Pfizer GLOBAL SUPPLY

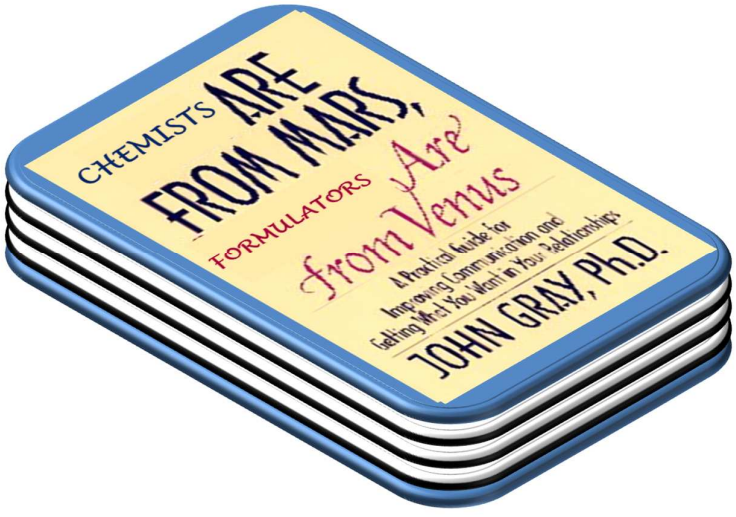
The Impact of Materials Sciences in Increasing Understanding of Drug Product Performance and Manufacturability

Fiona Clarke

Its All About Relationships

Pfizer GLOBAL SUPPLY

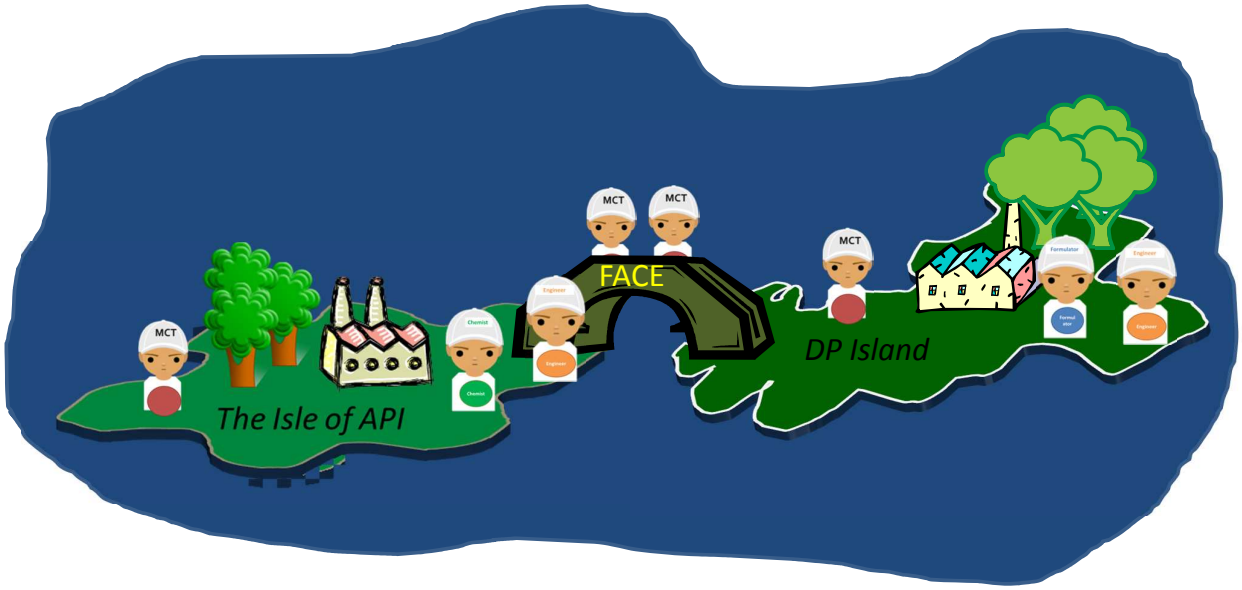
Materials Science will be the language of “reconciliation”



FACE

ormulator
nalyst
hemist
ngineer

Bridging with Characterisation



FACE is the bridge between the world of API and DP, facilitated by material characteristics.

Equipment

Chemical Imaging / Spectroscopy

- Near-infrared, Infrared, Raman and X-Ray Fluorescence Microscopes
- Terahertz Imaging
- Tablet Press
- Microtome and Rapid Trim
- X-Ray µTomography
- Near-infrared, Raman and infrared spectroscopy

Physical Characterisation/ Surface Properties

- Malvern and Sympatec Laser Diffraction
- Light Microscopes
- QicPic
- G3
- Specific Surface Area
- Kruss Tensiometer
- Surface Energy Analyser (IGC)
- Multi-Station Dynamic Vapor Sorption

Physico-Chemical / Crystallisation

- Powder X-Ray Diffraction
- Crystal 16
- Thermal Gravimetric Analysis coupled with Mass Spectrometer
- Hyper and Heat Flux Differential Scanning Calorimetry
- Simultaneous Analyser coupled with infrared spectroscopy
- Dynamic Mechanical Analyser

Particulate Matter

- Light Microscope
- Inverted light microscope
- Infrared Microscope
- Scanning electron microscopy coupled with energy dispersive X-rays

Material Assessment

- Kinexus Rheometer
- Powder Rheometer
- Ring Shear Tester
- Helium Pycnometer
- Air Jet Sieve
- Compaction Simulator
- Texture Analyser

Non-Solids

- Ultrasonics Spectroscopy
- Brightwell Image Analyser
- TurbiScan
- ZetaSizer
- Rheolaser

Chemical Comparability

- Complete Orthagonal Method Evaluation (Liquid Chromatography)
- Inductively Coupled Plasma-Optical Emission Spectroscopy
- Nuclear Magnetic Resonance
- Structural Elucidation (through ARD)

Regularly Outsourced

- Residual Solvents (GC)
- Solid State NMR
- Gel Permation Chromatography
- Time of Flight –Secondary Ion Mass Spectrometry/X-Ray Photon Spectroscopy

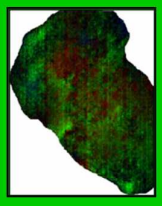
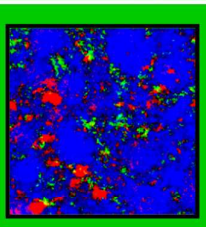
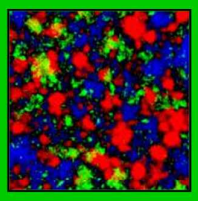
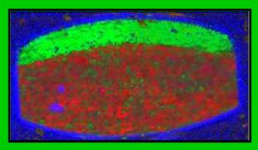
Note: Equipment can be used in different work area, but one shown is where there has been greatest application

Technologies for Chemical Imaging

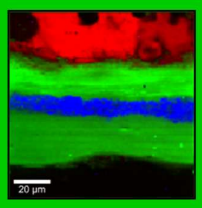
Pfizer GLOBAL SUPPLY

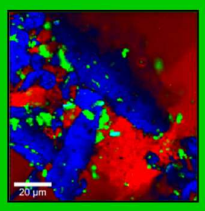
Matrix Elucidation

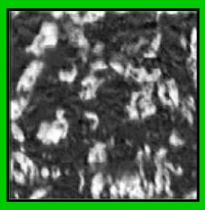
Near-Infrared Microscopy

Raman Microscopy

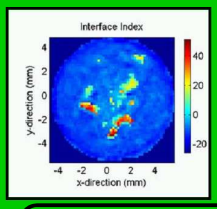



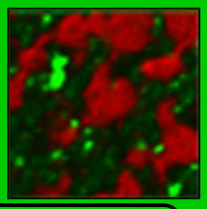




Mid-Infrared Microscopy

Terahertz Imaging



X-Ray Fluorescence Microscopy

X-Ray µTomography

Toolbox for Liquid and Suspension Formulations

Pfizer GLOBAL SUPPLY

Optical Microscopy

- Used to determine particle morphology
- Structural information by phase contrast microscopy

