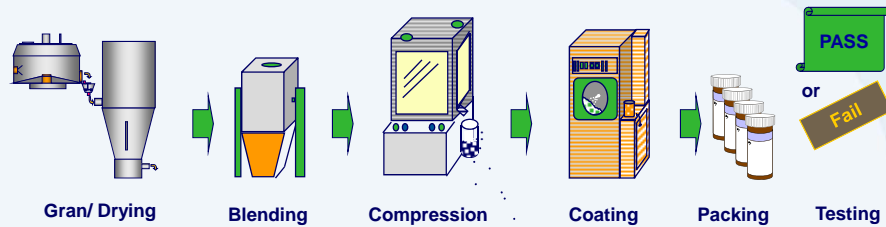
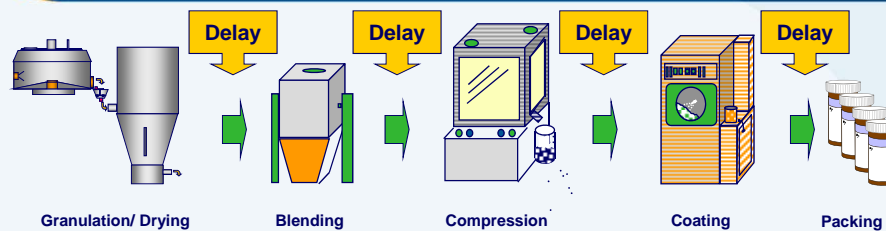


Traditional OSD Secondary manufacturing process...



End Product Testing alone is insufficient to understand the complex interaction of product and process

Where Are We Going Wrong ?



Result is high inventory including “work in progress”, long lead times, disconnected processes, long changeovers, high process losses off line analysis, low utilisation etc

V Blenders: lab and pilot plant scale



Lab scale



Pilot Plant Scale

...and Commercial Scale !!!



Current Situation - Key Measures

<i>Key Measure</i>	<i>Typical</i>
<i>Material waste (mass balance)</i>	5% upwards
<i>Manufacturing lead time</i>	6 weeks
<i>Manufacturing stock (including work in progress)</i>	2 months
<i>Manufacturing complexity & potential for errors</i>	high
<i>Overall equipment effectiveness</i>	30%
<i>Total transit distance</i>	miles
<i>Labour utilisation on added value tasks</i>	15%

Continuous Processing programs at GSK

- Continuous Blending – Direct Compression (DC)
- Continuous Hot Melt Extrusion – Blending – Compression
- Continuous Roller Compaction – Blending – Compression
- Continuous HSWG / FBD – Blending – Compression

- Also create a “**Continuous**” version for R&D of the same “**Plug Flow**” representative Scale
- Continuous Development: 80 – 90% reduction in API requirement from PoC through to completion of Phase III studies
 - “DoE in a day”

Design Space

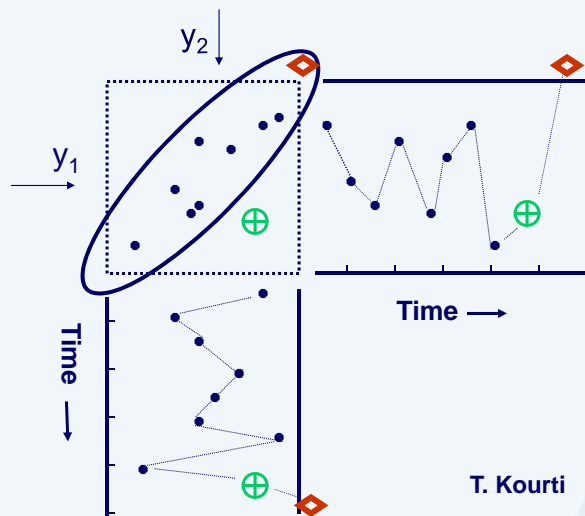
“...the multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality”

Working within the design space is not considered as a change

(It is GTM's view is that determining new areas outside of the registered Design Space is really Continual Improvement)

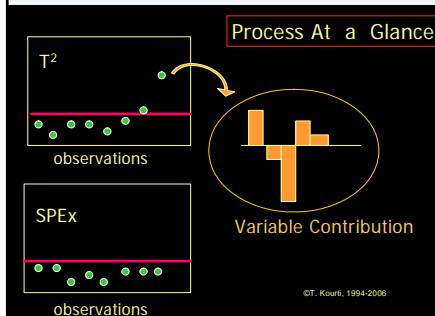
Multivariate Analysis (MVA)

