Exploring the Drug Substance/Drug Product Interface—Opportunities to Innovate Toward Enhanced Performance and Efficiency

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Problem Statement

• Problem Statement:
  – Currently, the space between the DS and DP boundaries exists as a relative “No Man’s Land”, filled with both real and perceived obstacles that limit pursuit of potentially high-value options that can improve quality and efficiency

  ![Image of a no man's land sign]

  – Novel approaches to “integrated” drug substance (DS) and drug product (DP) production that are inconsistent with the traditional definition of the DS and DP are rarely pursued…and those that are tend to be viewed as carrying high regulatory risk
Opportunity

• Exploit API/Pharm synergies at a new porous boundary:
  – Remove constraints around the traditional definition of the DS/DP interface in order to provide a more integrated approach to product development that allows implementation of the true global optimum in terms of process robustness, speed, assurance of supply, and manufacturing efficiency that can be translated to reduced patient cost
  – Establish new technologies that allow the conceived opportunities to be realized
    • Develop particle engineering technologies that straddle the DS/DP interface to rationally design products toward improved cost and quality
    • Target technologies can extend the value proposition of continuous manufacturing
The Challenge—From a Regulatory Perspective

• Integrated strategy challenges the traditional way of thinking about the interface between the API and Pharm components of the final product and its associated filing
  – How do we unshackle from out-dated constraints in order to embrace the opportunities that modern approaches (e.g., PAT/RTR) afford?
  – How do we translate this modernization into improved quality and a positive patient impact?
  – Practical considerations:
    • How would we document and evaluate end-to-end process that seamlessly integrates across the DS and DP interface?
    • Is this…
      – …an evolution (start with “baby-steps” that blur the DS/DP boundary) or
The Challenge—From a Regulatory Perspective

- Is this…
  - …an evolution (start with “baby-steps” that blur the DS/DP boundary) or
  - …a step-change (making the leap to fully continuous “raw materials-in/pills-out” model)?

- Opportunity: proactively develop strategies with Regulatory Agencies to ensure alignment on expectations before moving drug candidates forward under a new paradigm
Anticipated Benefits of Implementing Synergistic DS/DP Options

• Provides opportunity for product cost reduction through:
  1. Elimination of processing steps (crystallization, filtration, drying, dry milling)
     • Avoid logistical challenges associated with potent compound isolation
     • Avoid challenging isolation of small particle size API (nano to micron size)
  2. Elimination of “artificial” constraints on DS quality attributes whose control and measurement add cost (residual solvent levels, API phase purity, etc.).
     • Control CQA’s at the appropriate point in the process
  3. Improved DS and DP processing with potential to shorten processing times and/or improve robustness

• Potential to streamline process development—minimize wasted resources trying to make a clearly non-optimum “traditional” solution work
  – E.g., struggling to deal with the isolation of API phase that experiences phase changes or compromise of physical attributes during isolation
Case Study: Solvate Devolatilization via Hot Melt Extrusion

- **Solvate Benefits**
  - Unique impurity rejection capabilities
  - Robust crystallizations; often favorable low aspect ratio, 3D crystals

- **Processing strategies:** solvate avoidance or processing to meet ICH residual solvent specification constraints
  - Solvent switches to avoid solvating solvent systems
  - Exceptionally long drying times (time cycle impact or capital to debottleneck)
  - Recrystallizations to generate more readily dried non-solvate

For solid dispersions...

- **Strong industrial (non-pharma) precedent for devolatilization in extruders:**
  - Twin screw extruders capable of removing up to ~ 50 wt % volatiles with a multi vent port design
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**Natural opportunity—why aren’t we seizing the opportunity?**
HME Devolatilization Example

- Scenario: API isolated as a heptane solvate
  - Removal of heptane during drying results in a mix of desolvated solvate and amorphous API; amorphous API stable

