EU orphan drug launch and supply using ‘one stop shop’ model

David Downey, VP Commercial Operations
Agenda

• The ‘one stop shop solution’ – understanding the value in integrating CMO and distributor.
• Planning and defining an orphan drug product launch strategy.
• Considering risk-assessment and mitigation tools to ensure product supply to end-user.
• Orphan drug launch case study.
Orphan Drug Market
"Orphan drugs" are medicinal products intended for diagnosis, prevention or treatment of life-threatening or debilitating rare / orphan diseases. (Eurordis)

The definition of an orphan disease varies, slightly: in the US it is one with a prevalence of less than 200,000 affected person: in the EU it is one with a prevalence of less than 5 per 10,000 of the population.” (NICE)

5,000 - 8,000 distinct rare diseases exist today (EMA)
- Overall affect 6% - 8% of world population
- Estimated population of 25m for USA and 30m for Europe

10% are currently treated
## Orphan Drug Designations

Overview for orphan medicinal product designation procedure since 2000

<table>
<thead>
<tr>
<th>Year</th>
<th>Applications submitted</th>
<th>Applications discussed in reporting year</th>
<th>Positive COMP opinions</th>
<th>Applications withdrawn</th>
<th>Final negative COMP opinions</th>
<th>Designations granted by Commission</th>
<th>% Submitted vs Granted</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>97</td>
<td>106</td>
<td>73 (69%)</td>
<td>31 (29%)</td>
<td>2 (2%)</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>2009</td>
<td>164</td>
<td>137</td>
<td>113 (82%)</td>
<td>23 (17%)</td>
<td>1 (1%)</td>
<td>106</td>
<td>65</td>
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<tr>
<td>2008</td>
<td>119</td>
<td>118</td>
<td>86 (73%)</td>
<td>31 (26%)</td>
<td>1 (1%)</td>
<td>73</td>
<td>61</td>
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<tr>
<td>2007</td>
<td>125</td>
<td>117</td>
<td>97 (83%)</td>
<td>19 (16%)</td>
<td>1 (1%)</td>
<td>98</td>
<td>78</td>
</tr>
<tr>
<td>2006</td>
<td>104</td>
<td>103</td>
<td>81 (79%)</td>
<td>20 (19%)</td>
<td>2 (2%)</td>
<td>80</td>
<td>77</td>
</tr>
<tr>
<td>2005</td>
<td>118</td>
<td>118</td>
<td>88 (75%)</td>
<td>30 (25%)</td>
<td>0 (0%)</td>
<td>88</td>
<td>75</td>
</tr>
<tr>
<td>2004</td>
<td>108</td>
<td>101</td>
<td>75 (74%)</td>
<td>22 (22%)</td>
<td>4 (4%)</td>
<td>72</td>
<td>67</td>
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<tr>
<td>2003</td>
<td>87</td>
<td>96</td>
<td>54 (56%)</td>
<td>41 (43%)</td>
<td>1 (1%)</td>
<td>55</td>
<td>63</td>
</tr>
<tr>
<td>2002</td>
<td>80</td>
<td>76</td>
<td>43 (57%)</td>
<td>30 (39%)</td>
<td>3 (4%)</td>
<td>49</td>
<td>61</td>
</tr>
<tr>
<td>2001</td>
<td>83</td>
<td>92</td>
<td>64 (70%)</td>
<td>27 (29%)</td>
<td>1 (1%)</td>
<td>64</td>
<td>77</td>
</tr>
<tr>
<td>2000</td>
<td>72</td>
<td>32</td>
<td>26 (81%)</td>
<td>6 (19%)</td>
<td>0 (0%)</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>1157</td>
<td>1096</td>
<td>800 (73%)</td>
<td>280 (26%)</td>
<td>16 (1%)</td>
<td>751</td>
<td>65</td>
</tr>
</tbody>
</table>

Committee for Orphan Medicinal Products (COMP)
EMA/COMP/364048/2010
26 July 2010
Orphan Drug Designations

Orphan medicinal product designation procedures (2000-2010)

* Figures for 2010 as per 30 April 2010.