Quality is Multivariate



PROCESS SIGNATURE: T^2 + Squared Prediction Error (SPE)

Combination of all the variables affecting the process and product and their correlations both at each time interval but also their time correlations for the duration of the process (auto and cross correlations for the entire batch or as a continuous operation)



They are therefore a more powerful tool to describe the “**overall process signature**”

T. Kourti

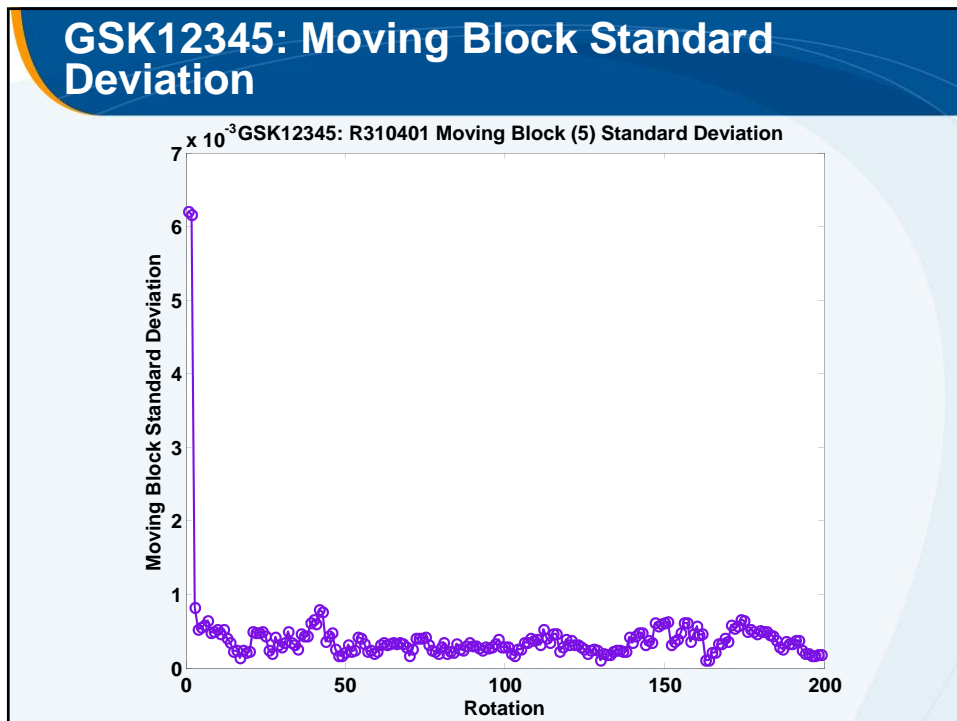
Design Space

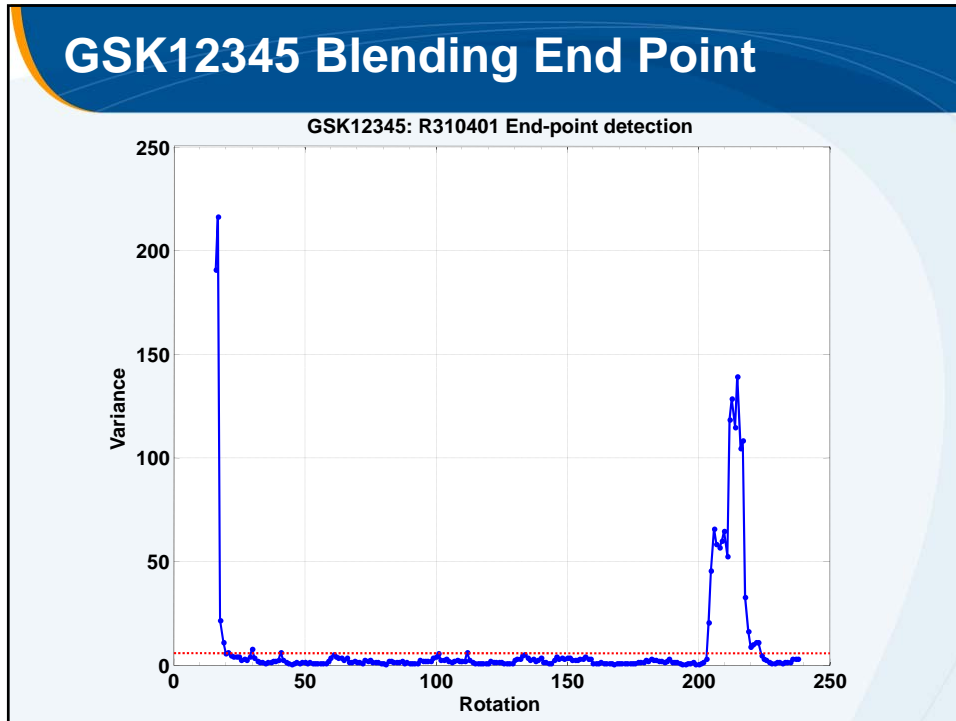
MSPC indices can be directly related to the concept of the Design Space