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Solvate Form I

↓

Desolvated Form I

Heat and/or Shear Stress

Amorphous, T_g = 45°C
```
HME Devolatilization Example

- Scenario: API isolated as a heptane solvate
  - Removal of heptane during drying results in a mix of desolvated solvate and amorphous API; amorphous API stable
  - Removal of final several % of heptane leads to prohibitively long drying cycle time

![Graph showing heptane content vs. total elapsed drying time with a target of <0.5 wt%](graph.png)
HME Devolatilization Example

- Scenario: API isolated as a heptane solvate
  - Removal of heptane during drying results in a mix of desolvated solvate and amorphous API; amorphous API stable
  - Drying from 3% to 0.5% heptane leads to prohibitively long drying cycle time
  - Powder flow into HME depends on ability to granulate during agitated drying
    - Drying to < 3% heptane = risk of compromised physical properties

9PM sample from dryer, Normal granules
11PM sample from dryer, Amorphous lumps present

Robustness/reproducibility risk
Pilot Plant Agitated Drying

Drug Product Issues:
- API with poor flow properties created serious challenges in feeding API at desired rate during HME formulation—inconsistent performance

Solvate Form I
↓
Desolvated Form I
↓
Heat and/or Shear Stress

Amorphous, $T_g = 45^\circ C$

After PPB6

Agitated Filter Dryer

Summix Conical Screw Dryer

After PPB7
Path Forward

• **Options:**
  - Remove heptane to <0.5% during API drying and accept long drying time and need to carefully manage API attributes
  - Deliver API with 3% heptane and devolatilize in HME

• **Heptane removal**
  - Across range of screw speeds, vacuum levels, and starting heptane starting levels, remove 70-90% of heptane
  - Maximum patient exposure of 0.7mg heptane in tablets made with desolvation extrudate
  - 70x below ICH limit of 50mg per day for n-heptane
Spray Drying Solvate vs Anhydrous Example

• Scenario:
  – API isolated as an ethanolate to enable product purification
  – No stable anhydrous or hydrate forms identified
  – Product spray dried to ASD

• Options
  – Deliver solvate and remove EtOH during spray drying
  – Perform final pure precipitation to isolate solvent-free amorphous API
    • Adds a processing step
    • Amorphous isolation often presents filtration and drying challenges

• Why?
  – Fear of the unknown
  – Perceived timeline and regulatory risks
Merck DS/DP Porous Boundary Initiative

- Remove constraints around the traditional definition of the DS/DP interface in order to provide a more integrated approach to product development that allows identification and implementation of the **true global optimum option**.

- In order to reduce the activation energy for implementation and minimize timeline impact if such approaches are selected, proactively establish an implementation plan including:
  - Establishing the key criteria that must be satisfied in order to justify these non-traditional approaches
  - Identifying the critical data that must be generated in order to develop and subsequently file these non-traditional processes
  - Identifying existing and needed internal infrastructure

<table>
<thead>
<tr>
<th>Options</th>
<th>Data Required to Support the Option</th>
<th>Analytical/Quality considerations</th>
<th>Logistical concerns (shipping, eqpt, facilities)</th>
<th>Enabling vs Efficiency?</th>
<th>Enabling in What Manner</th>
<th>Efficiency</th>
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<tbody>
<tr>
<td>Delivering Slurries</td>
<td>Solids are hard to isolate due to (i) filterability, (ii) adverse particle property change upon isolation as a solid, (iii) adverse form change upon drying</td>
<td>Physical stability (in solvent); solvent with low solubility and viable for SD; Solvent volatilization</td>
<td>Particle stability (agglomeration, re-dispersability, ripening); need for stabilization with additives, extraneous level from media milling (e.g., for inhalation)</td>
<td>Establish appropriate stability study protocols (storage/shipping)</td>
<td>Quantification of particle ripening kinetics; slurry settling/resuspen sion (content uniformity); thermal stability studies (T oscillations)</td>
<td>Shipping slurries (cost); storage time; storage conditions (temperature); co-located API/pharm processing; packaging (avoid solids loading change)</td>
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<td></td>
<td>Physical stability (in solvent); solvent with low solubility and viable for SD; Solvent volatilization</td>
<td>Engineering considerations</td>
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</table>

- Physical considerations
- Engineering considerations
- Chemical
- Physical

- Analytical/Quality considerations
