



3D Printing Pharmaceutical Dosage Forms at Commercial Scale: Aprecia's Journey

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Virtual Workshop on Technical and Regulatory Barriers to Innovations in
Pharmaceutical Manufacturing

First 3DP Pharmaceutical Product Approved by the FDA, Launched in US

- Disintegrates directly in the mouth in seconds with a sip of liquid
Alternate dosing by dispersing in a small amount of liquid in a cup.
('Tablets, for Oral Suspension').
- Same strengths as KEPPRA® tablet

Spritam[®]
(levetiracetam)

ZipDose[®]
TECHNOLOGY

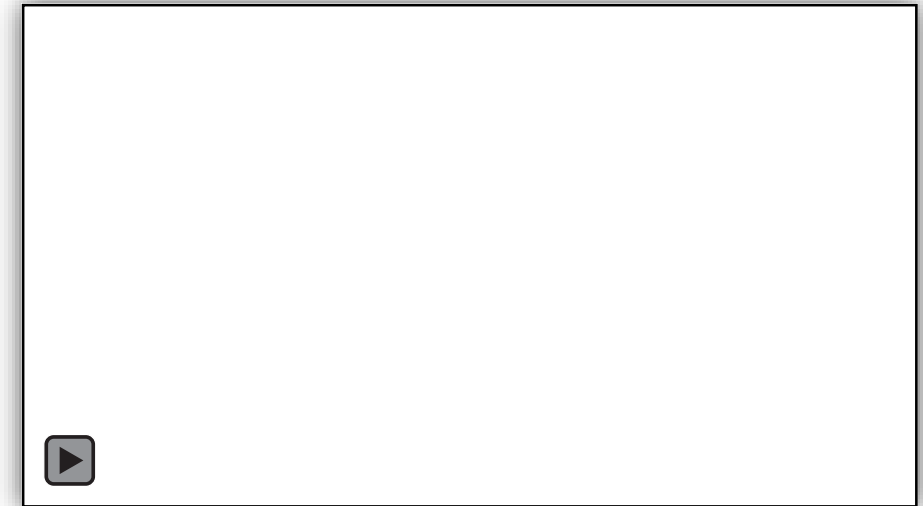


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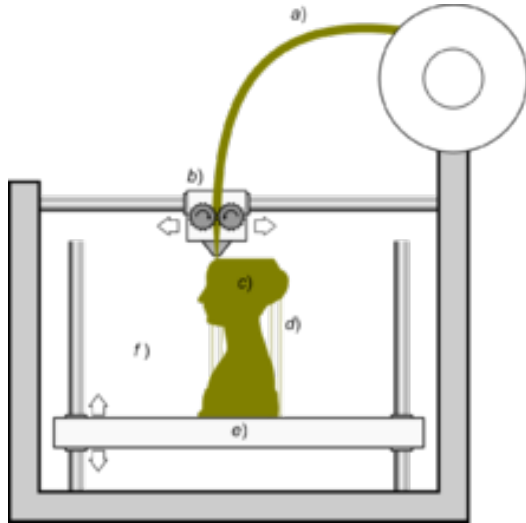
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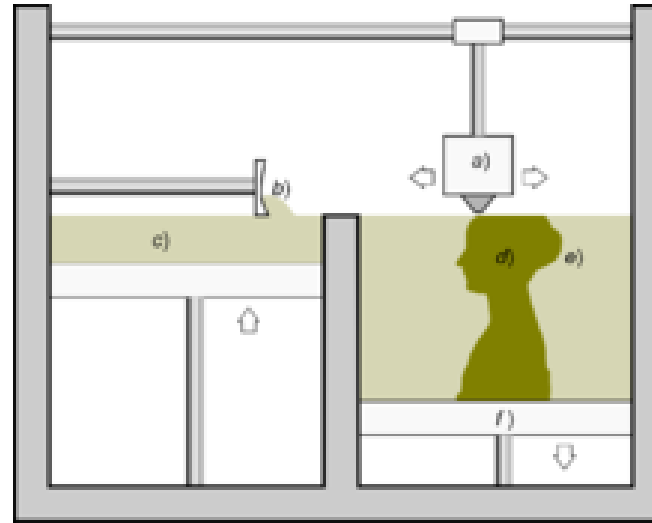
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3D Printing of Pharmaceutical Dosage Forms

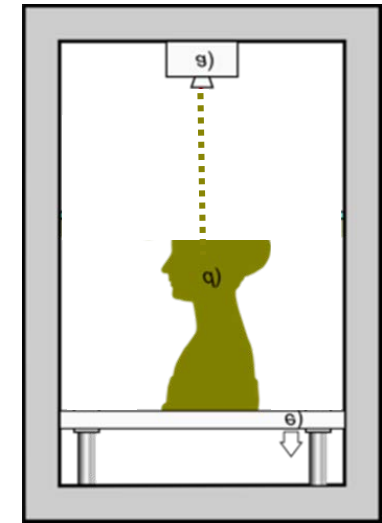
3D Printing: The action or process of making a physical object from a three-dimensional digital model, typically by laying down many thin layers of a material in succession.



Fused Deposition Modeling
(Material Extrusion)



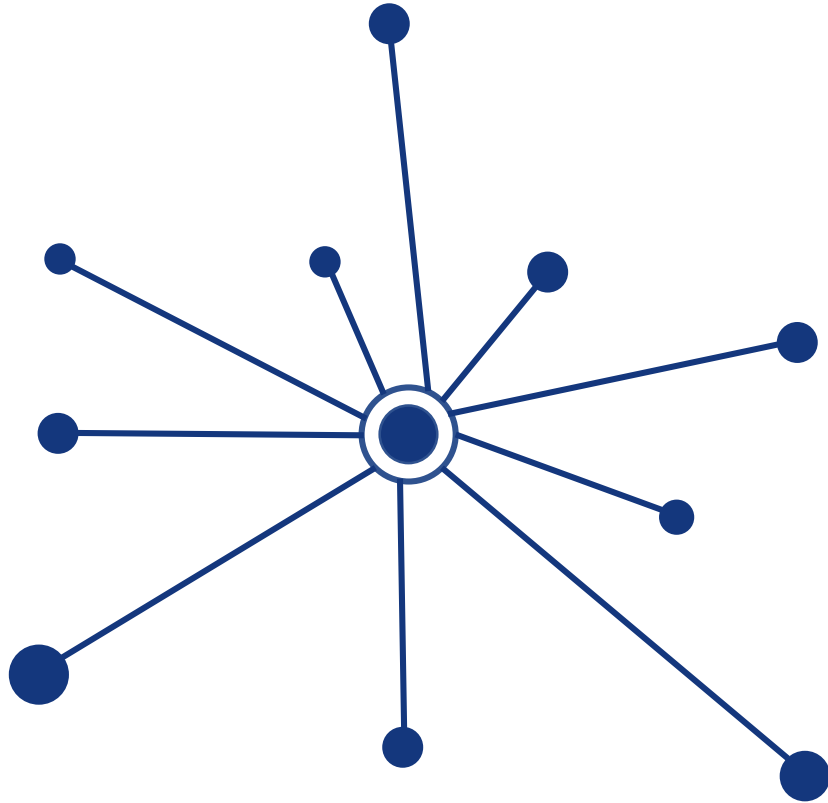
Powder-Liquid Deposition
(Binder Jetting)