Scanning Electron Microscopy

- Particulate matter or particle morphology
- Surface characteristics

Rheology

- Rheology for structural information
- Stability of a liquid product

Rheolaser

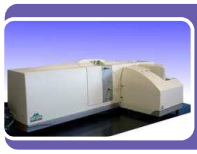
- For sedimentation and structural properties
- Stability of a suspension

Tensiometer

- Wetability of powder beds for wet granulation and dissolution issues

Sympatec Laser Diffraction

- Particle size for liquid dispersions with focused measurement range



Malvern Laser Diffraction

- Particle size for liquid dispersions with wide measurement range

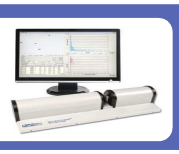


Image Analysis

- Optical particle sizing technique

Turbiscan

- De-stabilisation of a network structure i.e. Sedimentation or creaming

Zeta-Sizer

- Zeta potential
- Sizing

Pfizer GLOBAL SUPPLY

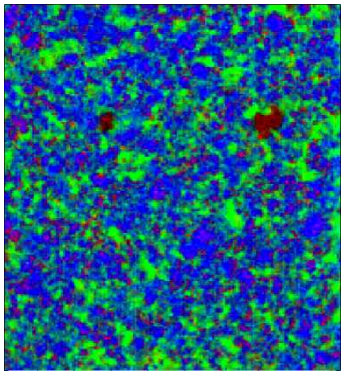
Roots in Drug Product Characterisation

Using Chemical Images to Understand Product Performance

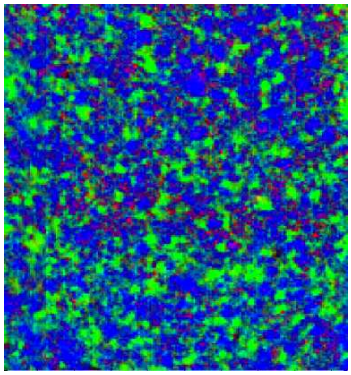
Matrix Elucidation Providing Insights into Slow Dissolution

Pfizer GLOBAL SUPPLY

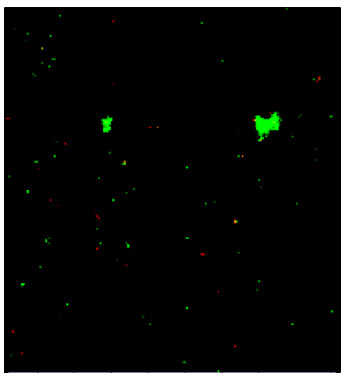
Typical

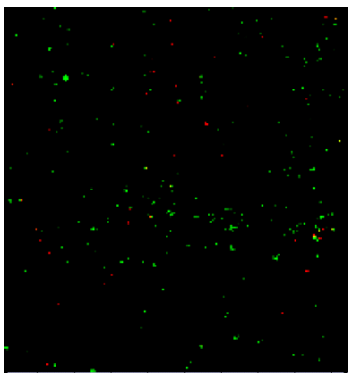


Slow Disso



No differences in distribution of major components

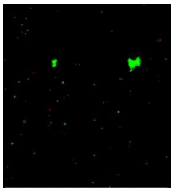


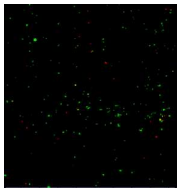


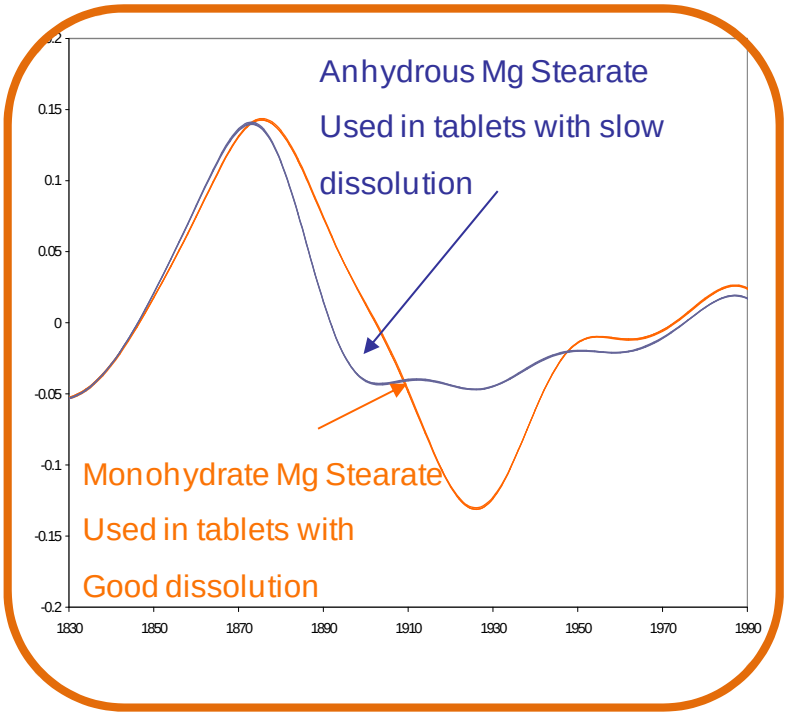
Focuses Investigation Team of Raw Material Variation or Blending Operation

Excipient Variability

- CoA comparison of Raw Materials Identified no variations
- Characterisation Identified difference in hydration state of magnesium stearate
- Now known as a critical attribute for this product

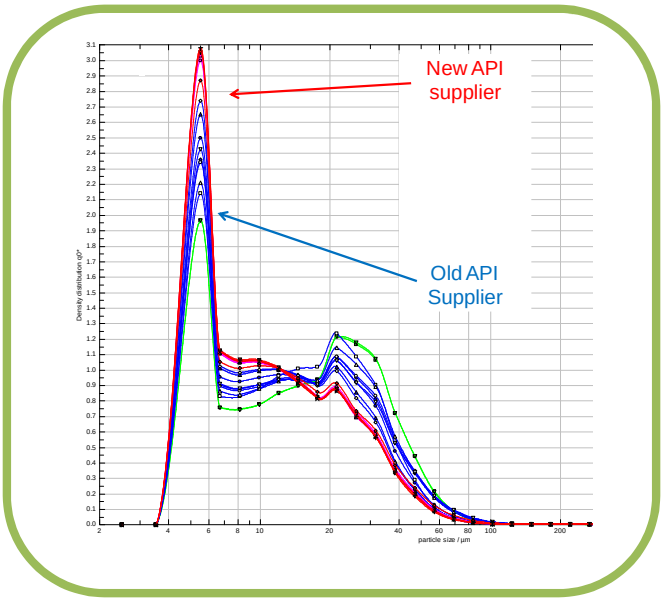




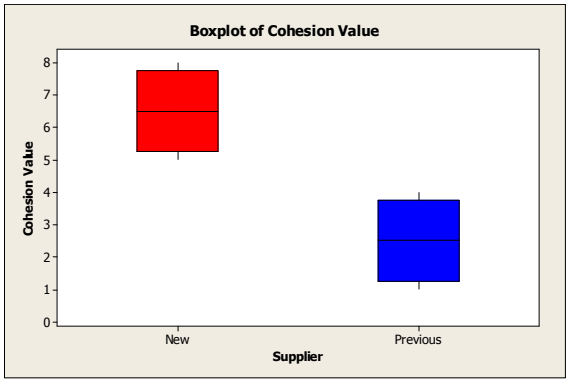


Drug Product Issue – Blend Uniformity

- Flow issues during DP manufacture resulted in blend uniformity issues following an API source change.
  - API from new supplier had passed all specifications



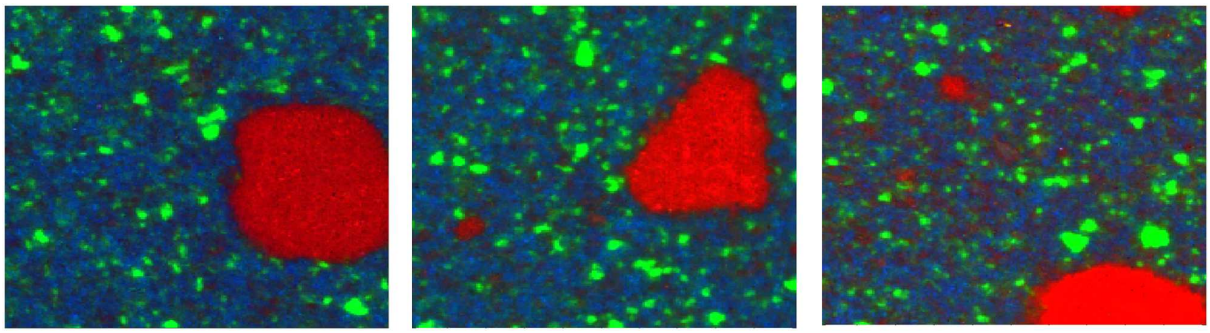
Characterisation Studies identify new API has a greater proportion of fines (<10 µm) which results in different cohesion properties.