3 May 2010
EMA/279601/2010
The ‘One Stop Shop’ Solution – understanding the value
EU Import Analysis

All Pharmaceutical Products must be analysed in line with the spec contained within the MAA upon entry into the EU.

**Why?**
- Different Pharmacopeial requirements
- Different Regulatory Requirements
- due to licensing process
- No Mutual Recognition (MR)/Outside
- Mutual Recognition Scope
- How has shipment affected the batch?

**Why do I need to transfer a validated method?**
To ensure the methods can be applied accurately and consistently in a manner that can confirm the Drug product as fit for purpose.
Why is QP Release required in the EU?

To ensure that:

- Items are fit for intended purpose
- All aspects of manufacture comply with GMP
- All aspects of testing comply with GLP
- All aspects of storage/distribution comply with GDP

Why is QP Release not required in the US?

The Code of Federal Regulations states only that an “independent quality control unit” needs to release the batch.
Storage

- Extensive Storage Facilities
- Controlled Ambient (15°C-25°C)
- Refrigerated (2°C-8°C)
- Frozen (-70°C)
- Secured Vault (all schedules of controlled drugs)
- Returns Handling/Rejection/Destruction
- Full ERP Control

Benefits of ERP
- Real-time information
- Visibility into the performance of operational areas
- Data standardisation and accuracy
- Analysis and reporting for long-term planning
- Provides functionality to interact with other elements in the process
- Reduce inventory through better visibility and efficiency
- Reduction in non-value added activities (lean processing)
- Higher utilisation of employees (less transactional, more analytical)
- Improvement in decision making through more accurate and real-time data

System based Reporting & Tracking
Labelling & Packaging Design Services

• In-house facilities using the latest technology in packaging design

• Capability to design bespoke packaging solutions

• Facility to update existing packaging components

• Fast, electronic artwork approval system

• Electronic Artwork File Management
Order Processing & Financial Services

Order Processing
- 24/7 secure online ordering system
- Multilingual telephone & fax ordering
- Order management (metrics & KPIs)

Financial Services
- Product invoicing
- Debtor follow up
- Metric reporting of customer payments
Worldwide Distribution to End User

- Validation of shipping configurations
  - 48 hour to 120 hour validation period
  - Shipper range
    - Active
    - Passive
    - Reusable

- Route Qualification (Air / Road / Sea)

- Import / export documentation and customs clearance

- Courier / freight management (ambient & cold chain)
  - Service Level Agreements
  - Traceability / Proof of Delivery
Value of One Stop Shop

- Integrated supply & distribution project management
- Consistent quality
- Reduced handling
- Reduced lead times
- Knowledge and experience of the product
- Reduced cost of goods
- Reduced carbon footprint
- Reduced sampling
- Reduced stock holding
Overview of Historic Secondary Packaging Process

1. Text Submission & Approval
2. Translation
3. Artwork & Packaging Design
4. PPM Procurement
5. Generation of MBRs
6. Secondary Packaging
7. QA Review
8. QP Review

- Manufacture of Britestock
  - Secondary Packaging
    - Kenya
    - Nigeria
    - South Africa
    - Uruguay
    - Venezuela
    - Germany
    - Greece
    - Hungary
    - Iceland
    - Ireland
    - Italy
    - Japan
    - South Korea
    - Mexico
    - Morocco
    - New Zealand
    - Netherlands
    - Norway
    - Poland
    - Portugal
    - Romania
    - Russia
    - Spain
    - Sweden
    - Switzerland
    - Turkey

- Storage
- Distribution
- Order Receipt
Overview of Late Stage Customisation

Manufacture of Britestock

Assembly of Regional Packs (GMP Production Operation)

Storage

Order Receipt

Distribution
Country specific information which is presented in the official language(s) of the Member State concerned to make the pack Market Specific
Planning & Defining Your European Orphan Drug Product Launch Strategy
Patient Access

- Licensed vs unlicensed (named patient / compassionate use)
- Strategic balance based on patient numbers & cost of regulatory & supply.
- In the EU, the regulatory process is a mandatory via the centralised route – this enables rapid and full EU market access, however local authority pricing and reimbursement negotiations halt progress.
- Typically strategy is to launch in UK or Germany and at the same time supply named patient or compassionate use to other territories.
- Roll out launch countries (licensed) based on company strategy.