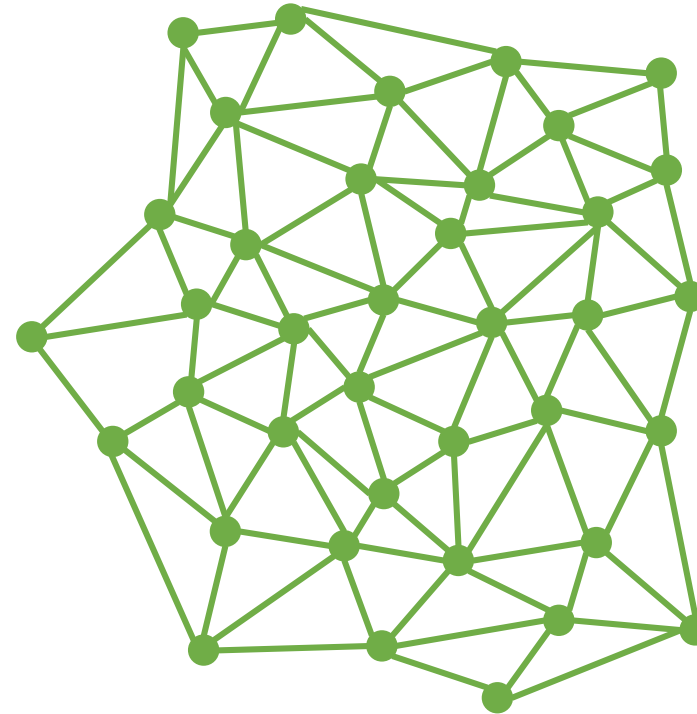
Polyjet
(Material Jetting)

Scopigno R, Cignoni P., Pietroni N., Callieri M, Dellepiane M (2017). "[Digital Fabrication Techniques for Cultural Heritage: A Survey](#)". *Computer Graphics Forum* 36 (1): 6–21. DOI: [10.1111/cgf.12781](#).

Centralized vs. Distributed Manufacturing Modes



Prominent Technical
Barriers

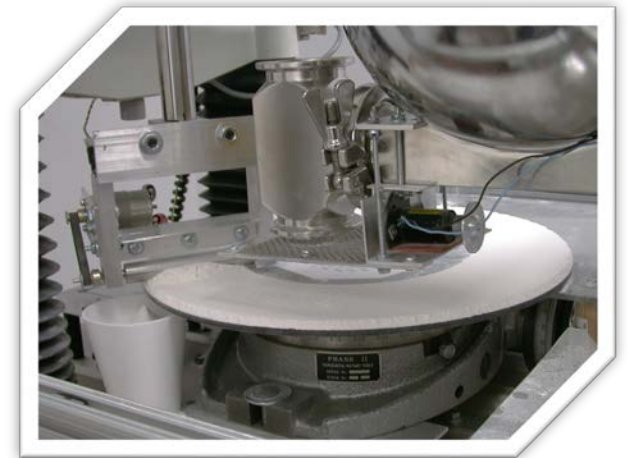
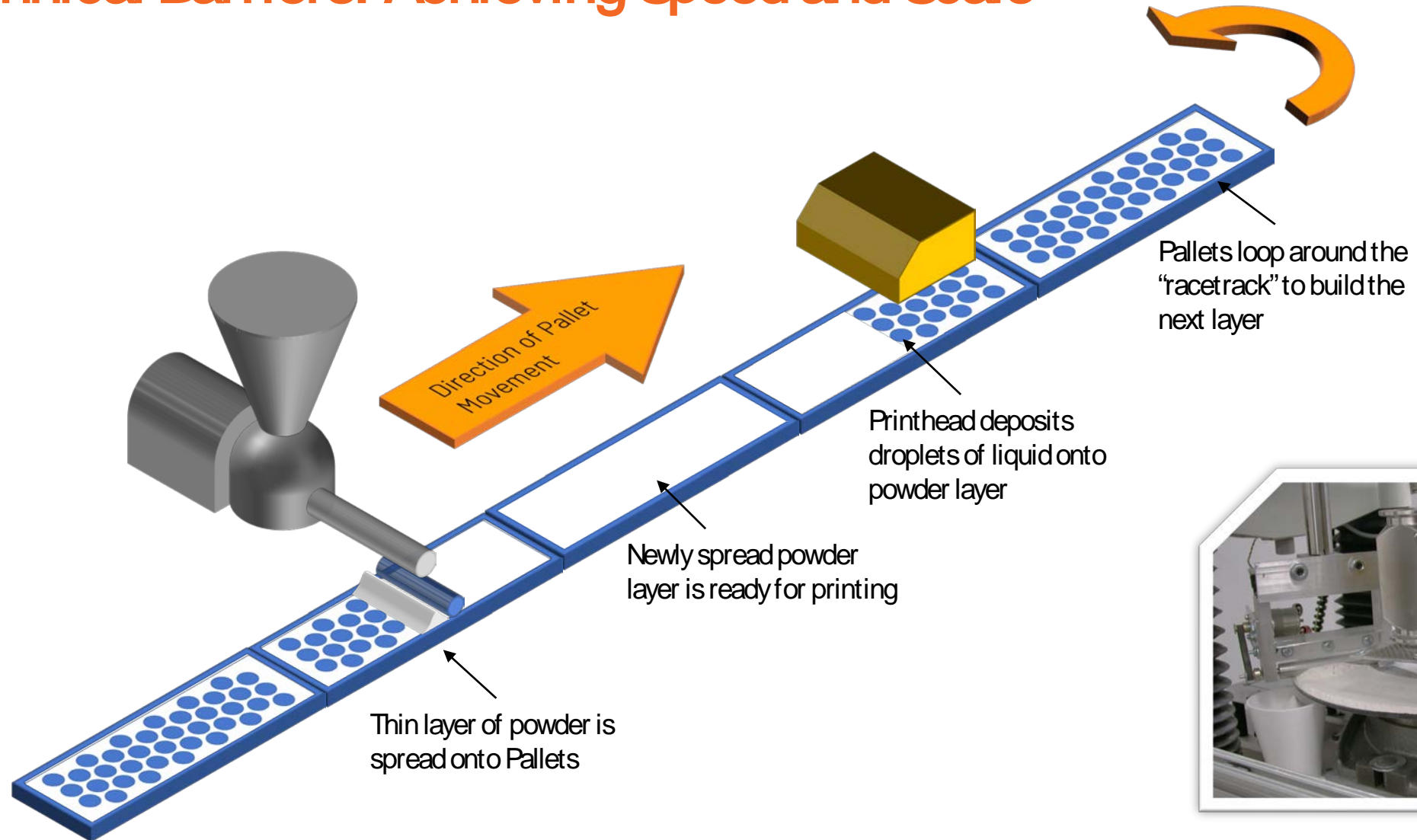