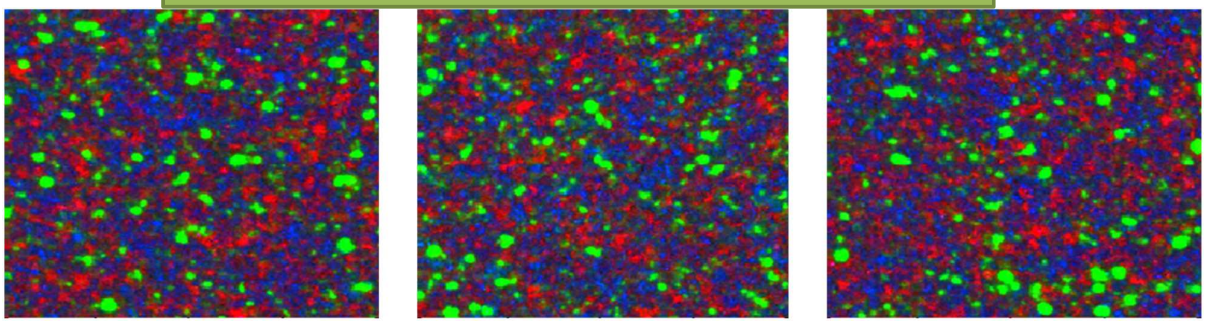
Supporting DP Trials

Pfizer GLOBAL SUPPLY

Trial Batch with New API Source



Commercial Batch with New API Source

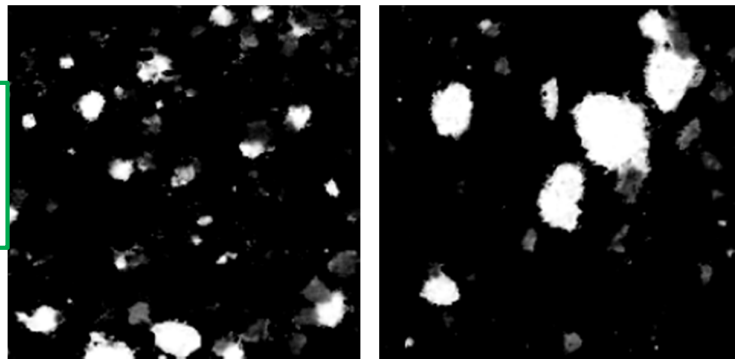


Inhomogeneity in Drug Product

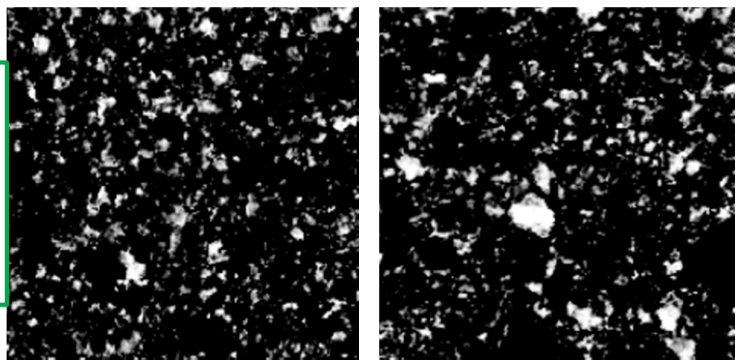
Pfizer GLOBAL SUPPLY

- Following a site change inhomogeneity observed in drug product results.
- Processing equipment and parameters had been comparable.
- Raw materials all meet CoA.

New Site

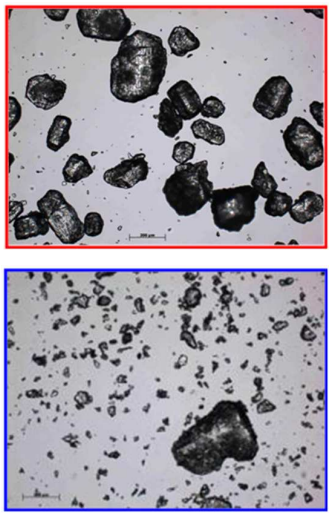


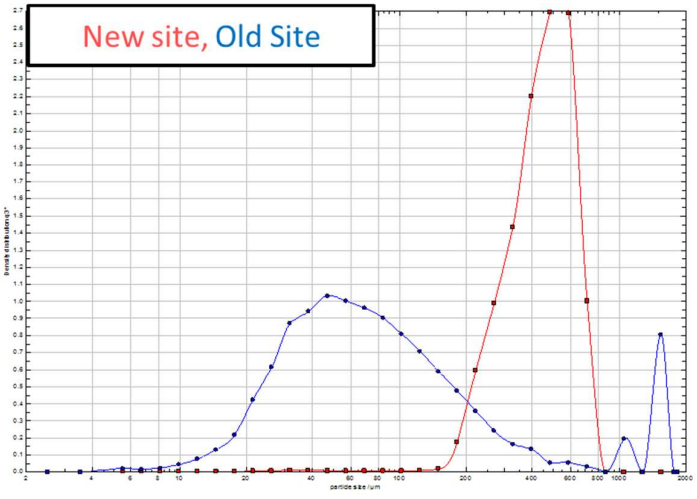
Previous Site



Excipient Evaluation

- Full characterisation of 15+ components identified differences in particle size and chemical content of some raw materials
  - Issues linked to particle size differences
- Utilisation of raw materials from initial DP site gave rise to good homogeneity

