Challenges and opportunities to include patient centered design in industrial drug development

Dr. Leonie Wagner, Small Molecule Pharmaceutical Development, F. Hoffmann-La Roche
Outline

☐ An industry in transition
  - The new pharmaceutical R&D paradigm
  - Challenges & Opportunities

☐ Re-imagining drug product development targets – a CMC perspective
  - QTPP within the framework of patient-centricity
  - Why do we need to re-visit existing standards

☐ EMA vision & reflections industrial drug development
  - Implications on Drug Product design – Administration & adherence
  - Examples

☐ Incentives and operating model in the new world

☐ Conclusions & Outlook
An industry in transition

- The new pharmaceutical R&D paradigm
- Challenges & Opportunities

Re-imagining drug product development targets – a CMC perspective

- QTPP within the framework of patientcentricity
- Why do we need to re-visit existing standards

EMA vision & reflections industrial drug development

- Implications on Drug Product design – Administration & adherence
- Examples

Incentives and operating model in the new world

Conclusions & Outlook
An industry in transition
Challenges and Opportunities

**Projects**

- Attrition: Current model >90% → Future state ↓
- Development time: Current model +8y → Future state ↓↓
- Number of patients: Current model 1000x → Future state ↓↓

**Value proposition**

- Improved target elucidation
- Accelerated regulatory pathways
- Niche indications, disease differentiation

- Speed to clinic & market
- ▼ Patient population = ? Product volume
- **PRODUCT INDIVIDUALIZATION** (dose flexibility)
Challenges and opportunities 2/2

Opportunities

- Invest in specialized technologies
- Implement strong patient focus
- Implement life-cycle management as default
An industry in transition
- The new pharmaceutical R&D paradigm
- Challenges & Opportunities

Re-imagining drug product development targets – a CMC perspective
- QTPP within the framework of patient-centricity
- Why do we need to re-visit existing standards

EMA vision & reflections industrial drug development
- Implications on Drug Product design – Administration & adherence
- Examples

Incentives and operating model in the new world

Conclusions & Outlook
Back to the drawing board

Re-imagining (Q)TPP in a patient-centric drug product development world

TPP* is expected to have a clear product focus aligned with the disease & patient needs

Refinement to TPP elements

Age distribution & posology
Adherence & administration
Disease specific attributes

Implications on QTPP

Formulation: Concept, size, dosing flexibility
Packaging: Ease of handling & protection
Device: Intuitive, accuracy & administration ease

*Concept as described in FDA draft guidance “Target Product Profile — A Strategic Development Process Tool” (March 2007):
De novo or déjà vu?

Inspirations & lessons learnt in pediatric development

**QTPP adult formulation**

<table>
<thead>
<tr>
<th>QTPP Element</th>
<th>Target</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of Administration</td>
<td>Oral, Ykg, with or without food</td>
<td>To ensure compliance of patients, efficacy, and safety.</td>
</tr>
<tr>
<td>Dosage Form</td>
<td>Immediate-release capsules</td>
<td>Immediate release design needed to meet label claims.</td>
</tr>
<tr>
<td>Dosage Strengths</td>
<td>( x ) mg and ( z ) mg</td>
<td>To achieve required efficacy and, for the ( x ) mg strength, allow for dose reduction and/or administration in patients unable to swallow a capsule, as necessary.</td>
</tr>
<tr>
<td>Drug Substance</td>
<td>API, as desired solid form</td>
<td>To ensure sufficient bioavailability, efficacy, safety, and quality. Used in pivotal clinical studies and shown to provide adequate dissolution, bioavailability and stability.</td>
</tr>
</tbody>
</table>

**QTPP pediatric formulation**

<table>
<thead>
<tr>
<th>Drug Product Attribute</th>
<th>Target</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>all conditions included in the category of ( XY ) and ( Z )</td>
<td>TTP.</td>
</tr>
<tr>
<td>Patient population</td>
<td>children (from birth up to children able to swallow capsules) and adults not able to swallow capsules</td>
<td>Patient convenience and compliance.</td>
</tr>
<tr>
<td>Environmental Settings</td>
<td>Ambulant in hospital</td>
<td></td>
</tr>
<tr>
<td>Drug Substance</td>
<td>API, as desired solid form</td>
<td>To ensure sufficient bioavailability, efficacy, safety, and quality.</td>
</tr>
<tr>
<td>Dosage form</td>
<td>Multiparticulate film coated solid dosage form</td>
<td>Patient compliance: Multiparticulate solid dosage forms can be coated to achieve taste masking and are easy to swallow. The multiparticulate solid dosage form is presented in easy to open capsules for administration with soft food or liquid (as sprinkle over food).</td>
</tr>
</tbody>
</table>