Prominent Regulatory Barriers

Technical Barriers



Technical Barriers: Achieving Speed and Scale

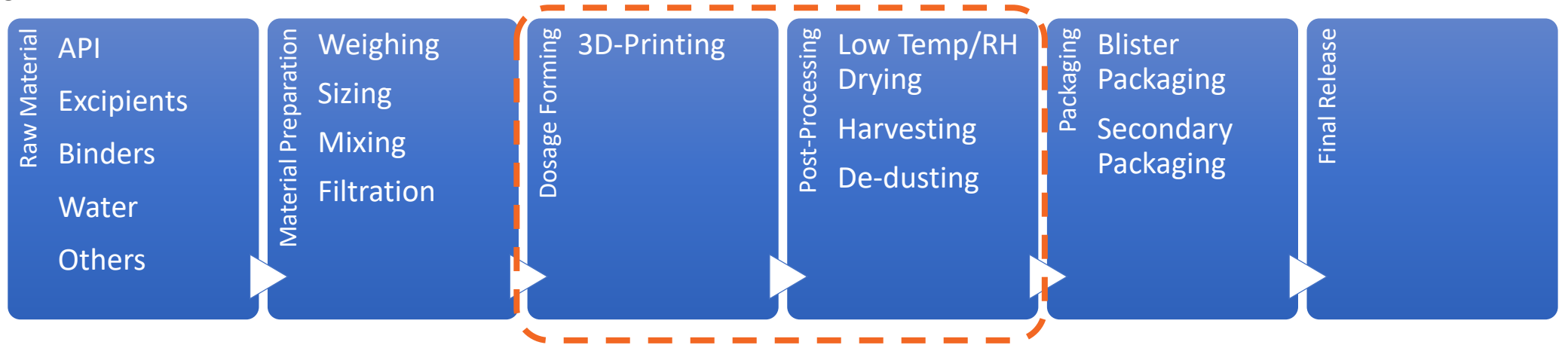


Technical Barriers: Achieving Speed and Scale

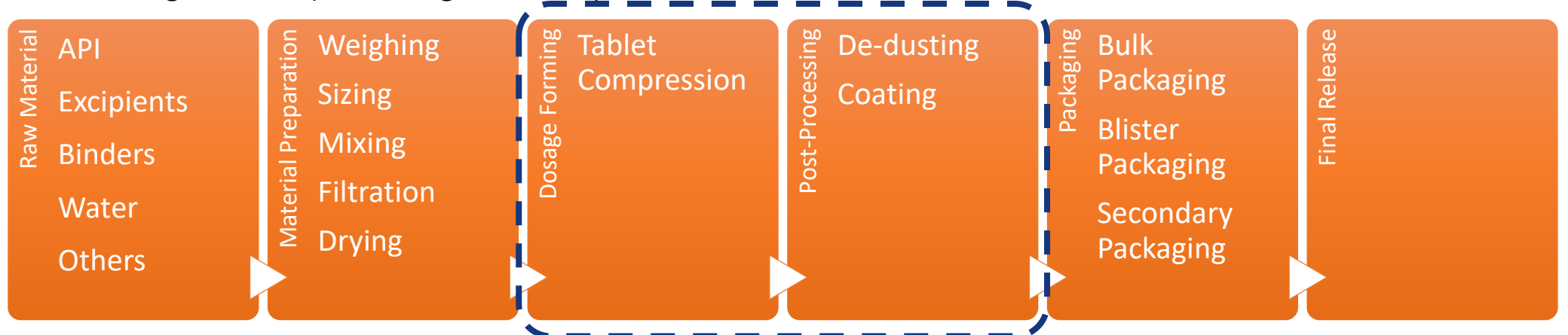


Technical Barriers: Completing the Process

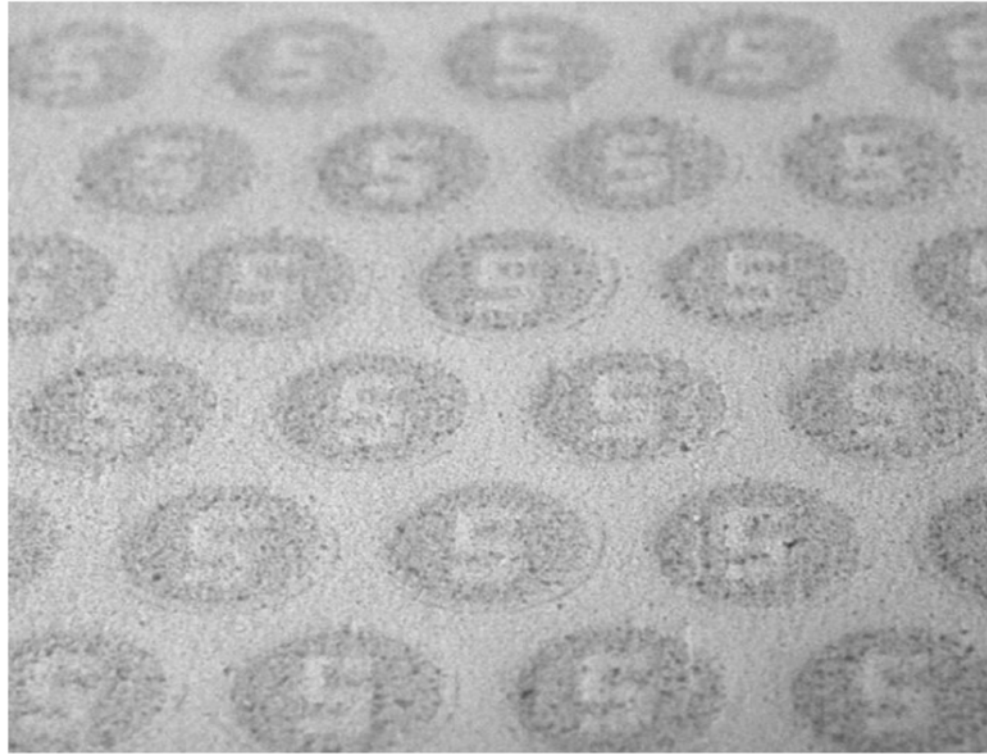
3D Printing Process



Conventional Tableting Process (with wet granulation)