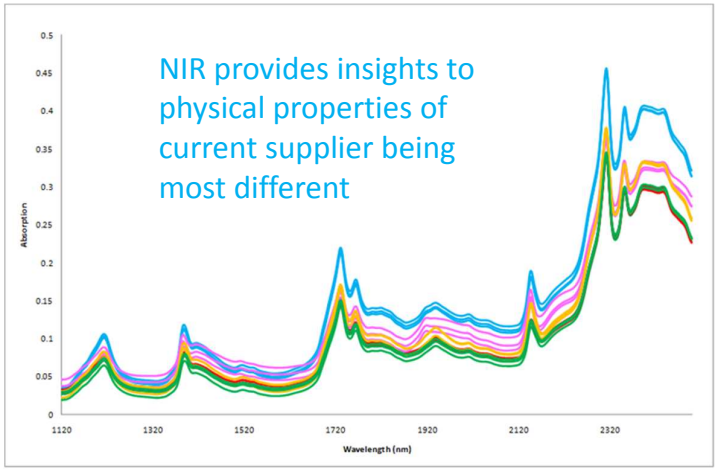


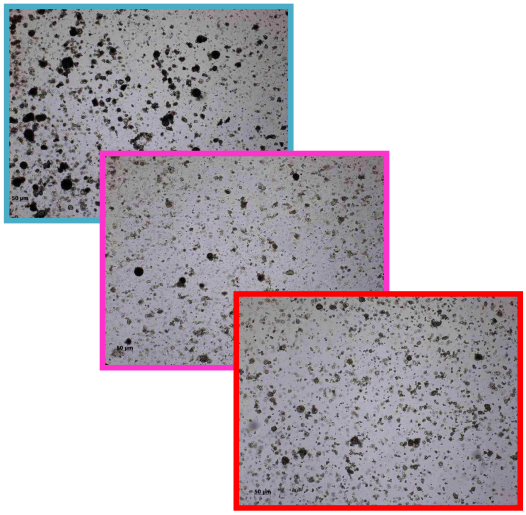


Selecting Excipient for Ophthalmic Suspension

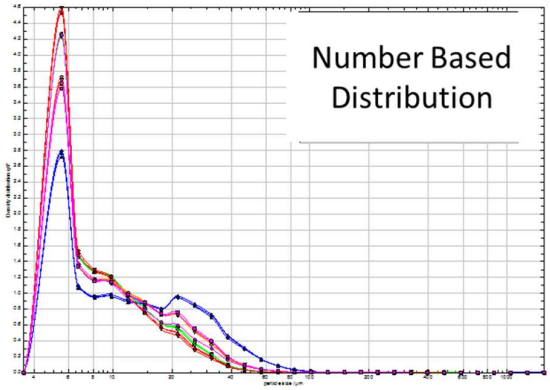
Excipient Identification

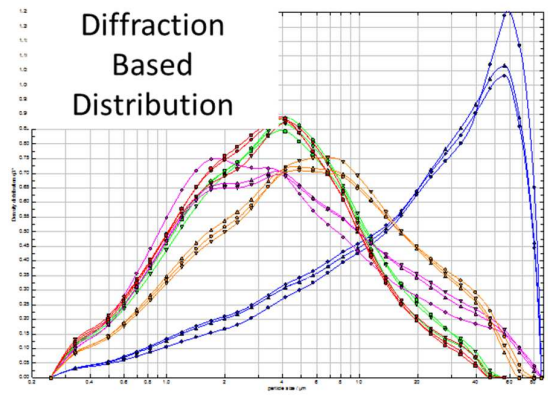
- Notified that current raw material supplier will be ceasing manufacture.
- Understanding of this material and its attributes in DP deemed a necessary for low risk change.
  - Material from 4 alternate suppliers sourced for comparison.

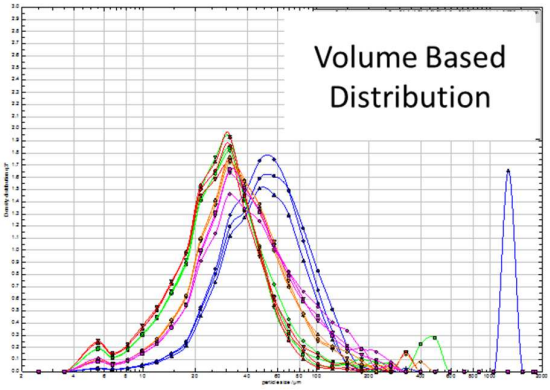




Assessing PSD



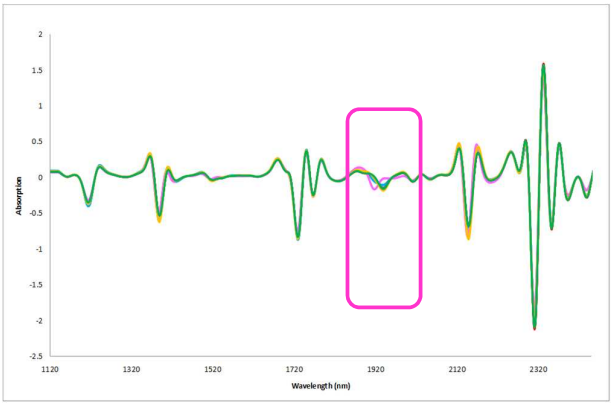


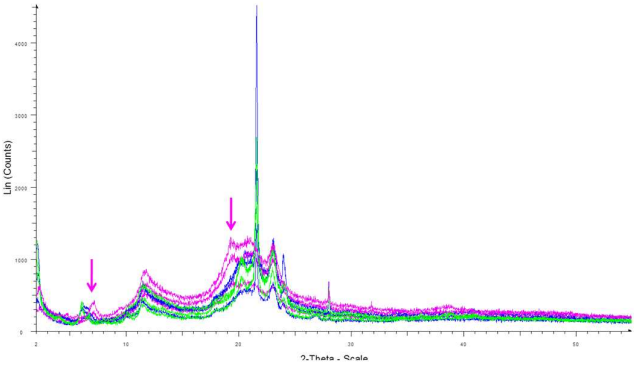


Alternate sources offer very different PSD from current source

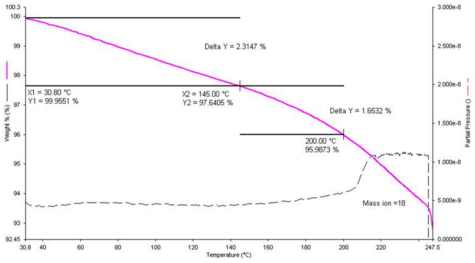
Evaluation of Physico-Chemical Properties

- NIR and PXRD identify chemical variations in one alternative source, which by EGA is shown to be a anhydrous form.

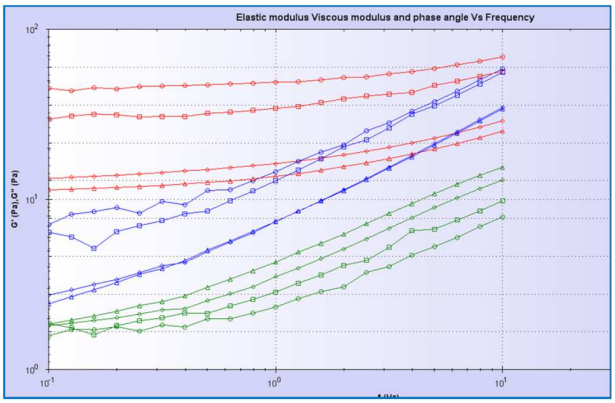


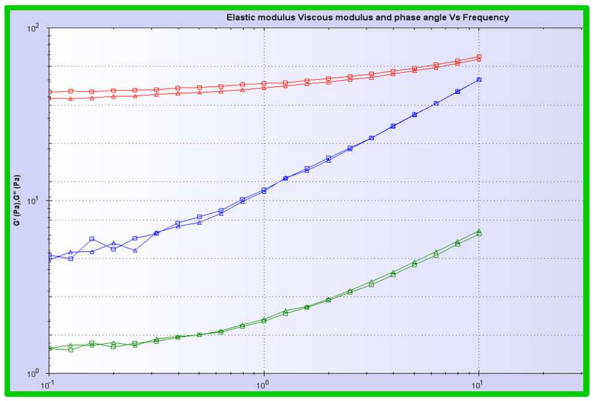


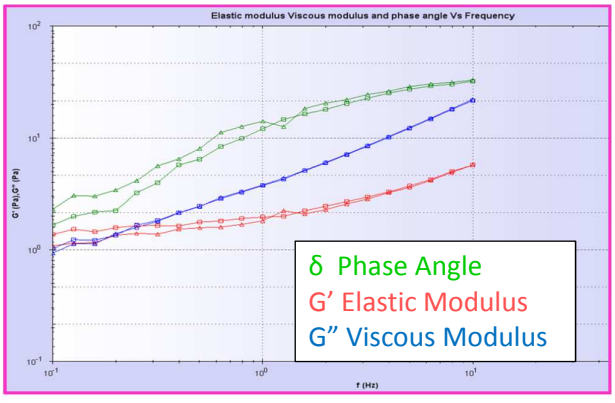
Sample	% Mass lost (30-145°C)
M Alternative	2.31
Current	0.83
P Alternative	0.77
F Alternative	0.60