**Could this serve as a blueprint for a patient-centric drug product QTPP?**
## De novo or déjà vu?

### Template of a patient-centric QTPP (1/2)

<table>
<thead>
<tr>
<th>Product description</th>
<th>Related to Patient centricity</th>
<th>Differentiators</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Disease focus</td>
<td>▶ Age-specific requirements in terms of dosing flexibility?</td>
</tr>
</tbody>
</table>
| **Route of administration/ Dosing frequency** | e.g. oral, parenteral         | ▶ Can be associated with age or patient specific requirements, e.g. swallowability/palatability  
▶ Sticking to a specific dosing regimen could be difficult for certain populations |
| **Dosage form**           | e.g. film-coated tablet, softgel, hard capsule, pen for autoinjection etc. | ▶ Could be critical with regards to size of dosage form, complexity (e.g. autoinjector) |
| **Strength**              | Efficacy related              | ▶ Based upon clinical efficacy studies  
▶ Barely dose levels are monitored in older populations with reduced DMPK functionalities (safety in terms of over-/under-dosing) |
<p>| <strong>Appearance</strong>            | Product identification and quality aspects | ▶ Should help to support compliance, avoid medication errors (colour, shape, size, imprinting) |
| <strong>Size</strong>                  | Product identification and compliance (beside technical requirements) | ▶ Critical in case of too large dosage forms (swallowability) |</p>
<table>
<thead>
<tr>
<th>Product description</th>
<th>Related to Patient centricity</th>
<th>Differentiators</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Excipients</strong></td>
<td>Safety of patients</td>
<td>► Certain excipients represent challenge in specific patient populations</td>
</tr>
<tr>
<td>Pharmacopeial</td>
<td>Safety of patients</td>
<td>► Drug product quality aspects in relation to patients safety</td>
</tr>
<tr>
<td>compliance</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mechanical strength</strong></td>
<td>Acceptability (mechanical integrity during usage)</td>
<td>► E.g. tablets should have sufficient mechanical stability to remove from blisters, breakability of tablets with score</td>
</tr>
<tr>
<td><strong>Container closure system</strong></td>
<td>Sufficient stability at patients homes, acceptability</td>
<td>► Strong impact on acceptance (e.g. senior friendliness of primary packaging) and drug product storage</td>
</tr>
<tr>
<td>Degradants and Impurities</td>
<td>Safety of patients</td>
<td></td>
</tr>
<tr>
<td><strong>Shelf life</strong></td>
<td>Sufficient stability at patients homes</td>
<td>► Drug product storage at patients homes</td>
</tr>
</tbody>
</table>
### Relationship between physiology and PK characteristics

**Example: Changes in physiology in geriatric populations**

<table>
<thead>
<tr>
<th>Physiological parameter changes</th>
<th>Possible PK effects (ADME)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastric physiology (Absorption)</strong></td>
<td></td>
</tr>
<tr>
<td>☐ Gastric pH increased (i.e. on top of intake proton pump inhibitors)</td>
<td>Reduced absorption of salts of basic compounds (same effects as with proton pump inhibitors)</td>
</tr>
<tr>
<td>☐ Gastric emptying delayed</td>
<td></td>
</tr>
<tr>
<td>☐ Absorption surface area reduced</td>
<td></td>
</tr>
<tr>
<td>☐ Gastrointestinal motility reduced</td>
<td></td>
</tr>
<tr>
<td>☐ Reduced splanchnic flow</td>
<td></td>
</tr>
</tbody>
</table>

| **Body fat/ water ratio (Distribution)** |                          |
| ☐ Body fat compartment increased | Higher $V_{\text{distr}}$ and $t_{1/2}$ for drugs with high log P |
| ☐ Lean body mass decreased |                          |
| ☐ Total water increased | Plasma concentrations of hydrophilic drugs increased |