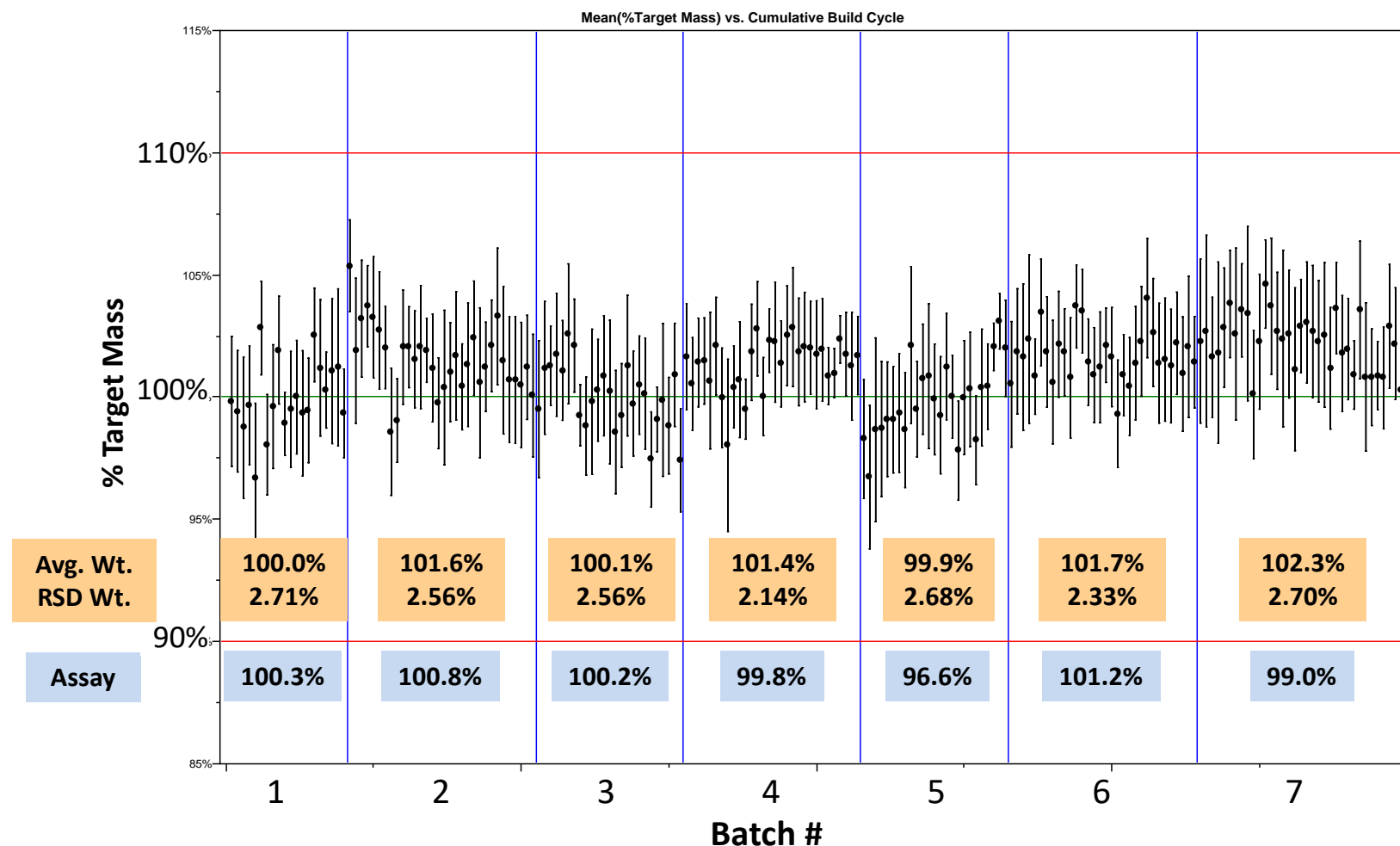


Technical Barriers: Completing the Process



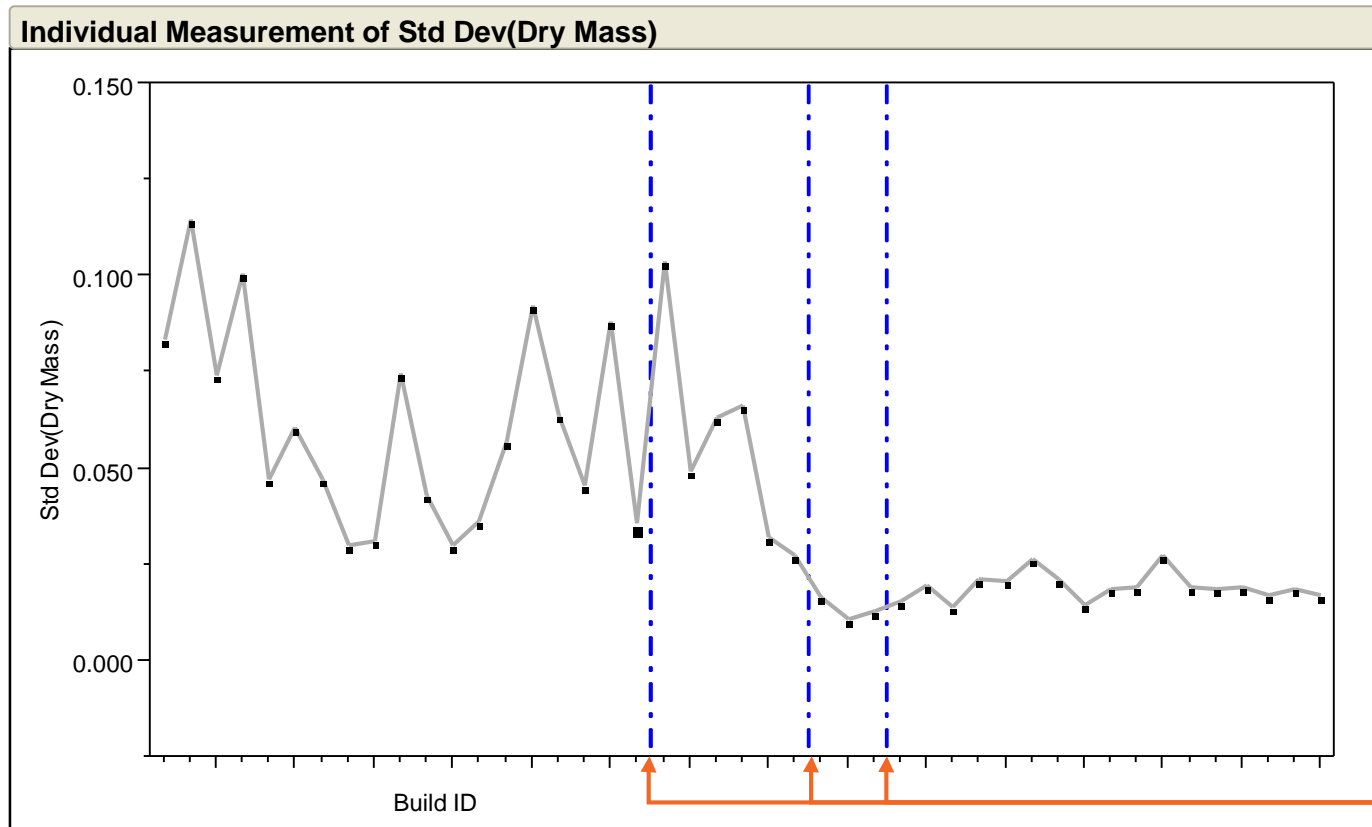
Technical Barriers: Completing the Process