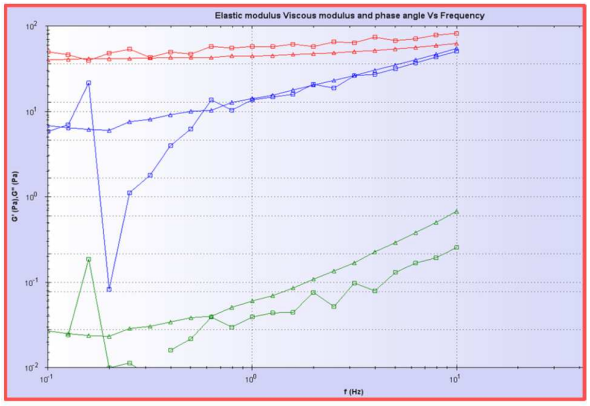


Viscosity of Lab Scale Formulations







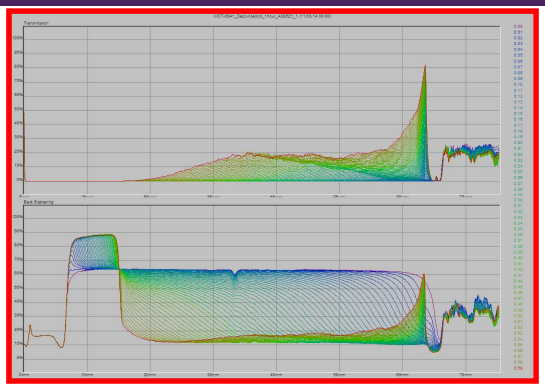


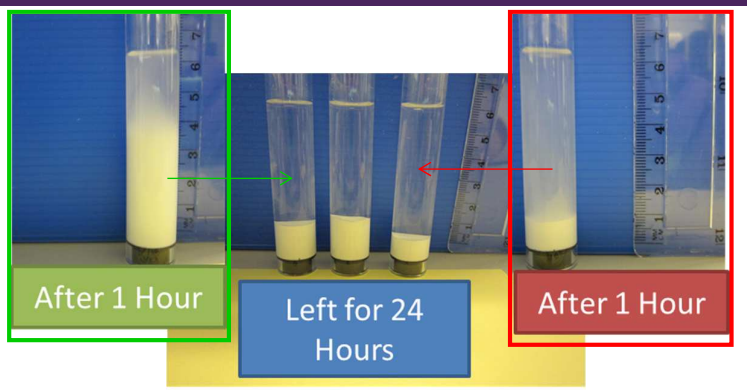
Pfizer GLOBAL SUPPLY

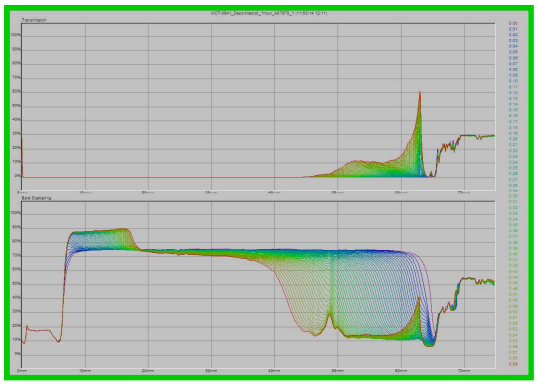
Suspension Properties

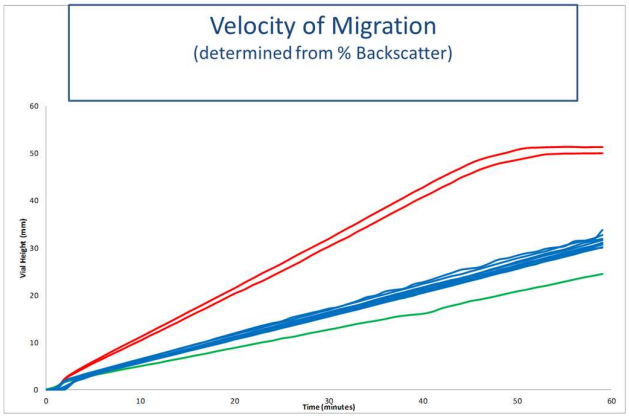
Variation in Settled Bed Height

Pfizer GLOBAL SUPPLY

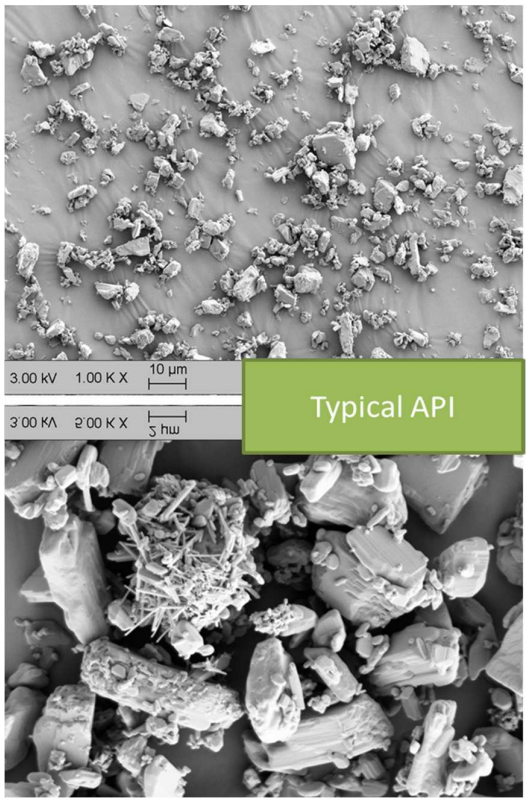


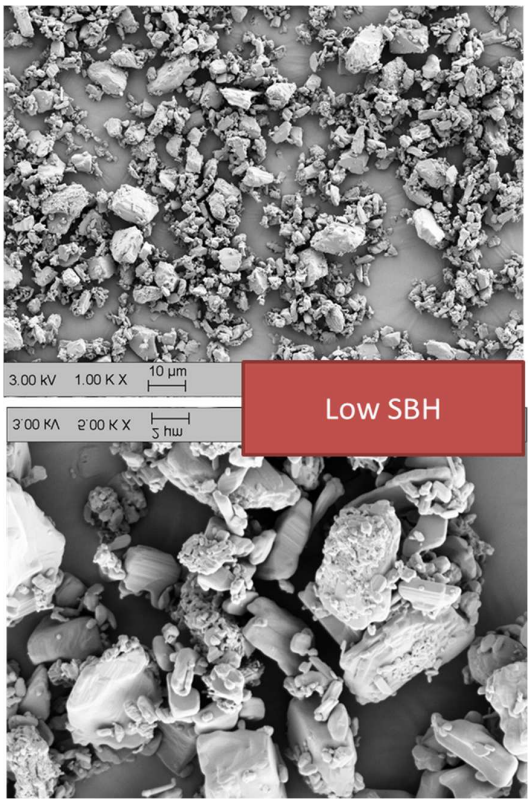




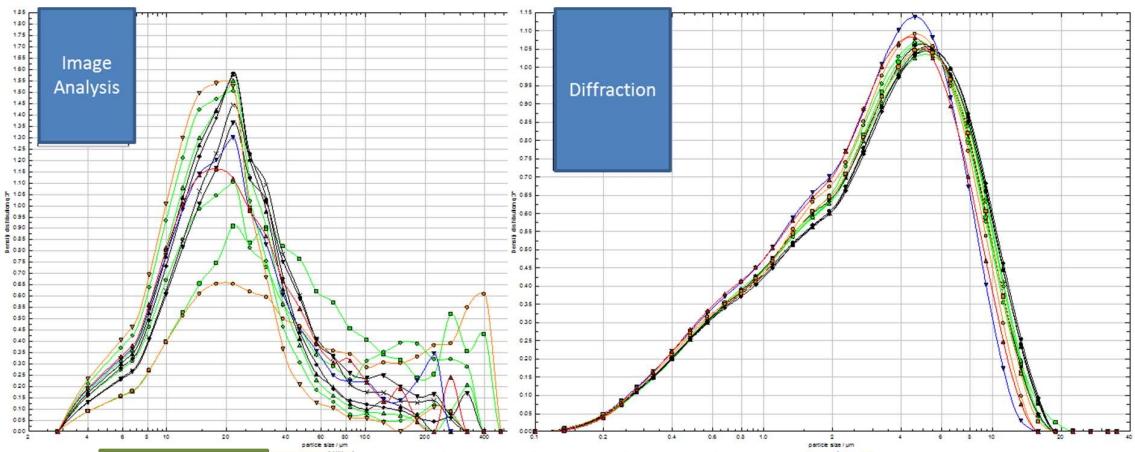


API Morphology

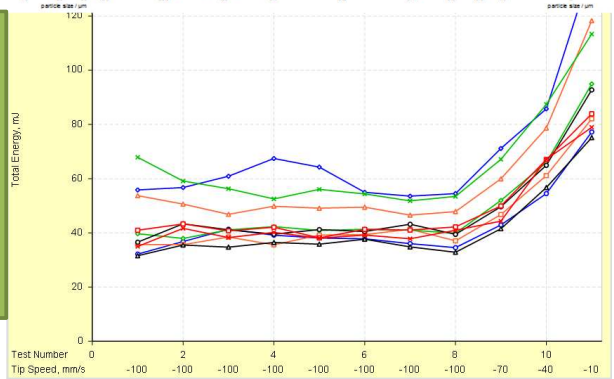




Size and Flow Attributes



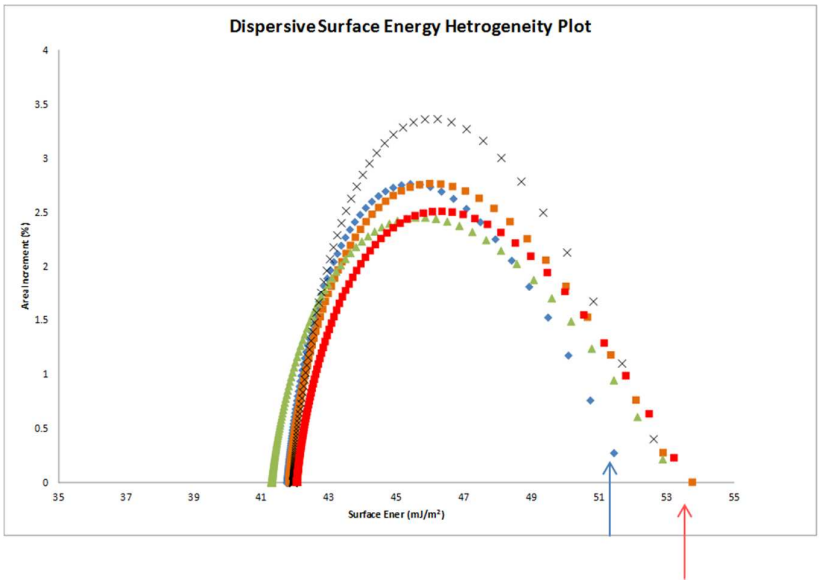
Powder Rheometry



Surface Area also evaluated with no correlation

Surface Properties Drive Sedimentation

- Issues lots have higher surface heterogeneity, which could be driving the stability of the suspension of the final drug product.



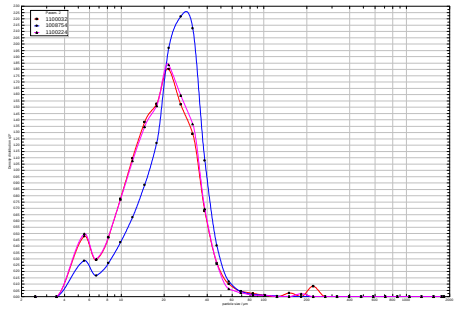
Pfizer GLOBAL SUPPLY

Variable Dissolution

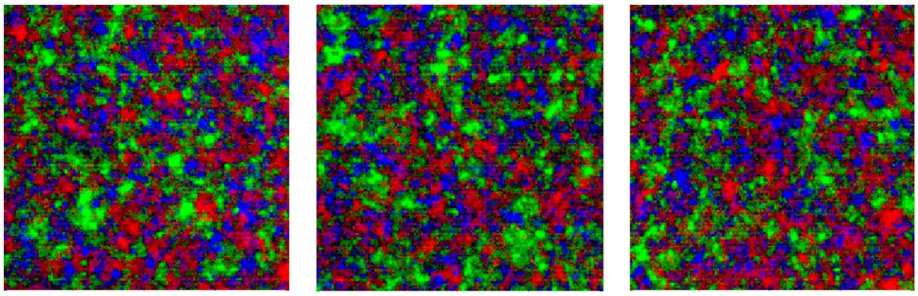
