Global Market Trends of Device Strategies for Patient Centric Therapeutics

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Device Strategy for Meeting Design Control Requirements
FDA audits and inspections can be scheduled or unscheduled. The focus of area include the chart illustrated plus document controls.
FDA – 483 Warning Letter – 2003-2013

Ref: 2013 Annual FDA Medical Device Quality System Data – 483 Observations and Warning Letter Citations, p.18., UCM416501
<table>
<thead>
<tr>
<th>QS Subsystem</th>
<th># of Observations</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>P&amp;PC</td>
<td>1,151</td>
<td>33%</td>
</tr>
<tr>
<td>CAPA</td>
<td>1,085</td>
<td>31%</td>
</tr>
<tr>
<td>MGMT</td>
<td>425</td>
<td>12%</td>
</tr>
<tr>
<td>DES</td>
<td>506</td>
<td>14%</td>
</tr>
<tr>
<td>DOC</td>
<td>367</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>3,534</strong></td>
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FDA Design control process enhances a new device’s functional performance. An innovative injector for home use not only encourages patients to take control of their disease state but also improves their treatment adherence and therapy outcome.

All injection devices follow Design Control Process. They look alike but may have different therapeutic indications and different patient populations. Therefore, Human Factor studies will be needed.

Ref: PharmaCircle, “Injection Devices - Reusable Injection Pens and Disposable Pens”, p.12, Updated on 19-Feb-2015
Design Planning
Collaborate with multiple functional groups to interact with regulatory affairs, marketing, clinical research, API and drug substance production are essential.

User Needs
Document User Needs through market research, focus group, and voice of patients.

Design Input
Conceptual input is important source of inputs but they do not equal to design input requirements. Design Input should be measurable properties.

Design Output
Design output can be diagram, drawing, specification, and procedures. Design output shall define the target value and acceptable tolerance range and limits.

Ref: Link closely to 820.50 and 820.130, “FDA Inspection Guides for Design Controls”, UCM 170251, http://www.fda.gov
Risk Assessment
Risk analysis should be addressed in the design plan. Risks should be considered throughout the design process and continued through the life cycle of the product.

Design Verification
Design verification activities include test, inspections, analyses, measurements, and demonstrations.

Design Validation
Design validation should demonstrate through objective evidences that the approved design met the predetermined user needs and intended uses by using initial production devices or the equivalents.

Design Review
Cross-functional group conducts Design Review throughout the key stages of product development.

Ref: Link closely to 820.100 and 820.120, “FDA Inspection Guides for Design Controls”, UCM 170251, http://www.fda.gov
**Design Transfer**

Design transfer should demonstrate that the approved design output was correctly translated into production specifications. These production specifications are documented in Device Master Record.

**Design Change**

Design change may include both the enhancement of the device and the improvement resulting from customer complaints. Post-production changes related to device design change must be assessed.

**Design History File**

Design history file contains document index of design control process. Design history file maintenance may include periodic review and update.

Ref: Link closely to 820.80 and 820.120, “FDA Inspection Guides for Design Controls”, UCM 170251, [http://www.fda.gov](http://www.fda.gov)
# Types of Injectable Devices

Cost to correct any design errors is lower during early design phase.

<table>
<thead>
<tr>
<th>Devices</th>
<th>Dosing</th>
<th>Frequency</th>
<th>Device Life</th>
<th>Device Type</th>
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</thead>
<tbody>
<tr>
<td>TwinJects</td>
<td>Variable</td>
<td>Single Use</td>
<td>Disposable</td>
<td>Autoinjector</td>
</tr>
<tr>
<td>Symlin Pen</td>
<td>Variable</td>
<td>Multiple Use</td>
<td>Disposable</td>
<td>Pen</td>
</tr>
<tr>
<td>Enbrel</td>
<td>Fixed Dose</td>
<td>Single Use</td>
<td>Disposable</td>
<td>Autoinjector</td>
</tr>
<tr>
<td>Forteo Pen</td>
<td>Fixed Dose</td>
<td>Multiple Use</td>
<td>Disposable</td>
<td>Pen</td>
</tr>
<tr>
<td>SimpleJet</td>
<td>Fixed Dose</td>
<td>Multiple Use</td>
<td>Reusable</td>
<td>Autoinjector</td>
</tr>
<tr>
<td>Flex Pen</td>
<td>Variable</td>
<td>Multiple Use</td>
<td>Reusable</td>
<td>Pen</td>
</tr>
</tbody>
</table>