BCS Class III Proof-of-Concept Drug



Technical Barriers: Completing the Process

Exploratory Work with a BCS Class III Proof-of-Concept Drug, Leading to Process Understanding and Improvement



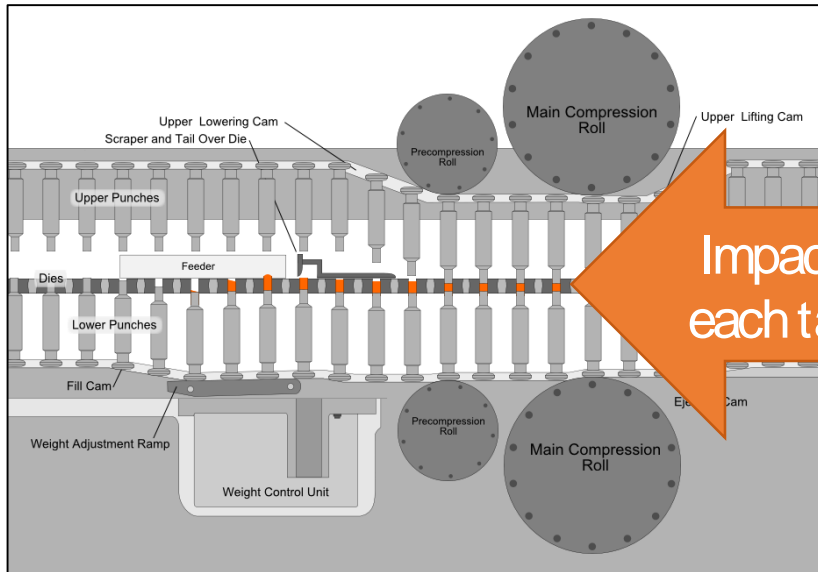
Process Changes
Implemented

The background features a complex arrangement of white, three-dimensional geometric shapes. On the left, there is a cluster of solid cubes of various sizes, some of which are partially obscured. To the right and extending towards the center, there are several wireframe cubes, which are hollow structures made of thin lines. These wireframe cubes are also of different sizes and are positioned in a way that they appear to be floating or interlocking with the solid cubes. The overall composition is abstract and modern, with a clean, minimalist aesthetic. The lighting is soft, creating subtle shadows and highlights on the surfaces of the cubes.

Regulatory Barriers

Regulatory Barriers: Scientific Reasoning vs. Conventional Wisdom

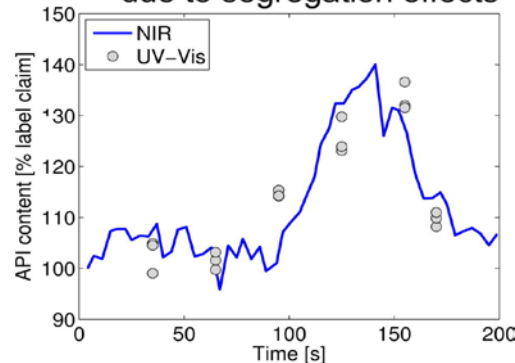
Hypothetical Scenarios: How important is it to keep the powder blend uniform?



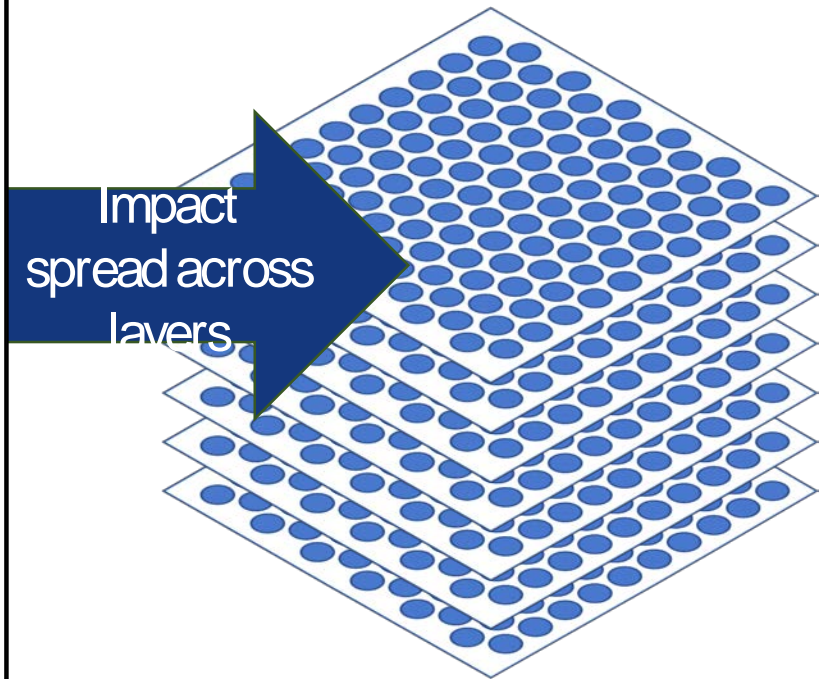
By Jeff Dahl - Own work, CC BY-SA 4.0,
<https://commons.wikimedia.org/w/index.php?curid=36060>
80

NIR Monitoring Example is shown here as a real life example of API segregation in a conventional tablet press

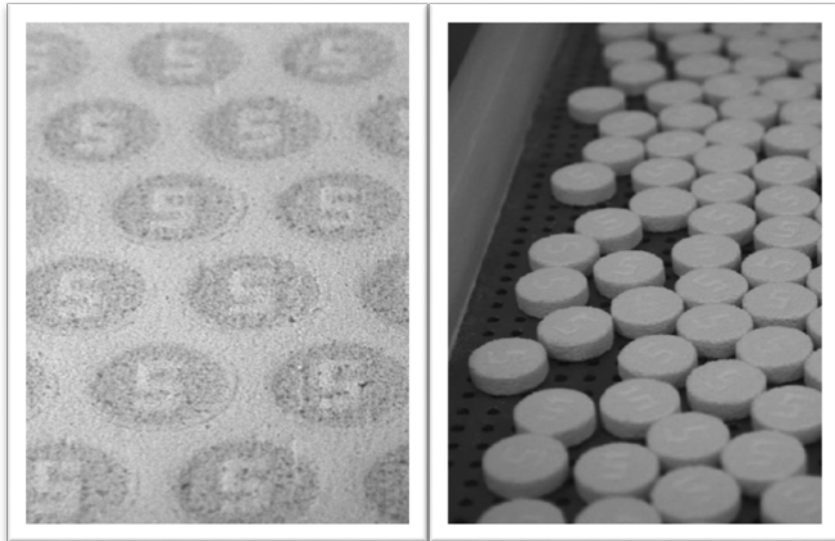
API excess at the process end due to segregation effects



