Pharmaceutical packaging – an overview including some considerations for paediatrics

Training workshop:

Pharmaceutical development with focus on paediatric formulations

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Beijing, 21 to 25 June 2010
Introduction

• Overview comments
  – The Roles of Packaging
  – Specific Paediatric Considerations

• Choosing the most Appropriate Primary Pack
  – Terminology and Pack Diversity
  – Considerations for Pack Selection
  – Barrier Properties
  – Bottles and Closures
  – Blister Packs

• Regulatory Considerations
  – China, US, EU, Pharmacopoeial
  – Extractable & Leachables

• Packaging Development considerations through to Product Launch
The Roles of Packaging (1)

• Protecting the product from the environment and vice versa
  – Physical and chemical stability of the medicine (being an effective barrier to light, moisture, oxygen, bacteria, volatiles, etc. as appropriate)
  – Mechanical trauma – protection from damage
  – During transit, distribution and storage of the product, maintaining product integrity until:
    • it’s in-use phase is completed or
    • the expiry date stated on the label has passed

• Providing all necessary information for...
  – Identification of the medicine (including strength)
  – Safe preparation of the medicine if required (e.g. reconstitution, dilution)
  – Safe use of the medicine (e.g. clearly worded instructions, pictograms) including precautions (food/drug compatibilities and side effects)
  – Storage and shelf-life of in-use product
  – Appropriate disposal of any unused medicine and the packaging itself

Labelling and Product Inserts/Patient Information Leaflets
The Roles of Packaging (2)

- **Enabling accurate dosing and compliance**
  - Spoons, cups or syringes for oral dose measurement and delivery
  - Dropper tubes for eye/ear/oral delivery of drops
  - Applicators (e.g. pessaries)
  - Dispensing devices, actuators, pre-filled syringes
  - Dose counting and calender devices

- **Ensuring supply-chain integrity of the medicine**
  - Pedigree and “Track-and-Trace” systems assuring “chain of custody”
  - Anti-counterfeiting measures
  - Counter-measures for illegal cross-border trading

Covert and Overt: e.g. holograms, digital watermarks, microdot patterns and other printing technologies, radiofrequency identification (RFID) technologies
Other specific paediatric considerations

• CMC pack considerations for paediatric and adult dosage forms are the same. However, there are particular areas of attention for paediatric products:
  – There may be lower limits of acceptable levels of impurities, extractables and leachables resulting from product/pack interaction.
  – Associated devices may be required to facilitate dosing or compliance, e.g.
    • spacers (inhaled medicines)
    • syringes (oral dosing)
    • giving sets (parenteral infusions)
  All contact materials must be suitable and well controlled. For new materials/devices, this will necessitate extensive evaluation.
  – Protection from risk of unsupervised access to medicines – this applies equally to paediatric and adult drug products. The need for child-resistant (CR) packaging will need to be assessed, balanced against the adjudged risk in accidental ingestion of the drug product itself; (some territories insist on CR packs; e.g. the USA).
ICH Packaging Terminology

- **Immediate (Primary) Pack**
  - Contains and protects the dosage form so it is normally in contact with it.
  - It bears appropriate label(s) providing content and usage information.
  - Immediate pack components are considered essential to the stability of their contents, whether or not in contact with them.

- **Secondary Pack**
  - A pack component with no product contact but may add protection to that provided by the immediate pack.

- **Container Closure System**
  - The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection (e.g. light barrier) to the drug product.