A physical attribute

Understand Root Cause of Dissolution Performance Variability using Imaging Methods

- Five capsule lots with variable dissolution performance



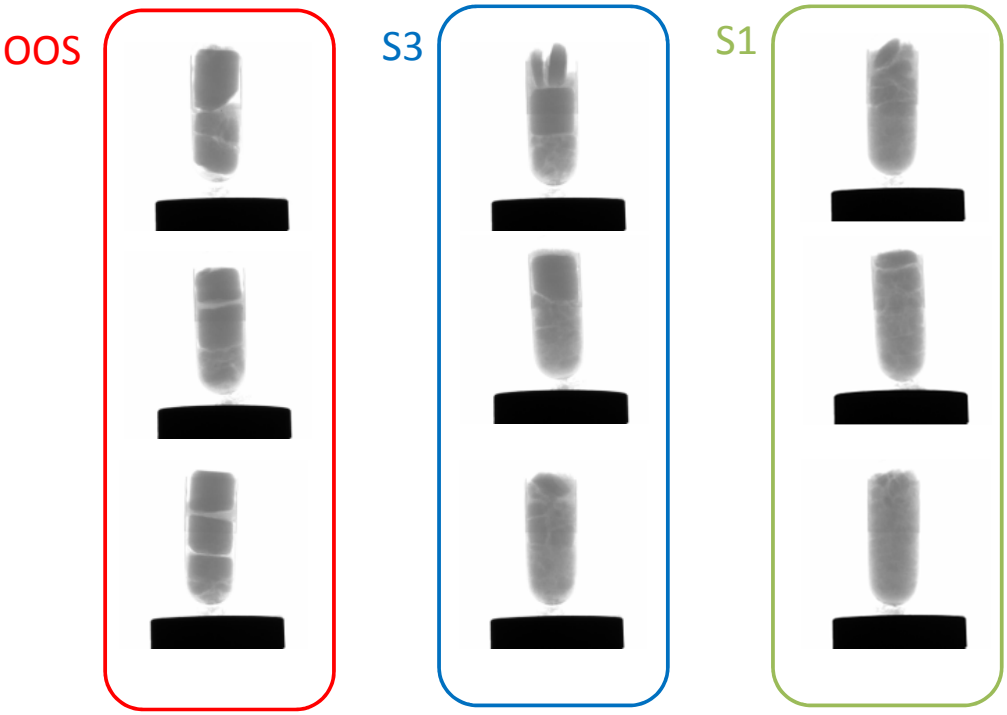
Only excipient with variation through characterisation testing was magnesium stearate



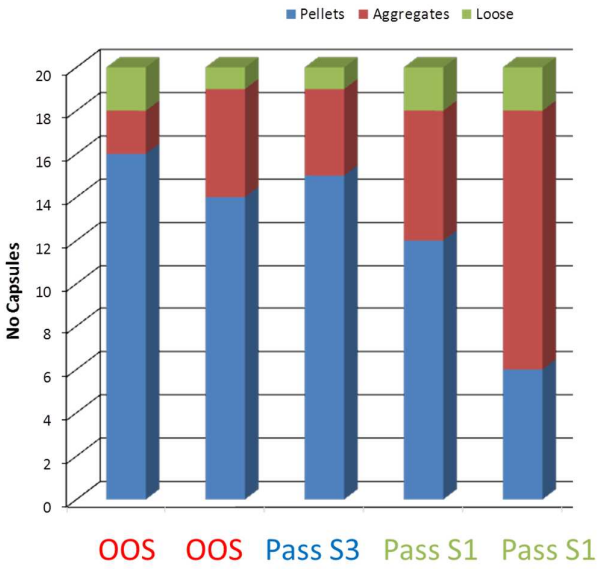
NIR Chemical Images Identify No significant Variation

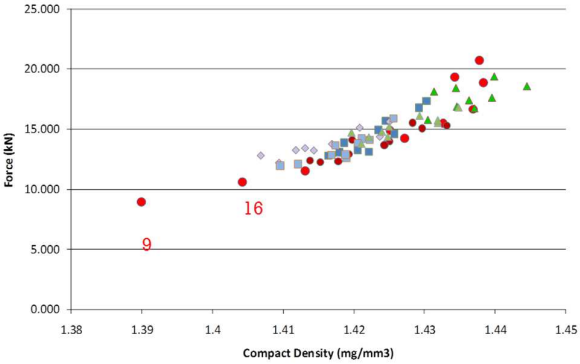
Looking at the Capsule Contents

- X-ray images reveal variation in powder packing



Crude Classification of Powder State in Capsules (Compaction)



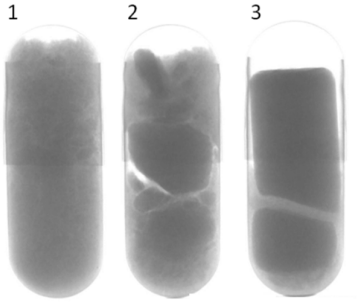


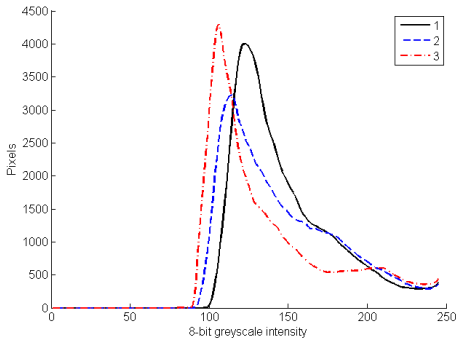
Using a compaction simulator, compaction behaviour of capsule contents were evaluated

Understanding Dissolution Performance of Capsule Product

- To build understanding of prediction ability of X-ray images, a 'calibration set' was generated using different tamping pin settings.