Wahl et. al., European Journal of
Pharmaceutics and Biopharmaceutics,
2014

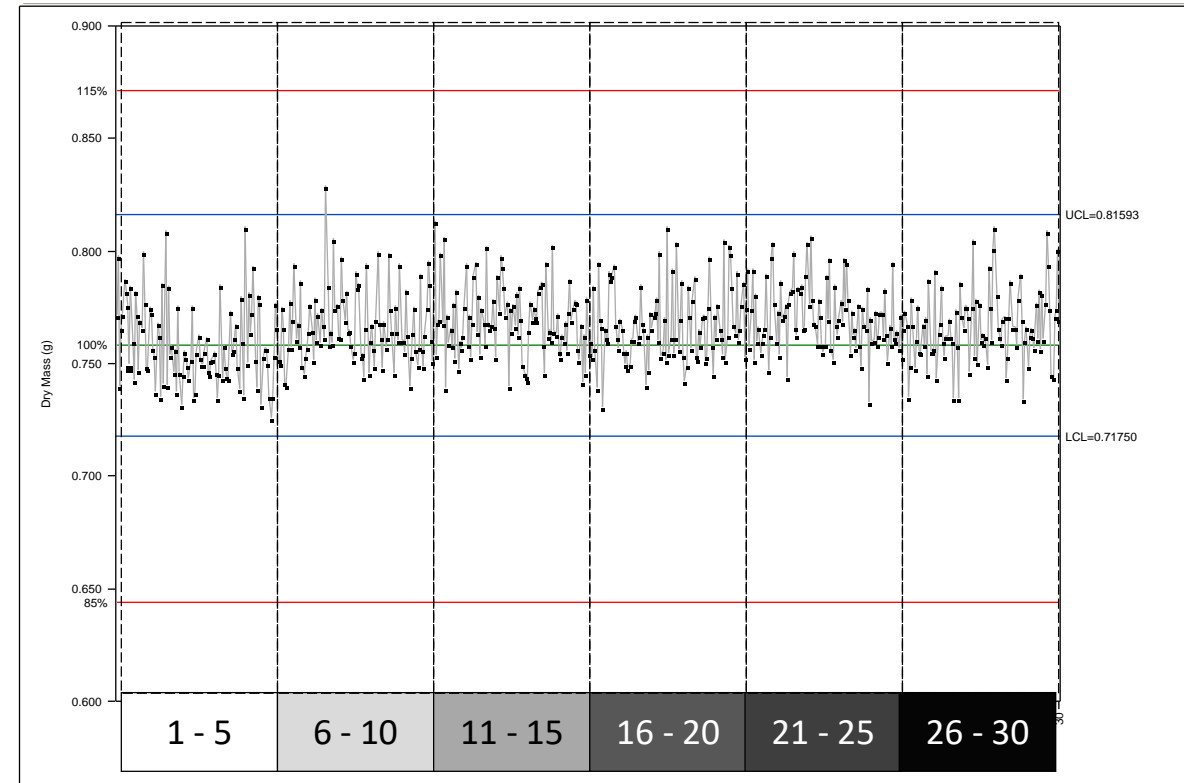


Regulatory Barriers: Powder Recirculation



Unbound powder is captured and fed back into the system. How does the recirculation impact product quality?

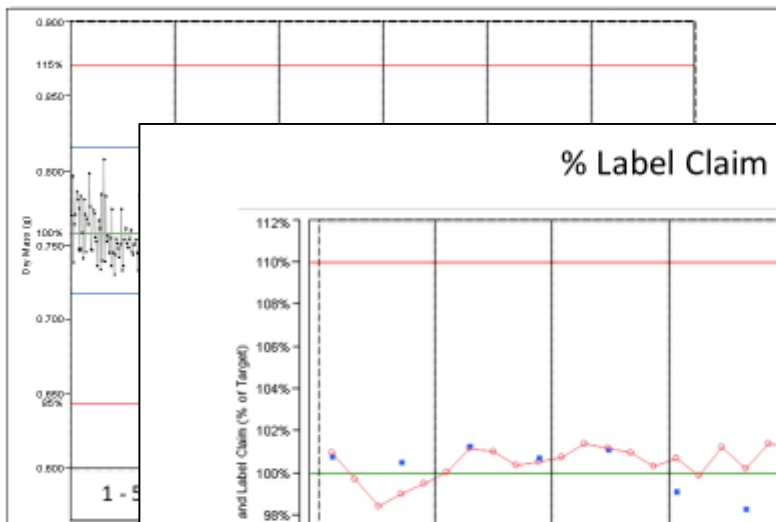
Weight of Dosage Units



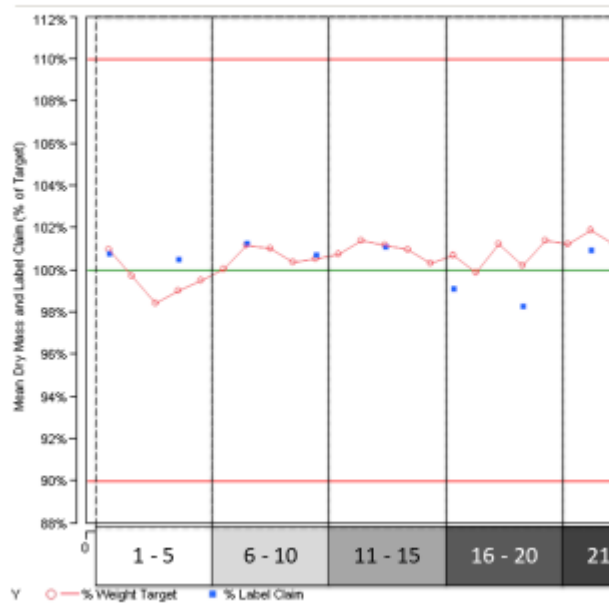
Use Data-Driven Approach to Generate Process Understanding

