Long Acting Injectable and Implantable Drug Product Development: Regulatory Challenges and Considerations

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OGD/ORS
Disclaimer

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Outline

• Introduction

• Challenges in development and evaluation of long acting injectable/implantable (LAI) drug products

• FDA’s GDUFA regulatory science program to support development of generic LAI drug products

• Summary
Long acting injectable/implantable formulations

• Oil-based injectable solutions
• Injectable-drug suspensions
• Polymer and lipid based LAIs
## Oil-based injectable solutions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Admin route</th>
<th>Dosing freq.</th>
<th>Indication</th>
<th>Company</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol decanoate</td>
<td>Haloperidol decanoate</td>
<td>IM</td>
<td>Once a month</td>
<td>Schizophrenia</td>
<td>Ortho-McNeil Pharm</td>
<td>Sesame oil</td>
</tr>
<tr>
<td>Estradiol valerate</td>
<td>Delestrogen</td>
<td>IM</td>
<td>Every 4 weeks</td>
<td>Hormone therapy</td>
<td>Monarch Pharm</td>
<td>Sesame oil</td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>Modecate</td>
<td>IM</td>
<td>Every 2-5 weeks</td>
<td>Schizophrenia</td>
<td>Sanofi-Aventis</td>
<td>Sesame oil</td>
</tr>
<tr>
<td>Zuclopenthixol decanoate</td>
<td>Clopixol Depot</td>
<td>IM</td>
<td>Every 2-4 weeks</td>
<td>Schizophrenia</td>
<td>Lundbeck</td>
<td>Sesame oil</td>
</tr>
<tr>
<td>Testosterone enanthate</td>
<td>Delatestryl</td>
<td>IM</td>
<td>Every 2-4 weeks</td>
<td>Hormone therapy</td>
<td>Endo Pharma</td>
<td>Sesame oil</td>
</tr>
</tbody>
</table>

Lipophilic drug dissolved in vegetable oil
# Long acting injectable suspensions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Admin route</th>
<th>Dosing freq.</th>
<th>Indication</th>
<th>Company</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paliperidone palmitate</td>
<td>Invega Sustenna</td>
<td>IM</td>
<td>Once a month</td>
<td>Schizophrenia</td>
<td>Janssen</td>
<td>WFI PS-20, PEG4000</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexa Relprevv</td>
<td>IM</td>
<td>Every 2-4 weeks</td>
<td>Schizophrenia</td>
<td>Eli Lilly</td>
<td>WFI PS-80</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>Depo provera</td>
<td>IM</td>
<td>Every 3 months</td>
<td>Hormone therapy</td>
<td>Pfizer</td>
<td>WFI PS-80, PEG3350</td>
</tr>
</tbody>
</table>

### Drugs with low solubility suspended in aqueous media
# Polymer and lipid-based LAR products

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Drug category</th>
<th>Admin route</th>
<th>Dosing freq.</th>
<th>Indication</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resperidone</td>
<td>Risperdal, Consta</td>
<td>Small molecule</td>
<td>IM</td>
<td>2 weeks</td>
<td>Schizophrenia</td>
<td>Janssen, Alkermes</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Sandostatin LAR depot</td>
<td>Octapeptide</td>
<td>IM</td>
<td>1 month</td>
<td>Acromegaly</td>
<td>Norvatis</td>
</tr>
<tr>
<td>Goserelin</td>
<td>Zoladex</td>
<td>Decapeptide</td>
<td>IM</td>
<td>1, 3 months</td>
<td>Prostate cancer</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Leuprolide</td>
<td>Lupron Depot</td>
<td>Nonapeptide</td>
<td>IM</td>
<td>1, 3, 4, 6 months</td>
<td>Prostate cancer</td>
<td>Takeda/Abbott</td>
</tr>
<tr>
<td>Triptorelin</td>
<td>Decapeptyl/Telstar/Pamoerlin</td>
<td>Decapeptide</td>
<td>IM</td>
<td>1, 3, 6 months</td>
<td>Prostate cancer</td>
<td>Ispen/Watson/Reddy/Debiopharm</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Bydureon</td>
<td>39-amino acid peptide</td>
<td>SC</td>
<td>1 week</td>
<td>Type 2 diabetes</td>
<td>Amylin/BMS/Alkermes</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>DepoCyt</td>
<td>Small molecule</td>
<td>Intrathecal</td>
<td>14 or 28 days</td>
<td>Lymphomatous meningitis</td>
<td>Pacira</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>Exparel</td>
<td>Small molecule</td>
<td>Direct to surgical site</td>
<td>Single dose, 3 days</td>
<td>Postsurgical analgesia</td>
<td>Pacira</td>
</tr>
</tbody>
</table>
Challenges in LAR product development