- **Marketing Pack**
  - Combination of primary and secondary packaging, whether or not the latter has any overt stability maintenance function.
# Pack Types

<table>
<thead>
<tr>
<th>Multidose/Reclosables</th>
<th>Unit Dose/Non-reclosables</th>
<th>Bulk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottles</td>
<td>Ampoules</td>
<td>Bottles</td>
</tr>
<tr>
<td>Aerosol packs</td>
<td>Blister packs</td>
<td>Drums/Kegs</td>
</tr>
<tr>
<td>Tubes</td>
<td>Prefilled syringes</td>
<td>Sacks/Bags</td>
</tr>
<tr>
<td></td>
<td>Vials</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sachets</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Form/Blow-Fill-Seal (FFS, BFS)</td>
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<tr>
<td></td>
<td>- various pack formats</td>
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</tbody>
</table>

**Boxes:** can be a secondary pack acting as a light protective barrier (in which case will be included in product stability assessment)
EXAMPLE OF PACK DIVERSITY: IH and IN Products

Metered dose inhaler

Dry Powder Inhalers

Nebules

Intranasal
Drug-Device “Combination Products”

- **US-FDA Term**
  - A product comprised of two or more regulated components (drug, device, biological) that are physically, chemically or otherwise combined or mixed and produced as a single entity
  
  - **Typical examples:**
    - Dry powder inhalers
    - Metered dose inhalers
    - Prefilled syringes
    - Injection/infusion systems
    - Pen injectors
    - Ophthalmic delivery systems
  
  - Performance stability data involving the drug-device combination will be required, tailored to the product in question, its anticipated storage/use profile and required functionality, e.g. reproducible and accurate dosing over multiple MDI actuations
PACKAGING: Choosing the pack (1)

● Target Patient Population
  – Dosing regimen
  – Route of administration
  – Need for dosing device
  – Patient/carer/medic dosing
  – Nature of disease/condition

● Commercial
  – Image
  – Preferred packs
  – Market requirements/trends
  – Dosing/patient compliance
  – Security/tamper evidence
  – Manufacturing issues
  – Economics – Cost of Goods

● Product Stability
  – Barrier requirements
  – Pack/product compatibility
  – Challenges with target territories

● Regulatory considerations
  – Global
  – Local
Some factors are territory-specific, e.g.

- **Presentation**
  - Local dosage form preferences, e.g. powder for oral suspension - multiple dose bottles vs. single dose sachets
  - Local pack preferences: e.g. for oral solid dose – bottles vs. blister packs

- **Environment**
  - EU Packaging and Packaging Waste Directive

- **Child resistance requirements**
  - US
    - Legal requirement with few exceptions
  - EU/RoW
    - Legal requirement in only 4 EU member states & for very limited list of products
Pack barrier capabilities may be critical to the viability of a medicine:

- Moisture ingress can lead to hydrolytic degradation or physical instability; high humidity territories may warrant extra precautions
- Air ingress can lead to oxidative degradation
- Some products are photolabile and need protection from light
- Bacteria must be excluded from sterile/sterilised products
- Other biological challenges need to be denied ingress, e.g. insects
- Leaking of liquid products from their pack must be avoided
- The egress of any volatile excipients must be prevented to maintain integrity of the product
The water vapour transmission rate (WVTR) through a container is determined by:

- Container wall thickness and permeability
- Difference between the external and internal relative humidity environments
  - Driving force for the water flux through the container
- Whole pack permeability, e.g. including the closure

NB: HDPE bottles are not an effective barrier, even with a lid induction seal to prevent permeation through the closure.
Packaging: Desiccants

- Desiccants used to control the exposure of products to ingress of moisture
- Desiccants vary in their capacity and the rate that they can adsorb/absorb ingressed moisture
  - *Silica gel* is very efficient at absorbing moisture at high relative humidities, but comparatively poor at lower relative humidities.
  - *Molecular sieve* desiccants - the opposite scenario prevails.
  - As a consequence, more molecular sieve is required at higher relative humidities and the greater the moisture exclusion challenge during packaging operations.
  - Molecular sieve approved in EU for pharmaceuticals, not by FDA in US.
  - Based on the calculated WVTR of known container components and the rate of moisture adsorbed by desiccants, the amount of desiccant required to maintain relative humidity within a specified range over the product’s shelf-life can be determined.
**BLISTER PACK MATERIALS: Comparative moisture barrier properties**

