Critical device and formulation controls required in achieving in vitro comparability

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March 2014 – GSK Injunction on Sandoz Forspiro DPI Device
Upon completing it’s German EU decentralized procedures for generic FP/SX

“We believe the use of the colour purple by Sandoz could lead to confusion amongst patients, pharmacists and healthcare providers, ”
Respiratory products are hard-to-copy - GSK comments

Ø Putative competitors have run into significant technical challenges in trying to develop inhaled medicines.

Ø It is an extraordinarily challenging scientific proposition

Ø It doesn't get any easier when you move into the factories

Ø There is a need to have a manufacturing process, which ensures it can be delivered repeatedly

Ø The manufacture of combination respiratory medicines, such as Advair, presents significant hurdles and remains extremely challenging

“The success of GSK’s inhaled programs over the last 40/50 years has been associated with their integration and strong relationships with their suppliers”
We have an over-reliance on in-vitro APSD testing

Ø Key product development decisions, release and acceptance criteria are measured post-processing using *in vitro* impactor experiments.

Ø These data provide limited or no insight into the complex relationship between device, material properties, powder processing and product performance.

Ø Has led the industry to rely on design of experiments (DoE) and multivariate data analysis (MVA) to support product development.

At best this approach has led to a two sigma (5-10% rejection) process, with the ever-reliant need for batch release testing.
Product development remains in a black box!

Ø We can only ever make statements of correlation between attributes and product functionality

Ø Our knowledge remain relatively primitive and transferability between processes and products is limited.

We need to understand the mechanisms and the categories of circumstances which influence product functionality?
The factors controlling drug delivery to the lung

Formulation
API + excipients blending, laagering

Device
Design, efficiency, performance

Patient Activation
Deaglomeration, inhaled dose

Absorption
Dissolution
Physiochem, fluid volume distribution

Lung deposition
Particle size
Impaction, sedimentation

PK (or local effect)
QbD requirements for OIPs

Inter-relationship between critical material attributes and critical process parameters are critical in:

Ø Developing bioequivalent OIPs
Ø Will ensure the critical quality attributes of the drug product
What are the long-term challenges for generic entry?

Ø Will need to maintain product quality and identify and address possible causes of product failure.

Ø The main challenge will be understanding and specifying the micromeric properties of raw materials.

Ø For inhaled products, control and reduction of risk can only be achieved by understanding how micromeric properties and processing conditions influence formulation structure and product functionality.
A specific grade of inhalation lactose is typically required to ensure product performance control in highly regulated markets.

The micromeritics can be controlled and modified by the use of a milling, classification and blending approach.

The level of lactose fines appears to dominate all other influences of the excipient properties on performance.

Requires the development and validation of a particle sizing method - typically done by dry dispersion.

How does the level of fines affect performance?
Correlations between lactose micromeritics and FPM$_{DD}$ performance in capsule based DPI devices

Correlation between lactose micromeritics and MMAD in capsule based DPI devices

The level of lactose fines %<4.5µm and %<15µm may need to be controlled down to the 1st or 2nd decimal place
Critical API controls required in achieving in vitro comparability

- The success or failure of all inhaled formulations is dependent on controlling particle size and the surface properties of the drug substance.

- Difficult to achieve with 1940’s processing technologies

- The ability to predict interparticulate forces in DPI systems would lead to the ability to predict and optimize DPI performance.

- The experience and integration of both primary and secondary API processing within Pharma R&D companies may become a major advantage.
What influences the surface properties of micronised powders?

Traditional CMC based perspective

- Presence of different crystal habits
- A change in polymorphic form
- Presence of amorphous material

Mechanistic based perspective

- Physical Geometry - Particle Roughness and surface morphology
- Interfacial chemistry - Process induced affects on interfacial forces between API and Excipient
What dominates API micromeritic properties

Interfacial Chemistry
- Surface Free Energy
- Cohesive-Adhesive Balance (CAB)

Physical Geometry
- Particle Morphology
- Surface Roughness
Physico-chemical characterisation of 3rd party sourced micronized FP

<table>
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<tr>
<th>FP Batches</th>
<th>$d_{10}$ (μm)</th>
<th>$d_{50}$ (μm)</th>
<th>$d_{90}$ (μm)</th>
<th>Surface Area (m²/g)</th>
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<tr>
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<td>0.76</td>
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<tr>
<td>FP Batch B</td>
<td>0.97</td>
<td>2.19</td>
<td>4.04</td>
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Cohesive-Adhesive Balance of FP Batches

<table>
<thead>
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<th>FP Batches</th>
<th>CAB</th>
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<tr>
<td>FP Batch A</td>
<td>0.75</td>
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<tr>
<td>FP Batch B</td>
<td>1.82</td>
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Blending Dynamics
Drug Product Performance

Large amount of blending energy would be needed to normalize API differences.
Interfacial differences of two batches of tiotropium bromide monohydrate

<table>
<thead>
<tr>
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<th>Tio Batches</th>
<th>CAB</th>
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<tr>
<td>Tio Batch A</td>
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<tr>
<td>Tio Batch B</td>
<td>1.12</td>
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2 fold increase in drug-lactose interaction for Batch B
In vitro performance of Tio (A and B) at 39 L/min

Performance differences sensitive to API-lactose interaction
In vitro performance of Tio (A and B) at 55 L/min

Performance differences sensitive to API-lactose interaction
Conclusion

Ø Are we treating the symptoms, not the root cause?

Ø We need to understand the mechanisms and the categories of circumstances which influence product functionality.

Ø Will require:

   Ø Identification of critical material attributes that provide a mechanistic link of the product quality to the manufacturing process.

   Ø Critical process parameters need to be combined with CMAs to describe the relation between inputs and outputs.

“Not everything that can be counted counts, and not everything that counts can be counted.”

Albert Einstein
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