Maintaining the T^2 and SPE within their good operation limits (obtained by relating process and raw material variability to acceptable product quality) is nothing more (or less) than ensuring that the operation (raw materials and process) is within the design space

continuously... in real time!

T. Kourti





GSK101010: 3D and 2D Slice Visualisation

- **Inputs:** Volume % and MPS for each constituent
- **Macropac Simulation Settings:**
 - Monodisperse constituents
 - Box Size 2400 x 1200 x 750 (arbitrary units)
 - Maximum Packing, maintaining volume fractions

Constituent	Particle colour
101010	
Avicel PH102	
SSG	

filled tablet

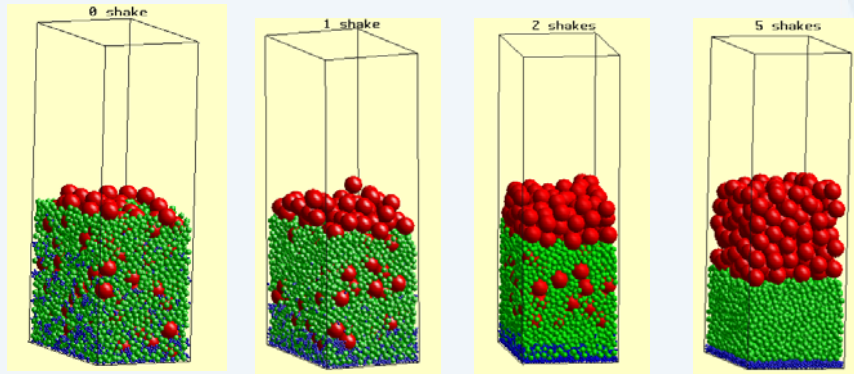
Z - axis cross section (20 -40 %)

P. Trusty

GSK101010: Sequential settling to investigate Segregation Susceptibility

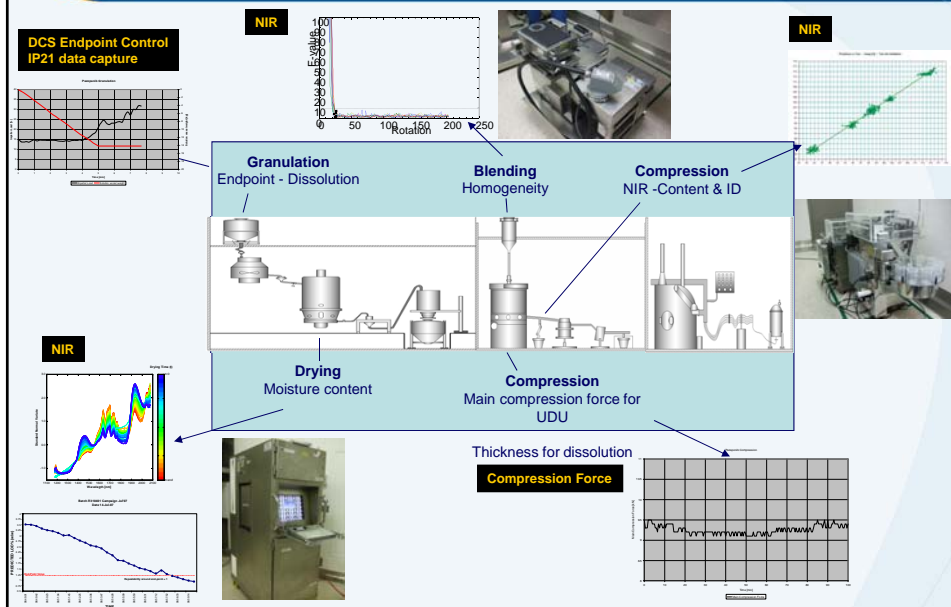
- **Inputs:** Volume % and MPS for each constituent
- **Macropac Simulation Settings:**
 - Monodisperse constituents
 - Box Size 4800 x 2400 x 1500 (arbitrary units)
 - 10000 particles packed, maintaining volume fractions