**Typical WVTR (g/m²/day 38°C/90%RH)**

<table>
<thead>
<tr>
<th>Material</th>
<th>WVTR</th>
</tr>
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<tbody>
<tr>
<td>Cold Form Aluminium</td>
<td>0.00</td>
</tr>
<tr>
<td>Aclar ® 33C</td>
<td>0.08</td>
</tr>
<tr>
<td>Aclar ® UltRx2000</td>
<td>0.11 - 0.12</td>
</tr>
<tr>
<td>Aclar ® 22C</td>
<td>0.22</td>
</tr>
<tr>
<td>Aclar ® SupRx 900</td>
<td>0.23 - 0.26</td>
</tr>
<tr>
<td>Aclar ® 22A</td>
<td>0.31 - 0.34</td>
</tr>
<tr>
<td>PVC/80g PVDC</td>
<td>0.31</td>
</tr>
<tr>
<td>Aclar ® Rx160</td>
<td>0.39 - 0.42</td>
</tr>
<tr>
<td>Aclar ® 33C</td>
<td>0.42</td>
</tr>
<tr>
<td>PVC/60g PVDC</td>
<td>0.47 - 0.6</td>
</tr>
<tr>
<td>PVC/40g PVDC</td>
<td>0.7 - 0.75</td>
</tr>
<tr>
<td>PP</td>
<td>0.7 - 1.47</td>
</tr>
<tr>
<td>PVC</td>
<td>2.4 – 4</td>
</tr>
</tbody>
</table>

*Aclar® film is a polychlorotrifluoroethylene (PCTFE) material used extensively in pharmaceutical and medical packaging (Honeywell)*
Similar considerations are relevant to protection of products that are labile to oxidative degradation.

The permeability of plastic containers to oxygen ingress has also been evaluated (OTR), and some data are summarised here.

<table>
<thead>
<tr>
<th>Pack</th>
<th>OTR (g. mm/(m². day))</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDPE</td>
<td>241</td>
</tr>
<tr>
<td>HDPE</td>
<td>102</td>
</tr>
<tr>
<td>Polystyrene</td>
<td>127</td>
</tr>
<tr>
<td>Polycarbonate</td>
<td>114</td>
</tr>
<tr>
<td>Polypropylene</td>
<td>89</td>
</tr>
<tr>
<td>PVC</td>
<td>4</td>
</tr>
<tr>
<td>PET</td>
<td>2</td>
</tr>
</tbody>
</table>
The theoretical rate of oxygen permeation through a standard 30-cc HDPE bottle when stored in a well sealed container has been determined:

- This equated to an uptake of ~0.2 mMol of oxygen per year

In addition to permeation through the container walls, the key vulnerability in an HDPE bottle is the screw-topped closure.

- for oxidatively labile dosage forms an oxygen-impermeable seal such as an induction heat seal is required

Levels of oxygen in the air headspace of the container-closure system can be significant enough to affect stability for some products:

- packaging under an inert atmosphere, although achievable (e.g. BFS adaptation), is a technical challenge
Packaging: Light protection

- Opacity of containers does not necessarily mean that the contained product is protected from light:
  - Plastic materials, e.g. HDPE bottles, opacified with titanium dioxide pigment can still allow significant light to be transmitted through because light scatters internally as well as externally
  - Brown glass is a barrier to the more damaging short wave-length light but is transparent at longer wavelengths
  - A secondary pack component can augment light protection

- Aluminium foil provides the best option for assured protection from light, e.g.
  - Suitable blister pack option (foil/foil)
  - Foil pouches for drug/device combinations
  - Foil covered infusion bags
PACKAGING: Bottles

BOTTLE

- Glass
  - type III (solids)
  - type I (for inhaled solutions)