Regulatory Landscape for Combination Products

- **Japan** – PMDA uses new regulation for medical devices and combination products. Device Master Record and Design History File are constantly requested for authority review during new drug applications.

- **China** – SFDA catches up with US and EU regulatory requirements for medical devices and combination products. Functional tests are reviewed in details. Its dedicated lab conducted the testing to verify the claims.

- **US** – FDA has requested that human factor study to be conducted with the patient populations in the countries planned for product launch. For example, if a new products is submitted for US approval, the human factor studies should include the patient population study in US.

- **Brazil** – ANVISA has requested device test methods for functional performance evaluation on medical device and combination product.

- **EU** – EMEA regulatory submission requires a formal process validation conducted on three batches of full production scale of new products.

Design Control Process for Devices

• Design Control Process Is Critical.
• Cross Collaboration Is Important.
• Risk Assessment Is Crucial.
Device Strategy for Achieving Patient Centric Therapeutics
Sanofi Lyxumia is marketed in EU and Japan currently.

Intarcia takes a different approach using Exenatide in an implant for 12-month sustained release.

GSK Tanzeum is weekly dosing GLP-1 launched in US in Apr-2014. It required mixing and has gentler side effect.

Lilly Trulicity is weekly dosing GLP-1 using prefilled syringe based autoinjector. It launches in 4Q2014. KOLs consider that Trulicity is a strong competitor to Victoza to penetrate market.

Novo Nordisk’s Victoza is daily GLP-1. In its pipeline, a weekly dosing ‘Semaglutide’ and an oral GLP-1 drug are in development. Clinical trials are in progress.
Global Revenue Growth of Top 10 Biologics

Ref: [http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales](http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales). High price tags have been observed in biologics e.g., Avastin is $4400 per month whereas Humira is about US$1650 for one weekly injection pen.
Global 2014 Pharma Sales and Earnings

Changes of Sales and Earnings from 2013 to 2014 of the top pharmaceutical Companies were summarized and compared.

Autoinjector and pen devices have been marketed for many therapeutics. Product recall or device malfunction were documented and learned by all.

The interactions among device, user, and environment were studied through human factor engineering and shared globally.

## Case Study on Autoinjector Recalls

<table>
<thead>
<tr>
<th>Autoinjector</th>
<th>Reason for Recall</th>
<th>FDA Date</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td>Enbrel SureClick</td>
<td>Syringe stalled due to insufficient siliconization; Cracked/broken</td>
<td>01-28-2010</td>
<td>Amgen SHL</td>
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<tr>
<td>Autoinjector</td>
<td>Prefilled Syringe with sterility concern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simponi SmartJet</td>
<td>Recalled in US and Germany Market due to insufficient dose delivery</td>
<td>22-Feb-2011</td>
<td>J&amp;J- Centocore &amp; Janssen in Germany</td>
</tr>
<tr>
<td>Autoinjector</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jext Ardrenaline</td>
<td>Approx. 1/2500 autoinjectors with manufacturing defect of needle</td>
<td>09-Dec-2013</td>
<td>ALK-Abello UK</td>
</tr>
<tr>
<td>Autoinjector</td>
<td>bent causing needle to curl up</td>
<td></td>
<td></td>
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<tr>
<td>Anapen Anaphylactic</td>
<td>Recalled due to a potential problem with slow speed and delivery of</td>
<td>24-May-2012</td>
<td>Lincoln Medical Limited</td>
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<tr>
<td>Injector</td>
<td>adrenaline</td>
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<td>Owen-Mumford</td>
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Ref: [http://www.wsj.com/articles/SB10001424052748704900004576152482593092542](http://www.wsj.com/articles/SB10001424052748704900004576152482593092542)  
"Johnson & Johnson Recalled around 395 autoinjectors and injection devices from US and Germany due to a potential defect resulting insufficient dosing, 22-Feb-2011"
Amgen marketed new on-body injector for Neulasta to treat neutropenia. With Patient’s ease of use at mind, the price is kept on par as the current autoinjector.
Micro-Pump, Patch Pump, and Bolus Injector