| **Metabolism, Elimination** |                          |
| ☐ Serum albumin reduced | Unbound drug fraction in plasma increased |
| ☐ Alpha1-acid glycoprotein increased | Unbound drug fraction of basic drugs in plasma reduced |
| ☐ Hepatic blood flow/hepatic mass reduced | $1^\text{st}$ pass metabolism reduced, phase 1 metabolism impaired |
| ☐ Reduced renal blood flow and GFR | Renal elimination deteriorated |
☐ An industry in transition
  - The new pharmaceutical R&D paradigm
  - Challenges & Opportunities

☐ Re-imagining drug product development targets – a CMC perspective
  - QTPP within the framework of patientcentricity
  - Why do we need to re-visit existing standards

☐ EMA vision & reflections industrial drug development
  - Implications on Drug Product design – Administration & adherence
  - Examples of drug product with patient-centric attributes

☐ Incentives and operating model in the new world

☐ Conclusions & Outlook
Table of contents

1 Introduction .................................................................................................................. 3
2 Discussion .................................................................................................................... 3
  2.1 General considerations ............................................................................................... 3
  2.2 Patient acceptability ................................................................................................. 3
  2.3 Route of administration and dosage form ............................................................... 4
  2.3.1 Preparations for oral use ..................................................................................... 4
  2.3.2 Preparations for dental, gingival, sublingual, buccal, oropharyngeal, oromucosal use 6
  2.3.3 Preparations for use in the eye or ear ................................................................. 6
  2.3.4 Preparations for nasal administration, inhalation and nebulisation ..................... 7
  2.3.5 Preparations for cutaneous and transdermal use ............................................... 7
  2.3.6 Preparations for rectal, vaginal and urethral use ............................................... 7
  2.3.7 Parenteral preparations ...................................................................................... 7
  2.3.8 Administration through enteral feeding tubes .................................................... 7
  2.3.9 Modifications to facilitate intake or to lower the dose ........................................ 8
  2.4 Dosage frequency .................................................................................................... 9
  2.5 Excipients in the formulation ................................................................................... 9
  2.6 Container closure systems ...................................................................................... 10
  2.7 Devices and technologies ......................................................................................... 10
  2.8 (Medicinal) product information ............................................................................ 11
  2.9 Medication management ......................................................................................... 12
3 Conclusions .................................................................................................................. 12
4 References ................................................................................................................... 13

Annexes ......................................................................................................................... 14

18 May 2017,
EMA/CHMP/QWP/292439/2017 Rev.: 4.0

Reflection paper on the pharmaceutical development of medicines for use in the older population

Draft
EMA reflection paper (draft) on industrial drug development & Vision

“...This reflection paper is intended to communicate the current status of discussions on the pharmaceutical development of medicines that may be used in the older population, and to invite comments on the topics addressed. The paper is not intended to provide regulatory or scientific guidance, although it may contribute to any such development in the future.”

Analogous to pediatric development requirements & strong focus on patient acceptability

Routes of administration (i.e. oral, parenteral, enteral feeding tubes) and dosage forms (i.e. oral solids, liquids, ODTs etc.) are described detailed

Modifications to facilitate intake or to lower the dose are discussed

Excipients, dosing frequencies, container closure systems
“What is the point of developing innovative medicines if our patients cannot take it?”

- Taste/mouthfeel/aftertaste → palatability
- Ease of swallowability
- Pill burden
- Safe, reliable and comfortable administration mode
Drug product design to improve administration

**Swallowability** | *(Oro)*dispersible tablets

**Manufacturing technology**
- Lyophilization (drug embedded in sugar & polymer)
- Direct compression (taste masked particles)
- Heat processing (e.g. hot melt extrusion)

**Technical challenges**
- Taste Masking & mouth feel enhancement
- Disintegration time
- Physical stability

**Features**
- **Administration:** Easy to swallow. Alternatively, dosed as suspensions
- **Intended patients:** All age groups, including those with swallowing difficulties
- **Specific requirements:** Standard tablet with rapid disintegration (<3 minutes) and fineness of dispersion spec.