- Plastic
  - low density polyethylene LDPE
  - high density polyethylene HDPE
  - polypropylene PP
  - polyester PET, PETG
  - Cyclo-olefin copolymer (COC)
PACKAGING: Closures

- Plastic - wadless or lined, CR (child resistant), CT (continuous thread), snap fit
- Metal - screw, ROPP
- Liner – cork, pulpboard, EPE
  - product contact materials/facings: PVDC, Saran, Saranex, Melinex, EPE, Vinyl, Foamed PVC
- Induction heat seals
PACKAGING: Solid Dose – Thermoform Blister Packs

- **THERMOFORM BLISTERS**
  - plastic base web
  - blister formed with aid of heating
  - low to high barrier

- **Lidding Foil** – typically 20 micron Al
  - Overlacquer
  - Print
  - Aluminium
  - Primer
  - Heat seal lacquer

- **Base Film** – e.g. PVC, PVC-PVDC, PVC-PE-PVDC, PVC-Aclar®
  - PVC or PVDC
  - PVC or Aclar®

**Product contact materials:**
- For PVC alone or PVC-Aclar® = PVC
- For PVC-PVDC = PVDC
- For Lid foil = heat seal lacquer
PACKAGING: Solid Dose – Cold Form Blister Packs

**COLD FORM BLISTER**
- blister formed mechanically (no heat)
- high barrier

Lidding Foil – (as before)

Foil Laminate Base – e.g. OPA-Al foil-PVC, or OPA-Al foil-PP

Product contact materials:
- For base = PVC (or PP)
- For lid foil = heat seal lacquer

- PVC (may be PP)
- Primer/Adhesive
- Aluminium foil
- Primer/Adhesive
- OPA Film
PACKAGING: Solid Dose – Tropicalised Blister Packs

TROPICALISED BLISTER
- thermoform blister plus cold form tray
- High barrier before use
- once tray opened, in-use life determined by primary thermoform blister

Lidding Foil – (as before)

Film – e.g. PVC, PVC-PVDC

Foil Laminate – e.g. OPA-Al foil-PVC

Product contact materials:
- For PVC alone = PVC
- For PVC-PVDC = PVDC
- For Lid foil = heat seal lacquer
Key Regulatory Guidance - China


Chapter VI: Control over Drug Packaging

Article 44 Immediate packaging materials and containers used by drug manufacturers

Article 46 The package, label and insert sheet of a drug

Article 47 The immediate packaging materials and containers, used by medical institutions for dispensing pharmaceutical preparations, as well as the labels and insert sheets
Key Regulatory Guidance - US

Guidance for Industry, Container Closure Systems for Packaging of Human Drugs and Biologics

Guidance for Industry, Changes to an Approved NDA or ANDA
CPMP/QWP/4359/03 – Guideline on Plastic Immediate Packaging Materials - specific to plastics only

Guideline on Dossier Requirements for Type 1A and Type 1B Notifications

KEY POINT TO NOTE
EU does NOT have a consolidated container/closure guideline (cf FDA)
**EXTRACTABLES and LEACHABLES: Definitions**

- **Extractables**
  - Compounds that can be extracted from packaging (i.e. elastomeric, plastic components or coating of the container and closure system) when in the presence of selected solvent or process.

- **Leachables**
  - Compounds that leach from packaging as a result of direct contact with the formulation of the drug product and thus could potentially be dosed to a patient.
  - Can also get interaction with a product component to produce an impurity that requires stability monitoring.
Past Examples of Leaching Issues

- Polyaromatic hydrocarbons (PAH) detected in CFC-filled MDIs (c.1990)
  - Prompted the first concerted efforts to look for leachables in MDIs

- Vanillin detected in solutions for inhalation packed in LDPE containers
  - Source: migration through LDPE container wall from cardboard outer packaging. Protective Al foil laminate overwrap introduced.