- Complex formulation and excipients
- Small process and raw material changes could result in significant product changes
- Complicated characterizations
- Release mechanisms (especially in vivo) are not fully understood
- No standard *in vitro* drug release assay
- Few models correlating *in vitro* drug release with *in vivo* pharmacokinetics
- Challenges in scale up

----------
<table>
<thead>
<tr>
<th>Drug Product (Active Ingredient)</th>
<th>Dosage Form</th>
<th>Route of Administration</th>
<th>Indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ozurdex (Dexamethasone)</td>
<td>Implant</td>
<td>Intravitreal</td>
<td>macular edema, non-infectious uveitis, and diabetic macular edema</td>
</tr>
<tr>
<td>Zoladex (Goserelin acetate)</td>
<td>Implant</td>
<td>Subcutaneous</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>Atridox (Doxycycline hyclate)</td>
<td>In situ forming gel</td>
<td>Periodontal</td>
<td>periodontitis</td>
</tr>
<tr>
<td>Eligard (Leuprolide acetate)</td>
<td>In situ forming gel</td>
<td>Subcutaneous</td>
<td>advanced prostate cancer</td>
</tr>
<tr>
<td>Lupron (Leuprolide acetate)</td>
<td>Microsphere</td>
<td>Intramuscular</td>
<td>endometriosis</td>
</tr>
<tr>
<td>Lupron Depot (Leuprolide acetate)</td>
<td>Microsphere</td>
<td>Intramuscular</td>
<td>advanced prostatic cancer</td>
</tr>
<tr>
<td>Lupron Depot-PED (Leuprolide acetate)</td>
<td>Microsphere</td>
<td>Intramuscular</td>
<td>central precocious puberty</td>
</tr>
<tr>
<td>Trelstar (Triptorelin pamoate)</td>
<td>Microsphere</td>
<td>Intramuscular</td>
<td>advanced prostate cancer</td>
</tr>
<tr>
<td>Risperdal Consta (Risperidone)</td>
<td>Microsphere</td>
<td>Intramuscular</td>
<td>schizophrenia and bipolar I disorder</td>
</tr>
<tr>
<td>Signifor LAR (Pasireotide pamoate)</td>
<td>Microsphere</td>
<td>Intramuscular</td>
<td>acromegaly</td>
</tr>
<tr>
<td>Vivitrol (Naltrexone)</td>
<td>Microsphere</td>
<td>Intramuscular</td>
<td>alcohol dependence</td>
</tr>
<tr>
<td>Arestin (Minocycline HCl)</td>
<td>Microsphere</td>
<td>Periodontal</td>
<td>periodontitis</td>
</tr>
<tr>
<td>Bydureon (Exenatide)</td>
<td>Microsphere</td>
<td>Subcutaneous</td>
<td>type 2 diabetes</td>
</tr>
<tr>
<td>Sandostatin LAR (Octreotide)</td>
<td>Microsphere</td>
<td>Subcutaneous</td>
<td>acromegaly</td>
</tr>
<tr>
<td>Signifor (Pasireotide)</td>
<td>Microsphere</td>
<td>Subcutaneous</td>
<td>cushing’s disease</td>
</tr>
</tbody>
</table>
Complex excipients

- Poly(lactic-co-glycolic acid) (PLGA) copolymer
  \[
  \begin{align*}
  m &= \text{number of units of lactic acid} \\
  n &= \text{number of units of glycolic acid}
  \end{align*}
  \]
  - Ratio of lactic acid to glycolic acid
  - Molecular weight/weight distribution

- Glucose star polymer, D,L-lactic and glycolic acids copolymer
  \[
  R = \left[ \begin{array}{c}
  \text{Sandostatin LAR depot} \\
  \text{(octreotide acetate microsphere)}
  \end{array} \right]
  \]

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Critical PLGA physicochemical properties

- Polymer composition (L to G ratio)
- Molecular weight and weight distribution
- Polymer architecture (linear vs star-shaped)
- Glass transition temperature
- Polymer end-cap
- Crystallinity

Generic parenteral PLGA microsphere drug products should be Q1/Q2 equivalent to Reference Listed Drug (RLD).

Q1: same excipient   Q2: same amount
Complex drug release

- **Multiple factors impact drug release**
  Polymer composition; polymer molecular weight; API chemical property; manufacture process; matrix size and shape; drug loading; pH; releasing media......