- Greyscale Histograms were generated from X-ray Images

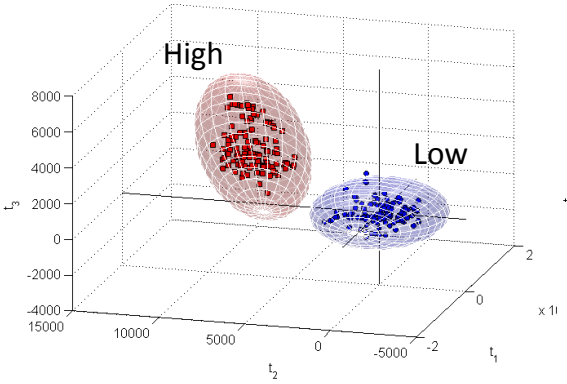


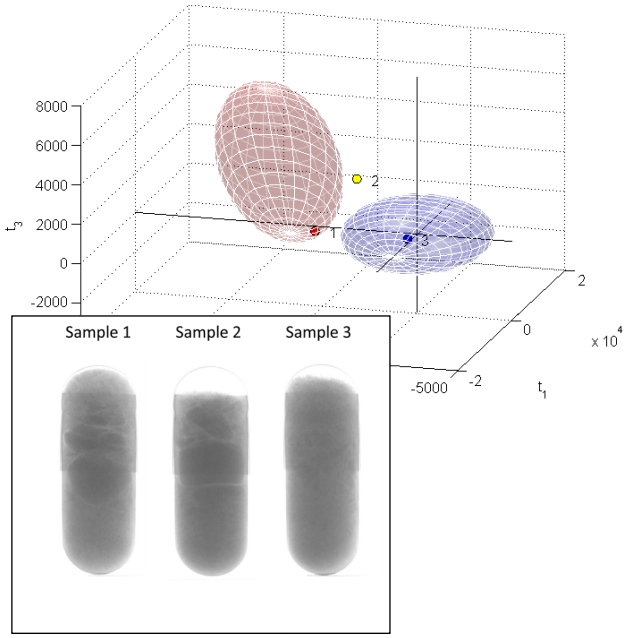


Work completed in collaboration with Professor Ryan Gosling, University of Sherbrooke

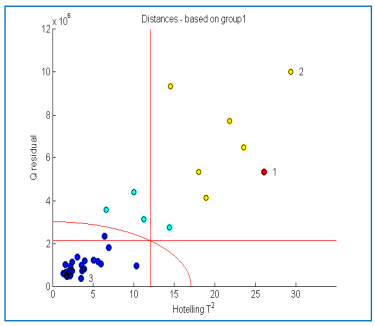
Understanding Dissolution Performance of Capsule Product

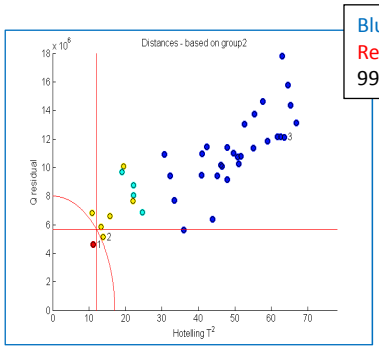
- A 2-class SIMCA model was created using low-pressure and high-pressure capsules.



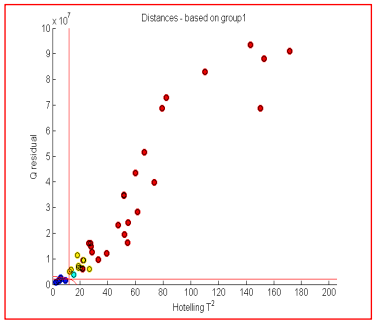


Chemometrics and Classification Success

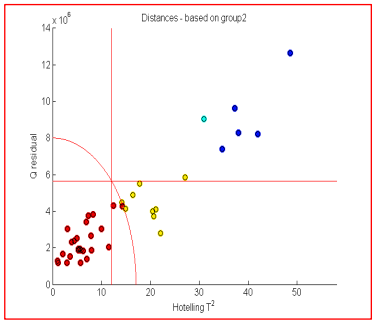




Blue and Cyan = Acceptable
Red and Yellow = Unacceptable
99% Confidence Limit Shown in Red



Low Pressure Plot



High Pressure Plot

- 6 Rotational Angles used to represent a capsule.
- Classification Success rates of 97.5% and 95% for unagglomerated and agglomerated validation sets.
- X-ray images coupled with greyscale histograms and chemometrics can be used to classify the performance of this product.

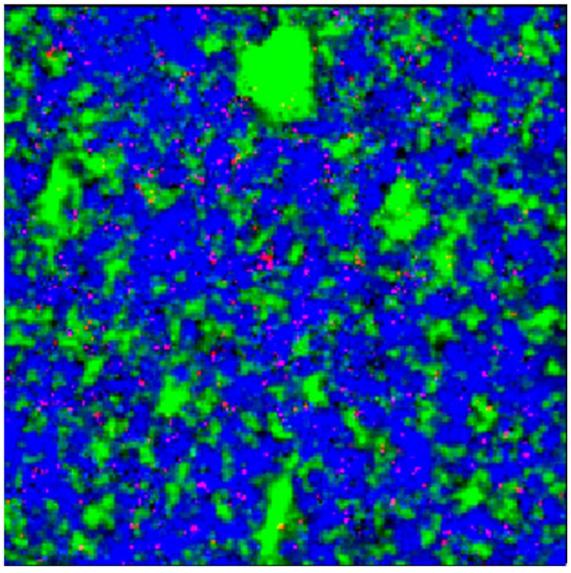
Pfizer GLOBAL SUPPLY

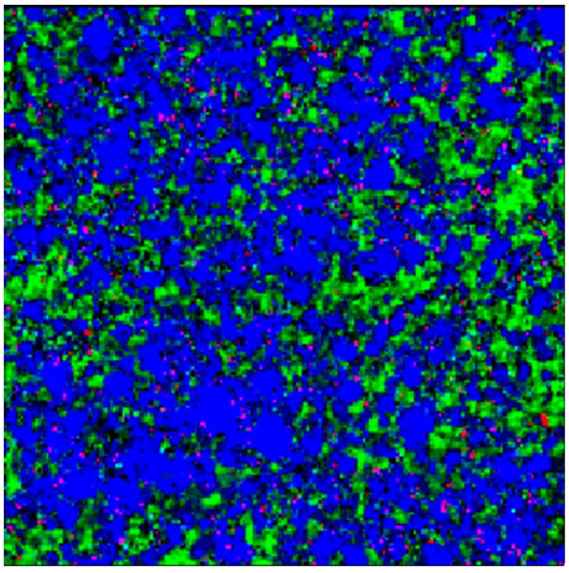
Solid State Characterisation for Understanding Impurity Levels

Question: Why are levels of 1 imp higher at one DP site?

