approval . . . Manageable**
HOW?

VIAL TO SYRINGE
REGULATORY STRATEGY

Formulation Study  Stability Study  Clinical Study  Filing
How?

REGULATORY STRATEGY

Formulation Study → Stability Study → Clinical Study → Filing

- Liquid
- Lyophilized
How?

REGULATORY STRATEGY

Formulation Study
- Liquid
- Lyophilized

Stability Study
- Container/Closure
- Extractables/Leachables
- Accelerated
- Long Term

Clinical Study

Filing
How?

REGULATORY STRATEGY

Formulation Study
- Liquid
- Lyophilized

Stability Study
- Container/Closure
- Extractables/Leachables
- Accelerated
- Long Term

Clinical Study
- Indication
- Administration route
- Degradation profile
- Impurity profile

Filing
How?

REGULATORY STRATEGY

Formulation Study
- Liquid
- Lyophilized

Stability Study
- Container/Closure
- Extractables/Leachables
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- Long Term

Clinical Study
- Indication
- Administration route
- Degradation profile
- Impurity profile

Filing
- Formulation
- Container/Closure
- Storage Conditions
- Clinical Data
### How?

**Pre-filled syringe filing details:**

<table>
<thead>
<tr>
<th>Attribute*</th>
<th>Move From Liquid Vial</th>
<th>Move From Lyo Vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Container/Closure</td>
<td>Similar? Leverage previous extractable/leachable studies. Functionality: siliconization may be needed.</td>
<td></td>
</tr>
<tr>
<td>Formulation</td>
<td>No change.</td>
<td>Change from freeze-dried powder to liquid.</td>
</tr>
</tbody>
</table>
| Storage Conditions | No change.  
    **Stability Study:** 3 months comparative accelerated and long term of at least 1 batch (3 may be required).  
    **Clinical Study:** If degradation profile or impurities profile change. | May change  
    **Stability Study:** 3 months comparative accelerated and long term data on 3 batches.  
    **Clinical Study:** If degradation profile or impurities profile change. |

* Indication and Administration Route changes need clinical data
WHO?

CMO REQUIREMENTS
Who?

Corporate Culture

CMO of Choice

Service
Who? Choosing your CMO . . .

- Experience
- Capacity
- Qualification
- Capability

CMO of Choice
Experience

**Regulatory**
- Global and local compliance
- Audit history
- Regulatory review and approval process

**Technical**
- Product Scope
- Seasonal Campaign
- Market/Industry Presence

**Product Type**
- Small Molecules
- Biologicals
Capability

Resources
✓ Part of global company
✓ Redundancy
✓ Multidisciplinary

Physical
✓ Facility
✓ Aseptic Formulation
✓ Cold Chain Management

Personnel
✓ Education
✓ Training
✓ Experience
Qualification

Good Manufacturing Practices
✓ Compliance
✓ Documentation
✓ Training
✓ Audit

Company Policies
✓ Business
✓ Quality
✓ Regulatory
✓ Manufacturing

Registration
✓ National entities
✓ Regulatory Agencies
Capacity

Equipment
- Preparation
- Formulation
- Fill, Lyophilization, & Cap
- Packaging

Laboratory
- Environmental monitor
- Product specific test
- Compendial testing

“Foot Print”
- Multiple lines
- Aseptic areas
- Waste treatment
- Supporting equipment and processes
Vial to Pre-filled Syringe:

Why? Value Proposition
- Market – differentiation, premium pricing
- Customer – safety, accurate dosing, self-administration
- Product – less API waste → more units filled

What? Regulatory Strategy
- Evaluate and compare syringe system to current presentation
- Need supporting clinical data?
- Perform stability study
Vial to Pre-filled Syringe:

How?  Vial to Syringe
  • Container/Closure - extractables/leachables
  • Formulation – liquid to liquid? Lyo to liquid?
  • Storage Conditions – stability study, degradation profile
  • Filing – clinical study? Stability supporting data

Who?  CMO requirements
  • Experience
  • Capability
  • Qualification
  • Capacity
References


2 Financial Model For Converting From a Vial To a Pre-filled Syringe. Michael Borlet, Director of Marketing, Baxter Pharmaceutical Solutions LLC. Presented at the PDA “The Universe of Pre-filled Syringes and Injection Devices”, San Diego, CA, October 6-7, 2008.

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Enbrel is a trademark of Immunex Corporation
PFS is a trademark of Pharmacia & Upjohn Company
SureClick is a trademark of Amgen Inc.
Shoot for Share: From Vial to Pre-Filled Syringe

• Thank you for participating in this complimentary webinar.
• If you have further questions or would like to contact me:
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  Baxter BioPharma Solutions
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  E-mail: raul_soikes@baxter.com

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