Constituent	Particle colour
101010	Red
Avicel PH102	Green
SSG	Blue



- Segregation with increasing number of "shakes" due to large particle size differential within blend

PAT use within the Control Strategy



Potential Answer... Integrated Manufacturing

Integrated batch or continuous manufacture applied to conventional granulated products

- Drive to reduce variability, achieve 6 sigma
- High yield, increased productivity
- Lower operating, inventory and capital costs ...increased competitiveness
- Small, fully enclosed processes, high level of automation, reduced manual intervention
- In-Process controls are “in-line” or “at line”
- Real Time Control
- Real Time Assurance of Quality

What we had to change...(for C HSWG)

- Change the Method of **wet densification**
- Change the Method of **blending**
- Change the Method of **coating** (still WIP)

What we could keep...

- Method of **drying** (but with some modification)
- Method of **compression**

What we removed...

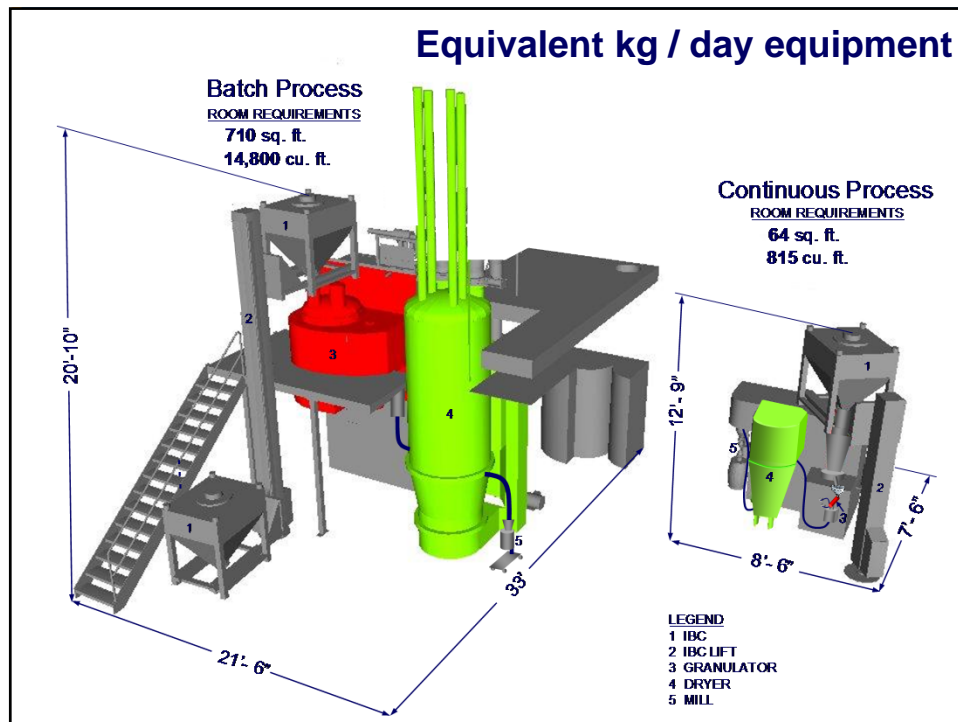
“Inertia” from the manufacturing system

Concept: 100 Kg / hr installation



Scale up?





What we think we can achieve...

Reduce the Size of Core Manufacturing Facilities by ~ 70%

Reduce Direct Manufacturing Costs by ~ 50%

Reduce Indirect Manufacturing Costs by ~ 50%

Reduce the Cost of Building New Capacity by ~ 30%

Reduce the time taken to build new capacity by ~ 33%

Make Manufacturing Capacity Modular and Mobile

Eliminate Scale Up to Full Capacity

Significantly reduce development costs: ~ 85% reduction in API

Acknowledgements



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Dora Kourti

Luke Bellamy

Paul Frake

Sander van den Ban

Paul Trusty

Patrick Hyatt

Dave Rudd

GEA

Siemens

Ray Scherzer

**Powder In - Tablets Out;
Continuous Manufacture**

**Gordon T Muirhead
Vice President
GlaxoSmithKline**