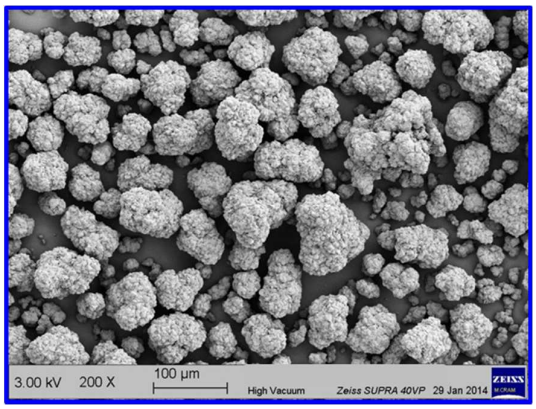
Pfizer GLOBAL SUPPLY

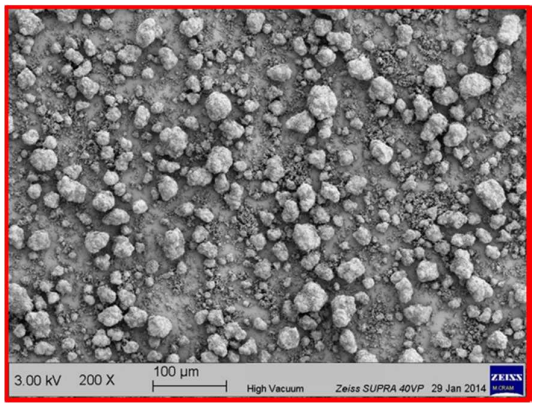
- Both sites use same API source
- Chemical Images reveal difference in one excipient.

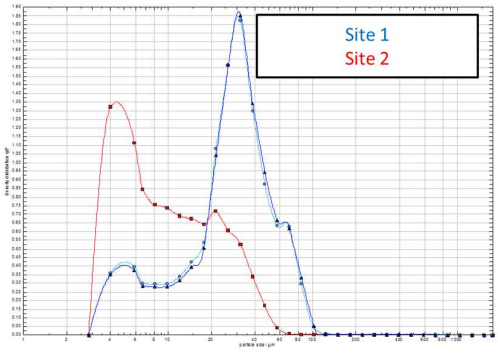


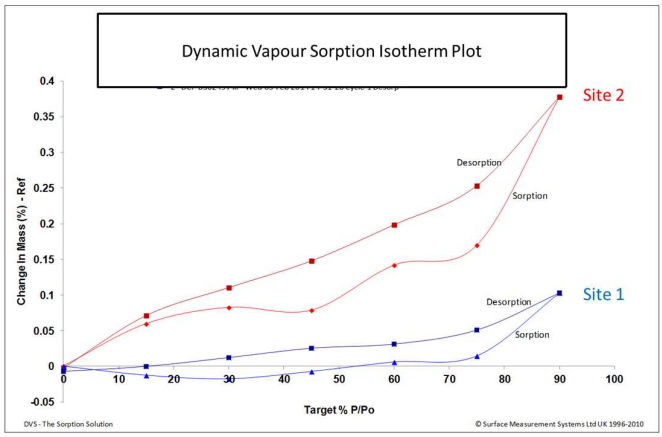


Comparison of Excipient Properties

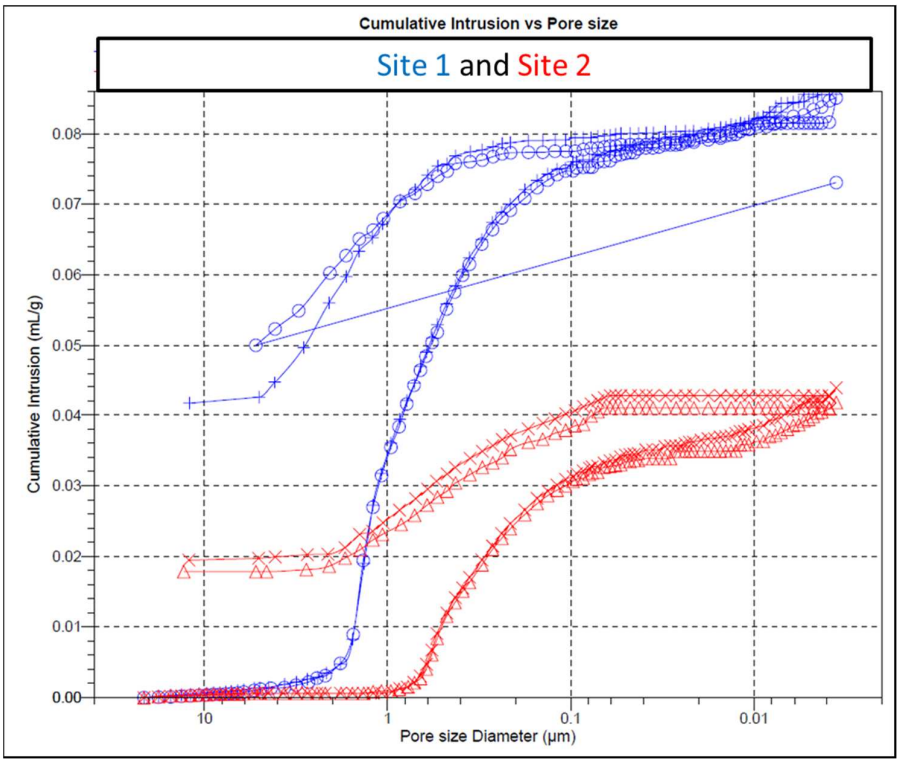








How does this impact Tablet Stability Performance?

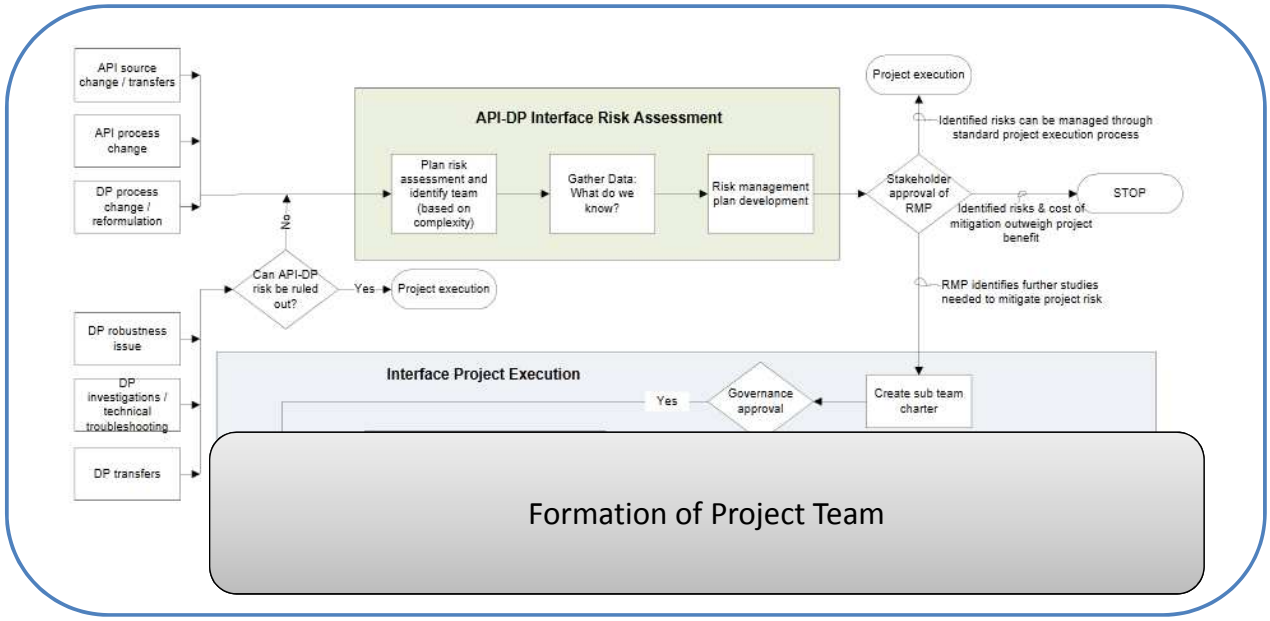


Pfizer GLOBAL SUPPLY

Implemented Learnings

Building Learnings into Workflow for API-DP

Pfizer GLOBAL SUPPLY



Leveraging API-DP Interface

- By building understanding of material characteristics (be that API, excipients or drug product) understanding of product attributes are increased.
- Leveraging this knowledge in combination with that of API and Drug Product enables more robust drug products.
- It also enables low risk transfers and sourcing decisions.