Disposable Micropump

Lapas micropump can be integrated with needle.

Sandoz received FDA approval on 06-Mar-2015 for Zarxio, a biosimilar Filgrastim. Zarxio was granted all indications approved in Amgen’s Neupogen.

Zarxio is the first biosimilar approved for US by FDA. Sandoz has not disclosed its pricing strategy. Sandoz’s Zarzio has marketed in EU since 2009.
• **Celgene** has launched its oral psoriasis drug, Otezla, in the UK on 25-Feb-2015. It was received the US trial results that Otezla is as effective as Enbrel.

• **Novo Nordisk** has positive Phase II trial results for its oral GLP-1 development. The research path has not been easy because the digestive system is harsh to proteins and peptides. In order to meet bioavailability criteria, heavier dose is needed compared to subcutaneous injection dose.

• **Biogen** successfully marketed its new oral medication, Tecfidera, in treating multiple sclerosis.

• **Pfizer**’s oral medication, Xeljanz (Tofacitinib), reaches targets in Phase III psoriasis trial on 20-Mar-2015. It can also treat Rheumatoid Arthritis.

• **Gilead**’s Sovaldi is the first all-oral interferon-free hepatitis C treatment.

• **Oramed**’s oral insulin has the potential to create a new paradigm in the treatment of diabetes.
Device Strategy for Manufacturing Biologics in Developing Countries
Blow-fill-seal technology gains momentum lately.

Advantages in shape, cost, and speed attract design possibility.

Extractables, drug compatibility, and protein temperature sensitivity are the focal points of biologics manufacturing process.
Biologics and vaccines in developing countries are often sold at manufacturing cost. Blow-fill-seal technology provides an attractive option for a feasible product cost.
## Price Transparency in Developing Countries

Average Price of Hep-B Vaccine in 2015 is USD $0.20/dose

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Supplier Name</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
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<tr>
<td>HepB vaccine in a single dose presentation</td>
<td>Crucell Switzerland AG</td>
<td>$0.5700</td>
<td>$0.5700</td>
<td>$0.5700- $0.6200</td>
<td>$0.4000</td>
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</tbody>
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Pre-Filled Devices: Blow-Fill-Seal Technology

Examples of pre-filled syringes and stoppered vials manufactured by blow-fill-seal
Injectable Devices for Developing Countries

Examples of pre-filled syringes suitable for using in developing countries
Device Strategy for Leveraging Transdermal and Inhalation Delivery
Micro-Needle technology has proceeded with clinical trial for vaccines and biologics development where COGS is estimated ~US$15.
Inhalation and Respiratory Delivery Devices

Afrezza – Insulin Inhaler

Landmark can be loaded up to 200 doses.

Insulair can be breath activated.

Drug is in Cartridge & blisters.

Decision Resource “COPD 2015” indicates low COPD compliance due to the unmet needs in lacking patient-centric inhalation devices.
Inhalation and Respiratory Delivery Devices

Pharma Circle Review illustrates Dry Powder Inhaler with rotary blister package loaded with multiple doses for patient convenience.
Patient Centric Device Strategy

- Visualized Advantages and Constraints in Pre-Filled Syringes in Designing Cutting Edge Devices
- Adopted Global Design Control Process in Meeting Country Specific Regulatory Expectations
- Led Concurrent Engineering Commercialization Model in Achieving Successful New Product Launch