TESTING AND RELEASE STRATEGIES FOR MINITABLETS

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The term “minitablets” commonly refers to compressed tablets with size smaller than typical tablets.

“Granules, Oral Granules, Sprinkles, Microtablets”

- No regulatory guidelines that define minitablets, the term has been used to describe tablets with diameters between one to four millimeters (mm).
- Oral dosage forms smaller than 2.5 mm → oral granules
  - Many minitablet products are focused at this size range, to take advantage of the potential flexibility in dosage form administration (e.g. mixed with soft foods).
## Few Examples of Minitablet Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Molecule</th>
<th>Indication</th>
<th>Product presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalydeco®</td>
<td>Vertex</td>
<td>Ivacaflor</td>
<td>Cystic fibrosis</td>
<td>~2 mm mini-tablets in stick pack</td>
</tr>
<tr>
<td>Lamisil®</td>
<td>Novartis</td>
<td>Terbinafine</td>
<td>Antifungal</td>
<td>~2 mm mini-tablets in stick pack</td>
</tr>
<tr>
<td>Orifil Long®</td>
<td>Desitin</td>
<td>Valproate</td>
<td>Epilepsy</td>
<td>~2 mm mini-tablets in capsules and stick pack</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Desitin</td>
<td>Levetiracetam</td>
<td>Epilepsy</td>
<td>~2 mm mini-tablets in stick pack</td>
</tr>
<tr>
<td>Desitin</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pancrease® MT10/MT20</td>
<td>McNEIL</td>
<td>Pancrelipase</td>
<td>Pancreatitis, cystic fibrosis</td>
<td>~2 mm mini-tablets in capsules</td>
</tr>
</tbody>
</table>
Opportunities Offered by Minitablets

Compliance

- Accurate and flexible dosing -> Reduce discards!
- Reduce user errors
- Less complicated human factor studies

Patient Friendly and Personalized Medicine

- Palatability (Easy to swallow and enhance palatability when mixed with food and drink
- Dose flexibility, unit dose options
- Multiple dose unit options which can combine different release kinetics/API

Production & Stability

- Utilize standard tablet presses/multiple-tip tooling, Coated or uncoated minitablets
- Ability to separate API interactions and increase palatability
- Various product presentations: Ease of capsule or sachet filling or desiccated bottles
Challenges Offered by Minitables

Customized Delivery System

Each Dose = Lower Production Volume

One bulk minitablet batch split into different product images

- More complex relationships for batch histories
- Potentially high analytical burden (testing & sample)
- Image proliferation

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Traditional vs Minitablet Batches?

- **Bulk Minitablet lot**
  - 10 minitablets
  - 50 minitablets
  - 100 minitablets

- **One/two final product image**
  - Dose 1
  - Dose 2
  - Dose 3
Why Not Traditional Testing?

Goal is to demonstrate product quality

Traditional testing = Repeat testing

- Repeat testing (e.g., same granule batch in different capsule batches)
- Analytical testing and quality release burden on several small scale batches (significantly higher numbers of tests)
- Utilizing a significant portion of the batch just for analytical testing

Increased supply chain flexibility - Lower volumes, Personalized medicine

- Make-to-order for final step:
  - Faster turnaround from demand to delivery
  - Unclear forecasts
  - Image proliferation

Many CQAs determined by the compression/coating steps
Collect industry/regulatory input on efficient product release for minitablets/granules by conducting testing at the right stage to ensure product quality

CASE STUDY

- **Product:** IR oral granule – Single entity product
- **Dosage form:** Capsules intended for sprinkling (could be stick packs/sachets too)
- **Quality attributes:** Identity, Content uniformity, Assay and Degradation products, Dissolution, Water activity, Microbial limits

- **Terminology used here:**
  - Oral granules = minitablets
  - Bulk minitablets = coated/uncoated minitablets prior to encapsulation
  - Unit dose = minitablets in capsules with varying counts based on the dose.
    - Lowest dose = 10 count
    - Highest dose = 100 count
Example Manufacturing Steps

Formulation Blend → Compression → Coating → Minitablets in Bulk

- **Encapsulation Unit Dose 1 (10)**
  - Each capsule contains 10 count minitablets

- **Encapsulation Unit Dose 2 (50)**
  - Each capsule contains 50 count minitablets

- **Encapsulation Unit Dose 3 (100)**
  - Each capsule contains 100 count minitablets

*Bulk minitablet manufacture and encapsulation are occurring at the same site*
3 Possible Approaches

1. Conduct release testing only after encapsulation - no testing of bulk minitablets

2. Conduct testing at bulk minitablet step AND for each unit dose after encapsulation

3. Hybrid approach:
   a) Conduct tests on bulk minitablets for CQAs that are not impacted by encapsulation step.
   b) Limited tests at minitablets in capsules