Source: compendium.ch

Source: https://www.itc.gov.hk/ch/
Drug product design to improve administration

Swallowability| Multiparticulates administered as sprinkle over food

**Features**
- **Administration:** With soft food (e.g., pudding) or in beverages (creating a suspension)
- **Intended patients:** Typically for pediatrics, but also for geriatrics
- **Specific requirements:** FDA guidance on multiparticulates labeled for administration via sprinkling: size 2.5 mm

**Manufacturing technology**
- Standard manufacturing processes
- Powders, granules, pellets in sachets or capsules → ‘sprinkles’
- Coated or uncoated (taste masking)

**Technical challenges**
- Taste-masking
- Food compatibility
- Administration to young children & via NG tubes

---

Drug product design to improve administration

Swallowability | Multiparticulates administered via drinking straw

**Features**

- **Administration**: Dry medication in form of film-coated taste masked pellets delivered in a controlled dose via co-administration with a liquid (drink)
- **Intended patients**: All age groups, including those with swallowing difficulties
- **Specific requirements**: Same requirements as dispersible tablets

**Manufacturing technology**

- Non-standard primary packaging
- Standard manufacturing of granules, pellets
- Coated or uncoated (taste masking)

**Technical challenges**

- Physical stability of micropellets in straw
- Integrating dose flexibility into design > commercialization
- Food compatibility

---


Source: https://www.raumedic.com/
Drug product design to improve adherence

Other approaches

- Fixed dose combination drug products (FDCs)
- Long-acting active ingredients
- Sustained release/extended release formulations when appropriate
- Alternative routes of administration (consider cost)
- Non-pharmacologic alternatives or interventions
Human factor studies and device interface

Human Factors of Device Use

HF CONSIDERATIONS

- USERS
- USE ENVIRONMENT
- DEVICE / INTERFACE

OUTCOME

- SAFE & EFFECTIVE
- UNSAFE, INEFFECTIVE

- Are patients/caregivers able to administer the medication?
- Does the design/environment allow safe administration

Should this also be applied to packaging?

Swiss Med Forum. 2008;08(09):176

An industry in transition

- The new pharmaceutical R&D paradigm
- Challenges & Opportunities

Re-imagining drug product development targets – a CMC perspective

- QTPP within the framework of patientcentricity
- Why do we need to re-visit existing standards

EMA vision & reflections industrial drug development

- Implications on Drug Product design – Administration & adherence
- Examples of drug product with patient-centric attributes

Incentives and operating model in the new world

Conclusions & Outlook
For drugs with blockbuster revenue (more than $1 billion annually), there is a clear benefit: With trials costing up to $25 million and average industry profit margins of 23 percent, blockbuster manufacturers have significant incentives: 300 million in value per drug against $25 million in trial costs.

However, for drugs with annual sales below $100 million, the incentives seem to be less alluring given the complexities and risks of conducting pediatric trials.

*Source: Nate Aumock, Jeff Smith, Seth Townsend, Do Incentives Drive Pediatric Research?, McKinsey Center for Government October 2013*
Pediatric clinical trial activity, for example, continues to be strong: 69 trials were reported at ClinicalTrials.gov in the first seven months of 2012 alone.

Since 1997, the additional six months of exclusivity has driven $71 billion in incremental revenue.

The top ten drugs garnered 31 percent of the total. The top ten companies accounted for 75%
Conclusions & Outlook

- Pharma industry is beginning to move away from the old blockbuster paradigm – new paradigm needs re-thinking of old development model

- The concepts of TPP, QTPP and QbD have proved to be potent in developing products of good quality. They should be further refined to integrate also «target patient product profile»

- Disease specific drug delivery concepts will allow to increase a patient-centric focus (see examples)

- The new EMA draft reflection paper represents an important step towards modern patient-centric drug development

- Key-learning from pediatric drug development could be used as a blueprint on patient-centricity

- Acceptability by the customer/patient and adherence to therapeutic regimes will drive the success of new drug products and needs to be systematically evaluated in development
Acknowledgments

• Dr. Carsten Timpe
• Dr. Sid Mujumdar
• Dr. Aniko Szepes
Doing now what patients need next