Regulatory Barriers: Powder Recirculation

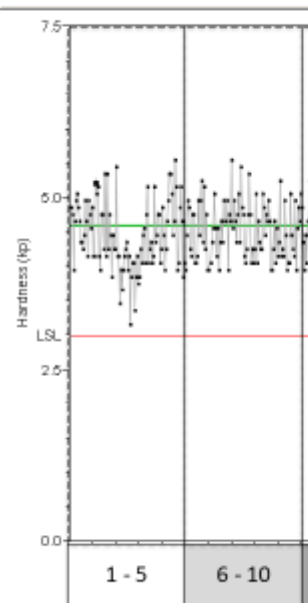
Weight of Dosage Units



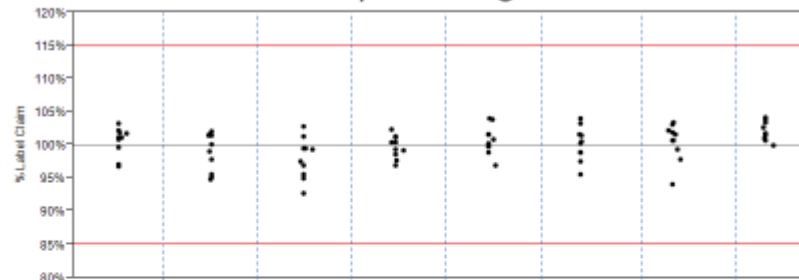
% Label Claim



Tablet



Uniformity of Dosage Units



| | Beginning of Batch | Middle of Batch | End of Batch | Entire Batch | Beginning of Batch | Middle of Batch | End of Batch | Entire Batch |
|---------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Weight Uniformity (n=10) | Avg: 101.4% RSD: 1.4% | Avg: 101.7% RSD: 1.8% | Avg: 101.1% RSD: 2.2% | Avg: 101.5% RSD: 1.5% | Avg: 99.2% RSD: 1.5% | Avg: 100.3% RSD: 2.1% | Avg: 101.1% RSD: 2.1% | Avg: 104.3% RSD: 1.6% |
| Content Uniformity (n=10) | Avg: 100.5% RSD: 2.1% | Avg: 98.8% RSD: 2.9% | Avg: 97.9% RSD: 3.1% | Avg: 99.6% RSD: 1.7% | Avg: 100.7% RSD: 2.1% | Avg: 100.1% RSD: 2.6% | Avg: 100.4% RSD: 2.8% | Avg: 102.0% RSD: 1.4% |
| Assay (n=20) | 100.3% | 99.5% | 99.5% | 99.0% | N/A | N/A | N/A | 101.4% |
| Related Compounds | 0.0% | 0.0% | 0.0% | 0.0% | N/A | N/A | N/A | 0.0% |

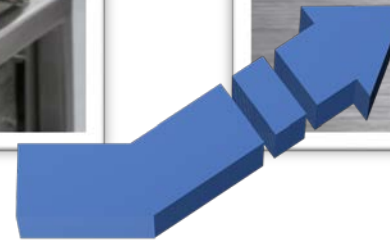
Regulatory Barriers: Continuous Process Improvement



Machine 0



Machine 1



Next Gen

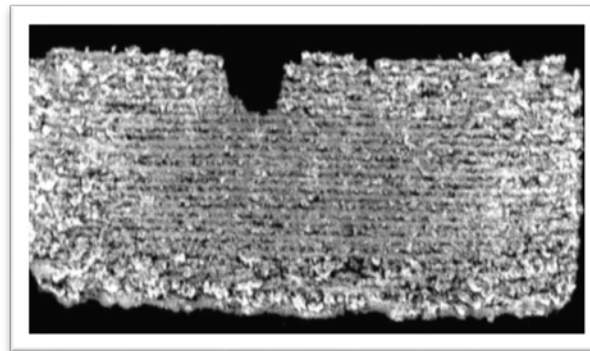


Other Barriers

Other Barriers: Discovering the Unmet Patient Needs

Features of 3DP Technologies

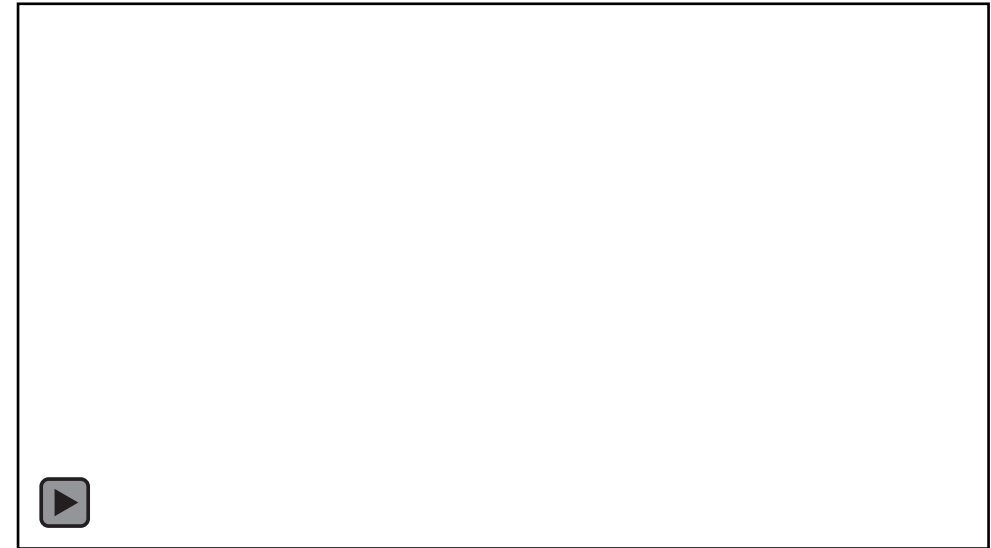
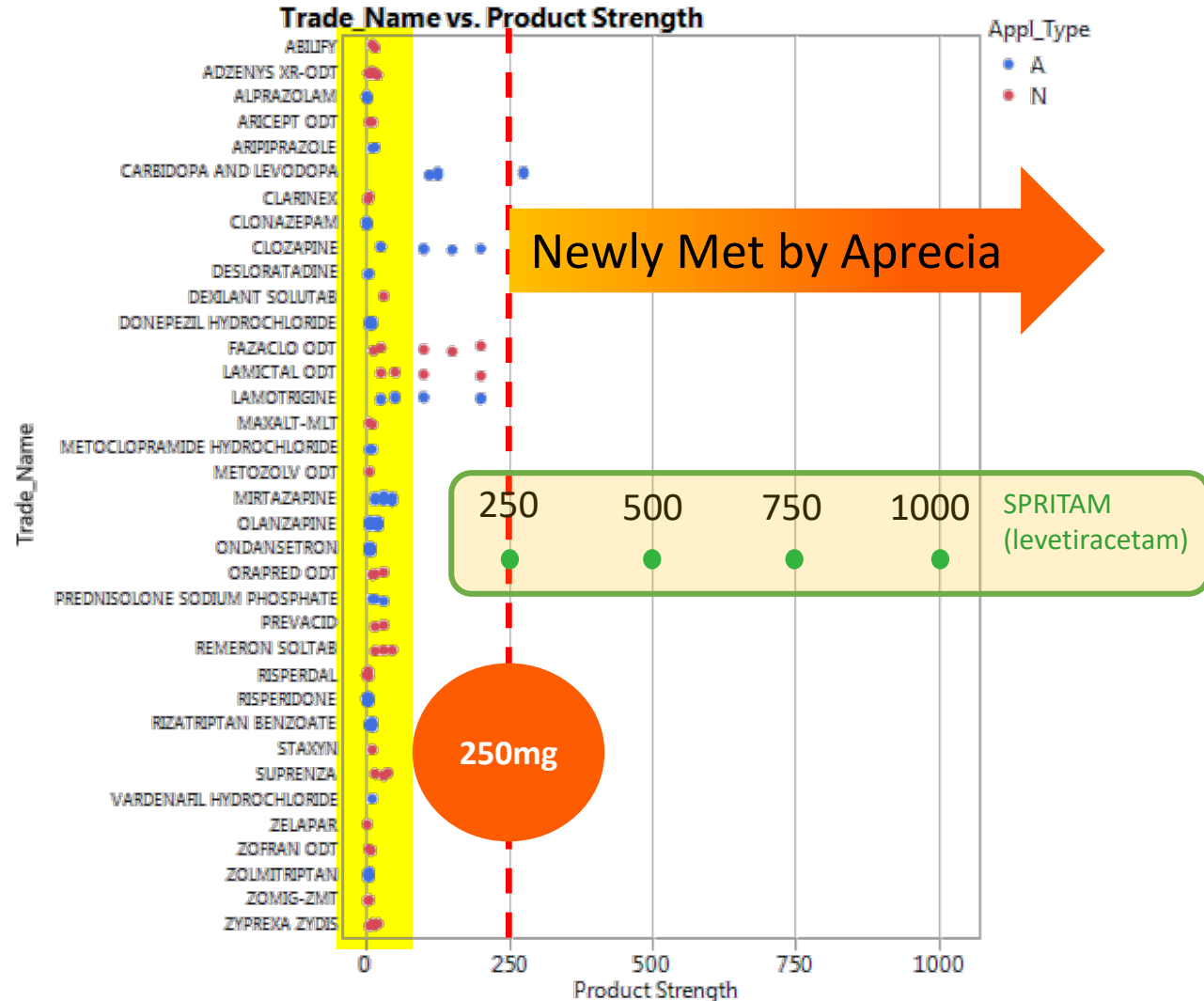
- Freedom of design
 - Control of internal and external geometry
 - Spatial control of composition
 - Compatibility with existing particle engineering technologies
 - Not limited by size
- Zero Compression Force