There will always be a **mix** of named patient and commercial supply, especially when you move into Rest of World (ROW) markets.
Patient Access

Expanded Access
Pre-licence

MA Granted in Country A
First Launch
Staggered Launches in Countries B, C, D

Temporary Supply Problems
Licence discontinued

Worldwide Distribution
### US vs EU Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>US (United States)</th>
<th>EU (European Union)</th>
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</thead>
<tbody>
<tr>
<td>Countries</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>Recognised Languages</td>
<td>1</td>
<td>23</td>
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<tr>
<td>Regulatory Bodies</td>
<td>1</td>
<td>30</td>
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<tr>
<td>Languages per pack</td>
<td>1</td>
<td>1-5</td>
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<tr>
<td>Typical leaflet size</td>
<td>250 x 353 mm</td>
<td>500 x 700 mm</td>
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</table>
One Stop Shop Product Launch Strategy

Almac Project Management for Launch
<table>
<thead>
<tr>
<th>Step</th>
<th>Weeks</th>
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<tbody>
<tr>
<td>Bulk Manufacture</td>
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<tr>
<td>QC Analysis</td>
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<tr>
<td>Shipment to Almac</td>
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<tr>
<td>Secondary Packaging</td>
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<td>QA Review</td>
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<td>QP Review</td>
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<td>Authorisation to Despatch</td>
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<tr>
<td>Transit to Distribution Centre</td>
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<tr>
<td>Receipt &amp; Reconciliation</td>
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<tr>
<td>Order Receipt, LSC &amp; Despatch</td>
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<tr>
<td>Delivery to End User</td>
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<tr>
<td>Invoice Raised</td>
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<td>Payment Received</td>
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**Typical Lead-time to End User**
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<tr>
<th>Activity</th>
<th>Wks 1-4</th>
<th>Wks 5-8</th>
<th>Wks 9-12</th>
<th>Wks 13-16</th>
<th>Wks 13-16</th>
<th>Wks 17-20</th>
<th>Wks 21-24</th>
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Risk Assessment & Mitigation
Risk Management

Good Risk Management = Speed, Quality & Success

Challenges

• Orphan drugs are unique and usually represent a challenge to manufacture, pack, test and distribute.
• They can be temperature sensitive and require special handling & distribution.
Risk Management - Quality

- QRM must be built into your Quality System as defined in EU GMP.

- QRM should be utilised to design and control your product from manufacture through the supply chain to the end user.

- QRM tools widely recognised and utilised include FMEA (Failure Mode & Effect Analysis & Risk Ranking).

- ALWAYS consider the 5 x Ps’ of PRODUCT, PROCESSES, PREMISES & EQUIPMENT, PROCEDURES & PERSONNEL

- All associated risks are managed and mitigated via a CAPA plan.
Risk Assessment - Packaging

- Packaging component & material selection
  - Key product requirements
  - Regulatory
  - Marketing expectations
- Key properties of various materials / systems
- Pack testing & evaluation
- Packaging component specifications
- Artwork generation & control
- Regulatory requirements
- Transit packaging
- Trade/supply chain requirements
Risk Assessment - End User Distribution

Selection of Shipping Procedure

Risk Assessment

- Product Value
- Shipping Cost
- Receiver Capabilities
- Transit Time
- Temp Requirement + Stability Data
- Despatch Quantity

Initial Selection

- Ambient
- Controlled Truck
- Bespoke Shipping System

Qualification

Satisfactory

Compile Distribution Instructions
Shipper / Route Qualification

Why is this a requirement?

EU (Orange Guide/MHRA)
Good Distribution Practice (GDP) require Distributors to ‘ensure that storage conditions are observed at all times, including transportation’.

US (USP 1079)
“The Distributor must maintain proper storage environments for individual articles to ensure a preparation’s integrity, including its appearance, until it reaches the user”.

