Moving multiparticulates from pediatric formulation to patient centric drug product design
What is patient centric product design?

The objectives of drug product development

- Quality
- Safety
- Efficacy => Effectiveness

Definition of patient centric pharmaceutical drug product design

The process of identifying the comprehensive needs of individuals or the target population and utilizing the identified needs to design pharmaceutical drug products that provide the best overall benefit to risk profile for that targeted patient population over the intended duration of treatment.
Target Product Profile for Pediatrics/Geriatrics

For example:
- Meet target release profile
- Provide good, consistent absorption
- Excipient selection and level

Performance and Safety

Patient Profile

Dosage Form Selection

For example:
- Taste/odor
- Identification
- Palatability
- Usability
- Acceptability

Optimal area:
High probability that the final dosage form will meet all needs

For example:
- Formulation / dosage form compatibility
- Scalability, packaging
- Usability, storage, convenience, permits dosing accuracy

FDA & EMA regulations require pediatric formulations to be developed for the majority of new drug applications.

The EMA has published a Reflection Paper for the older population in 2017, equivalent to the pediatric one in 2006.
Dosage Form selection

Key targets for the special targeted patient population:

- Dry solid stage (portability, storage, stability)
- Dose flexibility (ease of dose adjustment and titration)
- Patient needs (swallowing, taste, identification, usability, etc)
- Standard manufacturing equipment (global manufacturing, variable product demand)

Orally Disintegrating Tablets (ODTs) — Sprinkle Capsules — Sachets — Suspensions — Novel Devices

Coated LMP Capsules at 80% fill volume
Technology Selection
Distinguished by Particle Size & Processes

Rank technology options against criteria for:

- the spectrum of patients,
- the desired dosage form(s),
- and the drug properties

<table>
<thead>
<tr>
<th>Technology Description</th>
<th>Lipid Multiparticulates</th>
<th>Spray Layered Dispersions</th>
<th>Pellets</th>
<th>Mini Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP Image</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Process(es)</td>
<td>Melt Spray Congeal</td>
<td>Fluid Bed Coating &amp; Drying</td>
<td>Wet Granulation &amp; Spheronization</td>
<td>Dry Granulation &amp; Compression</td>
</tr>
<tr>
<td>Nominal Particle Sizes</td>
<td>0.1 – 0.4 mm</td>
<td>0.2 – 1.0 mm</td>
<td>0.5 – 1.5 mm</td>
<td>1.5 – 3 mm</td>
</tr>
<tr>
<td>Typical Drug Loadings</td>
<td>5 – 60%</td>
<td>1 – 40%</td>
<td>10 – 80%</td>
<td>10 – 80%</td>
</tr>
</tbody>
</table>
Technology Selection & Formulation Groundwork

Lipid Multiparticulate Example

Selecting correct technology for the problem statement and target product profile is critical to successful programs

- Define drug delivery needs and identify the appropriate attributes of the drug to get started
- Identify the right formulation approach within a technology for speed and risk-based decisions during development
LMP Process Train for MSC Based Applications

- Extrusion
- Melt Tank
- Melt Feed
- MSC
- Sieve
- Fluid Bed
- Encapsulation

Used during functional coating (Not required for non-coated LMPs)

PSD Control is Important for Coating Uniformity

Coated LMP Core

Oral pH

Gastric pH
LMPs Atomization & Congealing

Physical Situation

- Fundamental understanding of atomization drives optimization, scale-up and process robustness
- Proper atomization allows for precise control of particle size distribution

Melt Atomization

• Heat transfer rates control the solidification time and physical form of the formulation

Heat Transfer & Time of Flight
How It Works: Well Understood Release Mechanism

Aqueous diffusion through a porous matrix
Network characterized by a high density of drug crystals surrounded by a lipid-based matrix, but interconnected by small, water-soluble pores
Release governed by water permeation, dissolution of the pore former & drug within the matrix, and diffusion of the drug from the particle

Physical Situation / Model

Dissolution Characteristics
Dissolution as a Function of Time

5-minute soak (15% released)

10-minute soak (24% released)

15-minute soak (32% released)

30-minute soak (52% released)

60-minute soak (75% released)

All Images 300x magnification.
Early Feasibility Development Program

Timeline

- **Month 1**
  - Approved SOW
  - Project information from Client

- **Month 2**
  - Project start
  - Formulation Space Go/No-go
  - Prototype Manufacture Go/No-go

- **Month 3**
  - Stability Start Go/No-go

- **Month 4**
  - Initiate CTM Readiness and CTM SOWs

**Project Initiation**
- Task A
- Fit-for-purpose analytical methods
- Task B
- Formulation Screening
- Task C
- Prototype manufacture
- Task D
- Informal stability
- Task E
- CTM readiness SOW

**Immediate Release LMPs**

Formulation feasibility demonstrated in less than 4 months with less than 50 grams of API

**Lonza Pharma & Biotech | DDF 2018**
Multiparticulate Technology Flexibility
Commercial Product Examples

- **Suspensions & Sprinkles**
  - Taste masking + ER
    - **Zmax**
  - Pediatric sachet
    - **Lamisil**

- **Capsules**
  - Pulsatile release
    - Ritalin LA®
  - Extended release
    - Detrol LA®
  - Solubility enhanced
    - Sporanox®
  - Solubility enhanced ER
    - Focalin XR®
  - Fixed dose combination
    - Nuedexta®

- **Mixed & ODTs**
  - Delayed release
    - Nexium®
  - Orally disintegrating + DR
    - Prevacid®
Univ.-Prof. Dr. Sven Stegemann  
Lonza  
Bornem (Belgium)  
e-mail: sven.stegemann@lonza.com  
Mobile: +49 172 6054869