- Di-ethylhexyl phthalate (DEHP)
  - Plasticizer in PVC; detected, for example, in TPN fat emulsions probably via infusion tubing set
  - Neonates have particular sensitivity to DEHP
EXTRACTABLES and LEACHABLES: Considerations

**Clinical concerns:**
- Demonstration of safety for both acute and chronic administration
- Protecting a potentially sensitive, compromised (especially paediatric) patient population

**Regulatory requirements:**

**Extractables:** must control the quality of packaging materials through having a robust relationship with suppliers, e.g. change control.

**Leachables:** stability package tailored to product/pack after suitable risk assessment to identify focus areas – stability data required for the long-term storage condition and under accelerated storage conditions for drug product/pack combination to cover the stated shelf-life

- Consistency in materials/components (Specifications, DMFs)
- Control of packing material and product manufacture
- Control for unintended contaminants
There is a business need to simplify and smarten the process of pack selection – there is such a large range of packs and materials to choose from. Principles and benefits are:

- A preferred range of pack/material options to be selected and used for new products
- Well tested and understood materials of required consistent quality
- Options agreed between R&D and factory
- Identical global materials
- Fully aligned with Procurement sourcing strategies
- Secure/robust sourcing and strong relationship with suppliers
- Minimised R&D resource
- Supports supply site transfers (like for like; identical)
- Facilitates the adoption of “Q8 principles” for container closure systems
**Hierarchy of choice based on product stability**

- Material should preferably be opaque white unless clear is a specific market requirement (e.g. US, Japan)
- Aclar® should be restricted to applications where cold form is not technically or commercially acceptable due to product or pack size, i.e. larger products
Simplified Packaging Strategy: Bottles and Closures

- Reduction of complexity
- Standardisation and rationalisation of components
- Reduced number of change-overs at factory sites
- Reduction in resource demand
- R&D, Pack Dev, Procurement, Sites use ‘off the shelf’ solution for majority of products.
- Flexibility across factory sites without increased Regulatory activity.
- Risk Mitigation
- Commercial Leverage

Current

Future

Reduced Complexity
Maintaining Flexibility
Phase I – FTIH & Phase II Clinical Supply

Objective:
- Selection of simple packs (and maybe dosage forms) for clinical supply – neither pack nor dosage form may be representative of final commercial product

Strategy:
- Aim to use limited range of standard, well-characterised packs, e.g.
  - HDPE bottles for solid dose forms
  - Type 3 glass vials for reconstitutable powders
  - Diskhalers for inhaled powders
- Pack selection is supported by stability testing for each product
- Packs and materials chosen to ensure pharmacopoeial and regulatory compliance is well established
Phase II – III, Commercial Pack Development

**Objective:**
- Identification, development and testing of commercial pack options

**Approach:**
1. Identify Pack Options
2. Material Selection & Testing
3. Development Stability Testing
4. Controls Defined
5. Pack Selection
6. Pivotal Stability Testing
1. Identify Pack Options

- **Product profile** for target territories, e.g. dosage form, clinical requirements, target patient population
- **Product protection** needs, e.g. moisture & gas sensitivity, thermal stability, photostability, chemical compatibility, volatiles in formulation, etc.
- **Commercial requirements**, e.g. market presentation, pack sizes, market specific needs, patient handling needs

2. Material Selection & Testing

- Maximise pack and product knowledge and understanding and achieve commercial efficiency by using a limited range of “first intent”, **preferred pack materials**, wherever possible
- **Product contact materials** chosen to comply with global and local regulations
- Chemical characterisation and toxicological assessment of **extractables and leachables**
3. Development Stability Testing

- Development stability testing used to:
  - Explore and understand stability* and predict shelf-life in selected pack option (* product & pack)
  - Confirm product protection achieved or the need for more protective packs
  - Identify and explore pack/product interaction (NB: packs can degrade as well as drug product)
  - These are key data used to make a final pack selection

4. Controls Defined

- Data from material and product testing used to identify critical quality and process attributes for pack and packaging process:
  - Need for RH or headspace controls during packing
  - Seal integrity testing
  - Manufacturing controls/specifications for pack components
**5. Pack Selection**

- Data from the previous steps, together with the clinical, patient, commercial and manufacturing requirements, are used to identify and agree the intended market packs.