- **Complex drug release mechanisms**
  - Multi-phasic release profiles

- **No compendial in vitro drug release testing method**
  - Unlike oral formulations, no standardized test procedures (e.g., USP methods) for parenteral microsphere products.
  - The process of establishing release method and acceptance criteria is complicated.

- **Challenging to correlate in vitro drug release with in vivo pharmacokinetics**
GDUFA research

Since 2013, FDA/OGD has funded 9 grants/contracts for development and characterization of PLA/PLGA-based generic drug products:

– Characterizations of PLGA polymers and PLGA based microspheres and implants
– IVIVC
– Modeling and simulation
IVIVC of risperidone microspheres

• Q1/Q2 formulations:
  – Similar PLGA as that used in Risperdal® Consta®
  – Different manufacturing processes (homogenization, vortex mixing, solvents) resulted in different physicochemical properties (porosity, particle size)

• Two release methods investigated:
  – USP Apparatus II (Sample-and separate)
  – USP Apparatus IV

• Level A IVIVCs established in rabbits based on USP Apparatus IV data

<table>
<thead>
<tr>
<th>Sample</th>
<th>Solvent</th>
<th>Preparation method</th>
<th>Porosity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperdal Consta</td>
<td>--</td>
<td>--</td>
<td>43.97 ± 4.60</td>
</tr>
<tr>
<td>F1</td>
<td>DCM</td>
<td>Homogenization &amp; dry sieving</td>
<td>43.19 ± 4.60</td>
</tr>
<tr>
<td>F2</td>
<td>DCM</td>
<td>Homogenization &amp; wet sieving</td>
<td>46.04 ± 42.90</td>
</tr>
<tr>
<td>F3</td>
<td>EA</td>
<td>Vortex &amp; wet sieving</td>
<td>54.98 ± 1.25</td>
</tr>
<tr>
<td>F4</td>
<td>EA</td>
<td>Homogenization &amp; wet sieving</td>
<td>61.75 ± 1.08</td>
</tr>
</tbody>
</table>
Particle size distribution

**D50 value**

- **A**
  - Particle size (µm)
  - Risperdal® Consta®
  - Formulation 1
  - Formulation 2
  - Formulation 3
  - Formulation 4
  - Volume distribution
  - Population distribution

**Span value**

- **B**
  - Span value
  - Risperdal® Consta®
  - Formulation 1
  - Formulation 2
  - Formulation 3
  - Formulation 4
  - Volume distribution
  - Population distribution
In vitro release profiles

USP Apparatus II Sample and separate

USP Apparatus IV Flow through cell
In vivo release profiles

In vivo PK profile

Deconvoluted in vivo profiles
Level A IVIVC

**Formulations 2-4**

\[ y = 0.9264x + 0.0147 \]

\[ R^2 = 0.9825 \]

**Formulation 1**

- In vivo release profile, n=6
- Predicted in vivo release profile
Validation and prediction of IVIVC

<table>
<thead>
<tr>
<th></th>
<th>$C_{\text{max}}$ ($\mu g/L$)</th>
<th></th>
<th></th>
<th></th>
<th>$\text{AUC}$ ($\mu g/L \times \text{day}$)</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pred.</td>
<td>Obs.</td>
<td>%PE</td>
<td>Pred.</td>
<td>Obs.</td>
<td>%PE</td>
<td></td>
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<tr>
<td><strong>Internal validation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formulation 2</td>
<td>19.64</td>
<td>41.62</td>
<td>−52.81</td>
<td>188.26</td>
<td>200.41</td>
<td>−6.06</td>
<td></td>
</tr>
<tr>
<td>Formulation 3</td>
<td>40.49</td>
<td>29.98</td>
<td>35.06</td>
<td>219.14</td>
<td>229.07</td>
<td>−4.34</td>
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<tr>
<td>Formulation 4</td>
<td>35.58</td>
<td>28.68</td>
<td>24.08</td>
<td>201.12</td>
<td>220.95</td>
<td>−8.97</td>
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<tr>
<td>Average absolute %PE</td>
<td></td>
<td></td>
<td>37.32</td>
<td></td>
<td></td>
<td>6.46</td>
<td></td>
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<tr>
<td><strong>External validation</strong></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Formulation 1</td>
<td>26.71</td>
<td>27.99</td>
<td>−4.56</td>
<td>231.51</td>
<td>206.92</td>
<td>10.61</td>
<td></td>
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<tr>
<td><strong>Prediction</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Risperdal® Consta®</td>
<td>41.32</td>
<td>38.29</td>
<td>7.90</td>
<td>248.69</td>
<td>248.50</td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>
Level A IVIVC of naltrexone microspheres
Cage model to assess in vivo release

Understanding release mechanisms of drug from PLGA microspheres

Triamcinolone-loaded microspheres

Leuprolide-loaded microspheres
Understanding release mechanisms of Tr-A from PLGA microspheres

Characteristic times (in days) of release and erosion from Tr-A_1 and Tr-A_2 microspheres. Values represent mean ± SEM, n = 3. $T_{50}$ ratios were calculated from mean values of $t_{50,\text{release}}$ and $t_{50,\text{erosion}}$.