Benefits for Pharmaceutical Industry

- Dosage forms with unique properties
 - Instant dispersion at high drug loads
 - Fixed Dose Combination therapies
 - Complex release profiles
 - Ultra low dose precision
 - Anti-counterfeit features

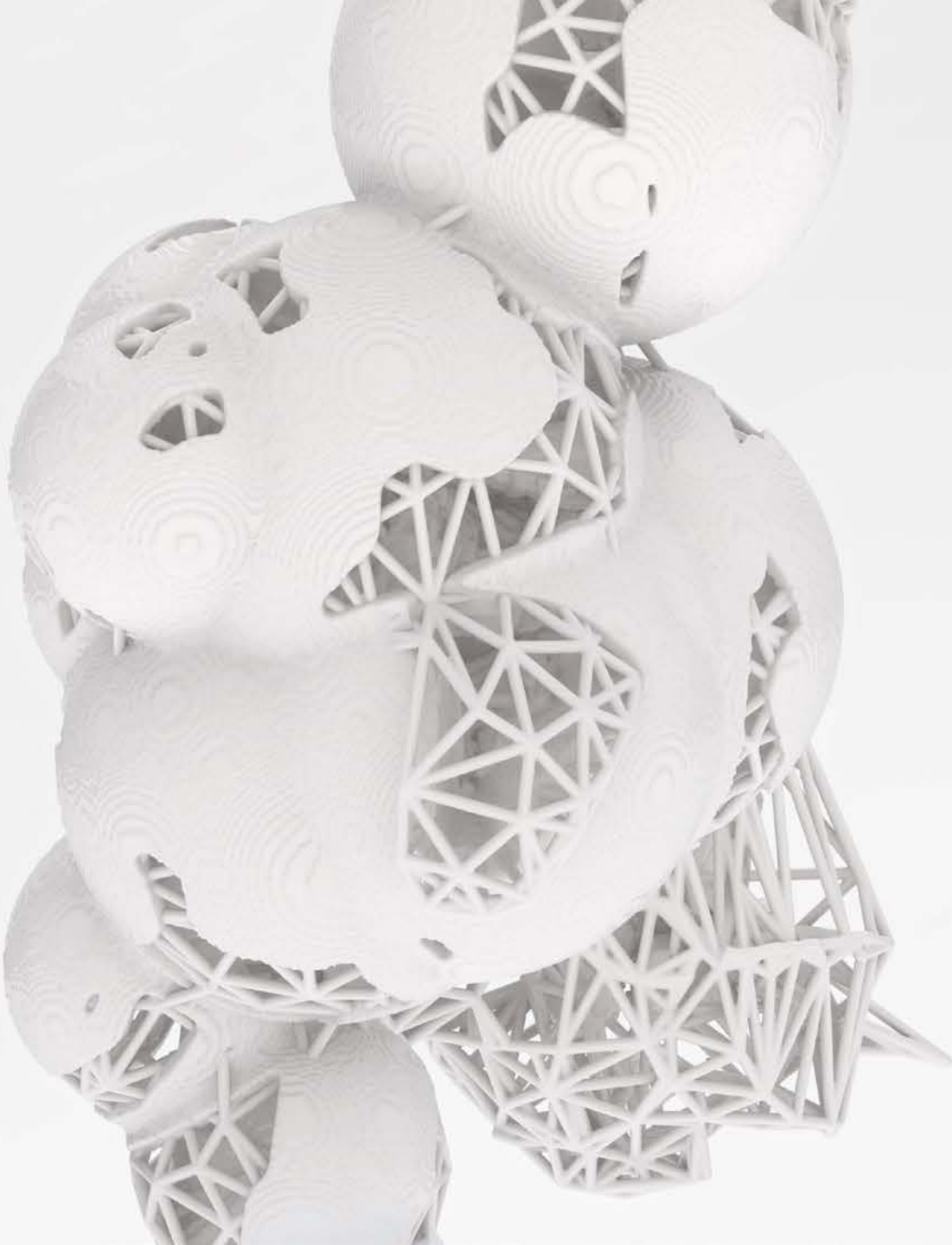
Other Barriers: Discovering the Unmet Patient Needs



Looking Back, Looking Ahead

- Barriers are expected when paving a new path
- Finding the right problem is often harder than solving problems
- Perceived barriers may be tougher to overcome than real barriers
- Continuous improvement requires careful planning and execution
- Balancing production vs. production capacity is key to continued innovation





Questions?

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