**6. Pivotal Stability Testing**

- **Pivotal stability testing** conducted in the selected markets packs, to:
  - Confirm compatibility and product stability
  - Generate data to support product registration submission
Phase 3 - Launch

Between Phase 3 and Launch

- Secondary packaging is defined
  - NB: if needed for product protection, this will be defined with the primary pack and included in pivotal stability

- Define market presentations, graphics, patient information leaflets, supplementary dosing devices

- Conduct line, engineering and technical trials on pack components and equipment

- Conduct any necessary validation of packaging processes
Pack Changes?

- **Recommended aim:**
  - to avoid pack changes between pivotal stability and launch by ensuring a Quality-by-Design (QbD) approach to pack selection and understanding of product stability and packaging.

- **However, changes can occur at late stage due to, for example...**
  - Unpredictable outcome in pivotal stability assessment
    - Newly identified impurities
    - Requirement for tighter specification limits

- **These tend to drive need for more protective packs, e.g.**
  - Inclusion of desiccant in bottle packs
  - Need for higher barrier (e.g. foil/foil) blister packs

**By use of a QbD strategy, there is a thorough understanding of materials used that will minimise impact of change and enable ready availability of well characterised alternative pack options.**
Summary

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  – Bottles and Closures
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  – Extractable & Leachables

• Packaging Development considerations through to Product Launch
THANK YOU!
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AI</td>
<td>Aluminium</td>
</tr>
<tr>
<td>API</td>
<td>Active</td>
</tr>
<tr>
<td>BFS</td>
<td>Blow-Fill-Seal</td>
</tr>
<tr>
<td>CMC</td>
<td>Chemistry, Manufacturing and Controls</td>
</tr>
<tr>
<td>COC</td>
<td>Cyclic Olefin Copolymer</td>
</tr>
<tr>
<td>CR</td>
<td>Controlled Release</td>
</tr>
<tr>
<td>DEHP</td>
<td>Diethylhexyl Phthalate</td>
</tr>
<tr>
<td>DMF</td>
<td>Drug Master File</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>EPE</td>
<td>Expanded Polyethylene</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (US)</td>
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<tr>
<td>FFS</td>
<td>Form-Fill-Seal</td>
</tr>
<tr>
<td>HDPE</td>
<td>High Density Polyethylene</td>
</tr>
<tr>
<td>LDPE</td>
<td>Low Density Polyethylene</td>
</tr>
<tr>
<td>MDI</td>
<td>Metered Dose Inhaler</td>
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# Glossary of Abbreviations (2)

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>OPA</td>
<td>Oriented Polyamide</td>
</tr>
<tr>
<td>OTR</td>
<td>Oxygen Transmission Rate</td>
</tr>
<tr>
<td>PET</td>
<td>Polyethylene Terephthalate</td>
</tr>
<tr>
<td>PETG</td>
<td>Polyethylene Terephthalate Glycol</td>
</tr>
<tr>
<td>PP</td>
<td>Polypropylene</td>
</tr>
<tr>
<td>PVC</td>
<td>Polyvinyl Chloride</td>
</tr>
<tr>
<td>PVDC</td>
<td>Polyvinylidene Chloride</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and Development</td>
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<tr>
<td>RH</td>
<td>Relative Humidity</td>
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<tr>
<td>RFID</td>
<td>Radiofrequency Identification</td>
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<td>ROPP</td>
<td>Roll On Pilfer Proof</td>
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<td>Rest of World</td>
</tr>
<tr>
<td>TPN</td>
<td>Total Parenteral Nutrition</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>WVTR</td>
<td>Water Vapour Transmission Rate</td>
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