<table>
<thead>
<tr>
<th></th>
<th>PBST pH 7.4</th>
<th>PBST pH 6.5</th>
<th>PBS + 1.0% TC</th>
<th>HBST pH 7.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tr-A_1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_{50,\text{release}}$</td>
<td>$19.0 \pm 0.4$</td>
<td>$16.6 \pm 0.4$</td>
<td>$8.0 \pm 0.4^*$</td>
<td>$17.6 \pm 0.2$</td>
</tr>
<tr>
<td>$t_{50,\text{erosion}}$</td>
<td>$25 \pm 8$</td>
<td>$18.6 \pm 0.8$</td>
<td>$15 \pm 1$</td>
<td>$18 \pm 2$</td>
</tr>
<tr>
<td>$t_{50,\text{release}}/t_{50,\text{erosion}}$</td>
<td>$0.77$</td>
<td>$0.89$</td>
<td>$0.52$</td>
<td>$0.96$</td>
</tr>
<tr>
<td>Tr-A_2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_{50,\text{release}}$</td>
<td>$46.8 \pm 0.6$</td>
<td>$50.1 \pm 0.8$</td>
<td>$25.0 \pm 0.3^*$</td>
<td>$46.1 \pm 0.3$</td>
</tr>
<tr>
<td>$t_{50,\text{erosion}}$</td>
<td>$46 \pm 3$</td>
<td>$39 \pm 2$</td>
<td>$18 \pm 2^\dagger$</td>
<td>$43 \pm 2$</td>
</tr>
<tr>
<td>$t_{50,\text{release}}/t_{50,\text{erosion}}$</td>
<td>$1.02$</td>
<td>$1.28$</td>
<td>$1.43$</td>
<td>$1.06$</td>
</tr>
</tbody>
</table>

$^*$ p < 0.05 compared to PBST pH 7.4.
$^\dagger$ linear regression was used.
Understanding release mechanisms of Leuprolide from PLGA microspheres
Understanding release mechanisms of Leuprolide from PLGA microspheres

Hirota K, et al.  
pii: S0168-3659(16)30550-8

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1. Erosion (mass loss)
   - Polymer
   - Peptide
   - Rapid peptide diffusion

2. Diffusion/pore healing (early phase)
   - PLGA microspheres
   - Diffusion through polymer pore network
   - Pore healing

3. Water-mediated
   - Peptide
   - Pore formation
   - Swelling
   - Osmotic pump
   - Peptide release

4. Desorption
   - PLGA → HO-CH-C-C-OH + cPLGA
   - Degradation
   - Ion pair
   - Rapid diffusion

5. Poorly soluble base-induced pore formation (specific for SM)
   - ZnCO₃(s) → Zn⁡⁺ + CO₃²⁻(aq)
   - Osmotic pressure
   - and
   - pore formation as degradation proceeds
   - HO-CH-C-O⁻ + HCO₃⁻
   - HO-CH-C-O⁻ + H₂CO₃
   - H₂CO₃ ↔ H₂O + CO₂

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QronoMetrics

- Predictive software for design and development of biodegradable polymer drug products
- To develop a predictive mathematical model linking dissolution and PK profiles directly to critical quality attributes

Outputs:
- Formulation design specs
- Drug delivery predictions
- Quality by Design (QbD) design space evaluation
Conclusions

• Understanding of PLGA properties is key for successful development of PLGA based LAI products

• Level A IVIVCs have been successfully developed for Q1/Q2 risperidone PLGA microspheres and Q1/Q2 naltrexone PLGA microspheres in an animal model

• A cage model has been validated to assess in vivo performance of microspheres

• Two model drugs have been tested in in vitro studies for further understanding of the mechanisms of drug release from PLGA microspheres

• Study results can be used to inform recommendations for product-specific guidances, pre-ANDA meeting requests, and Controlled Correspondences
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Questions?

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GDUFA Regulatory Science Website:

www.fda.gov/GDUFARegScience