ALMAC
Distribution Capabilities

- Central Distribution from Northern Ireland with 37 audited and contracted Depots worldwide
- 10,000 consignments dispatched each month
- 25% of consignments are temperature controlled (-70°C, -20°C, 2-8°C and 15-25°C)
- Product range includes Dangerous Goods, Controlled Drugs, Antibiotics and Animal Health material
- Consignments range from 1 vial to 70 pallets
- Storage capability for Controlled Ambient (8,000 pallets), Refrigerated (300 pallets), -20°C (30 pallets) and -70°C.
Supply Chain Solutions - Transportation

- Established network of approved couriers to manage any size of consignment
  - Express Courier
  - Premium Courier
    - Difficult transit routes & Customs management
    - Continuous consignment tracking and temperature monitoring
  - Air, Road & Ocean freight
  - Import & export clearance facilities
Supply Chain Solutions - Shippers

- A full range of shipper solutions validated to meet the needs of the product and transit route:
  - 4 litre payload to full pallet shippers
  - 48 hour to 120 hour validation period
  - Passive Shipper range
    - Polystyrene or Vacuum Insulated Panel (VIP) Insulation
    - Gel pack or phase change material energy source
  - Active Shipper range
    - High performance shipper with built in heating & cooling technology
    - Envirotainer, Kryotrans unit
    - Dedicated refrigerated vehicles
  - Reusable Shippers with a reverse logistics program
Case study – EU Orphan Drug launch and supply using the ‘one stop shop’ model
EU Product Launch Case Study

- **Product** - homogeneous lyophilised powder for suspension for infusion

- **Components**
  - Britestock from USA
  - Filters from Italy
  - Testing in Switzerland
  - QP release site in Ireland

- **Product Indication** - treatment of non-metastatic osteosarcoma (malignant bone cancer) following surgical removal of the tumor (resection) in children, adolescents and young adults.

- **Market Value** - ~ €3,000 per kit (varies depending on country)
Product Launch Case Study

Initial Project Scope
- Services
  - Secondary Packaging
- Markets
  - UK
- Regional Packs
  - Ambient

Final Project Scope
- Services
  - Packaging Design
  - Artwork Origination
  - Shipper Validation/Qualification
  - Secondary Packaging
  - Late Stage Customisation
  - End-user Distribution
- Markets
  - UK, Ireland, Spain, Italy, France, Netherlands, Germany, Austria, Greece, Portugal, Finland, Sweden, Norway, Denmark, Iceland
- Regional Packs
  - Ambient
- Storage/Shipping Conditions
  - 2 - 8°C
Product Launch Case Study

**Objective:** Successful launch of product onto EU market

**Challenges:**
- Acquisition of original client
- Communication
  - 3 time zones / multiple languages
- Change of project scope
- Multiple markets
- Printed packaging components
- Design & implementation of a secure online ordering portal
- Cold chain requirements
- Shipper qualification
Order Processing

ORDER PLACED

Order entered onto Pharma POP System

Order Processing

Pick

LSC (if required)

Pack

Despatch & Track

Invoicing & Dunning
Objective: Successful launch of product onto EU market

Keys to Success:

• EU based CDMO
  • EU Import Testing
  • QP release
  • EU market / regulatory experience & knowledge
  • Unlicenced and Licenced supply
  • Worldwide distribution
• Clear Technical Agreement
  • QA/QP/RP responsibilities
• Risk Management
• Project Planning & Management
• Open communication & regular meetings (F2F & Tcon)
• Sharing of documentation
Product Launch Case Study

- Project Initiation: Sept 3rd 2009
- MA Approval: Jan 19th 2010
- 1st Batch Releases: Jan 20th 2010
- 1st Order Received: Jan 25th 2010
- 1st Despatch to End User: Jan 25th 2010
- 1st Delivery to End User: Jan 26th 2010
- Project Duration: 21 Weeks
- MA Approval to 1st Delivery: 1 Week
EU Import Testing & QP Services

Order Processing & Financial Services

Labelling & Packaging

Storage

Worldwide Distribution

Named Patient Supply

points to consider