- Logistical concerns (shipping, eqpt, facilities)
- Enabling vs Efficiency?
- Enabling in What Manner
- Efficiency

- Eliminated steps
Remove constraints around the traditional definition of the DS/DP interface in order to provide a more integrated approach to product development that allows identification and implementation of the true global optimum option.

In order to reduce the activation energy for implementation and minimize timeline impact if such approaches are selected, proactively establish an implementation plan including:

- Establishing the key criteria that must be satisfied in order to justify these non-traditional approaches
- Identifying the critical data that must be generated in order to develop and subsequently file these non-traditional processes
- Identifying existing and needed internal infrastructure
- Identifying EM partners with the required capabilities (including co-location of API and Pharm manufacturing facilities)
- Establishing functional buy-in to support these non-traditional approaches, particularly from the key analytical and regulatory stakeholders

A natural consequence of blurring this boundary is the formation of a cross-functional API/Pharm technology development effort which would be expected to yield important benefits.
Flexible Particle Engineering Platform

Equipment, Excipients | Intent - Business Impact
--- | ---
High Shear Mixing | 1-5um crystalline API: alternative to jet milling for cost reduction
### Flexible Particle Engineering Platform

**Equipment, Excipients**  | **Intent - Business Impact**
--- | ---
High Shear Mixing  | 1-5um crystalline API:
| alternative to jet milling for cost reduction

| + Polymer and/or Surfactant  | 0.2-1um crystalline API

*When low level of polymer/surfactant as an alternative to media milling*

cPAD (co-Precipitated Amorphous Dispersions):

*Improved COG and supply chain flexibility vs. spray drying as a route to generate solid dispersions*
Integrated DS/DP Particle Engineering

- Enable new particle engineering opportunities that allow **rational design** of multi-component particles providing:
  - Improved product bioavailability
  - Modified release
  - Increased drug loading
  - Enhanced formulation performance: compressibility, flow, etc.
  - Unique product features for increasingly diverse customers
Solid Dispersion Example

Current Approach to Solid Dispersion Drug Product

Generate API molecule → Crystallize → Filter/Dry → Release → Ship

Ship → Release → Secondary Dry → Spray Dry → Dissolve

Blend → Roller Compact → Mill → Blend/Lubricate → Compress

Blurred DS/DP Approach

Generate API molecule → Direct precipitation of amorphous dispersion → Isolate → Release → Ship

Ship → Release → Secondary Dry → Spray Dry → Dissolve

Blend → Roller Compact → Mill → Blend/Lubricate → Compress

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**Solid Dispersion Example**

**Current Approach to Solid Dispersion Drug Product**

1. Generate API molecule
2. Crystallize
3. Filter/Dry
4. Release
5. Ship
6. Ship
7. Release
8. Secondary Dry
9. Spray Dry
10. Dissolve
11. Roller Compact
12. Mill
13. Blend
14. Blend/Lubricate
15. Compress

**Blurred DS/DP Approach with DS/DP Co-location and RTR**

1. Generate API molecule
2. **Direct precipitation of amorphous dispersion**
3. Isolate
4. Release
5. Ship
6. Ship
7. Release
8. Secondary Dry
9. Spray Dry
10. Dissolve
11. Roller Compact
12. Mill
13. Blend
14. Blend/Lubricate
15. Compress
Provocative Question (posed by colleague)

“What if we could co-process all APIs intended for solid oral dosage forms with particle characteristics of the appropriate particle size, good flow and compaction to enable direct compression? Further, the co-processed intermediate would need to take all BCS corners, so enablement would be a requirement. Assuming we can do that across the portfolio, how would this enable the realization of the future state of continuous processing/manufacturing?

Could this (i.e., DC) accelerate the uptake of CP/CM by simplifying and minimizing the process train for early development and seamlessly scale for FMF and supply?”

Does the MIT/Novartis conceptualization start to look less like a pipe dream and more like an achievable aspirational goal?
Closing Thoughts

- Traditionally there is a clear demarcation between drug substance and drug product in terms of process development, release, quality and regulatory aspects.

- Why?
  - Is this actually needed to ensure product quality or simply a consequence of an old system with opportunity for update?

Moving from local optimum to global optimum requires a holistic view
1. Looking across individual UOps/steps
2. Looking across the aggregate DS/DP process

- Is the ultimate realization an end-to-end, fully-integrated DS/DP process? ...are we ready for it?