Use of Applied Modelling: Approaches to improve product performance in design and setting meaningful specifications

A combined pharmaceutical science, materials science and chemical process engineering approach

16 October , Heidelberg, Germany

ir Sander van den Ban, CEng

Drug Product Development : Commercial View

proactively include context of Product Lifecycle & Commercial Drivers

product & product quality design criteria

manufacturability (technical) & commercial design criteria

e.g.
efficacy, safety
...

RISK

e.g.
"batch" size
processing route
supply chain
manufacturability

The Economics of Quality – the Quality Maturity Model

MATURITY LEVEL				ANSI/ISO/ASQ Q9004-2000	
1	reactive approach	3	cont. improvement emphasized	5	
no formal approach	2	stable formal system approach	4	best in - class	

LESS LIKE

reactive/corrective

Quality Management System used to comply

produce "product A/B/C"

…

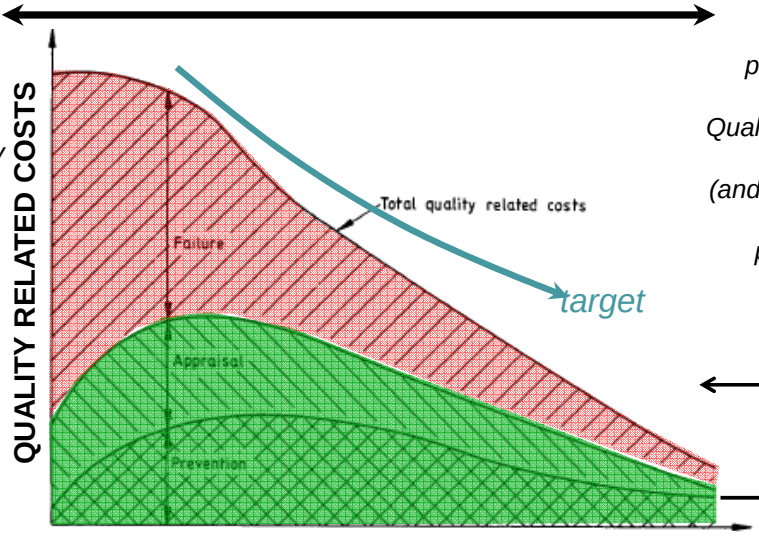
MORE LIKE

proactive/preventative

Quality Management System drives quality/cost (and competitive advantage)

produce "medicines"

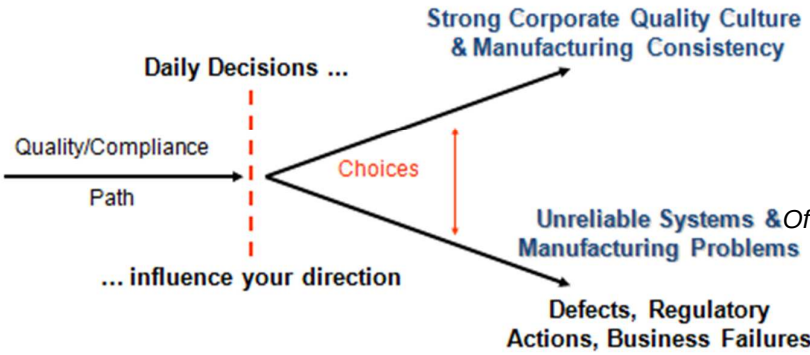
…



BS6143 Guide to the Economics of Quality part 1 process cost model, part 2 prevention, appraisal and failure model

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Leadership and the Corporate Quality Culture



Adapted from Richard Davis (2004)

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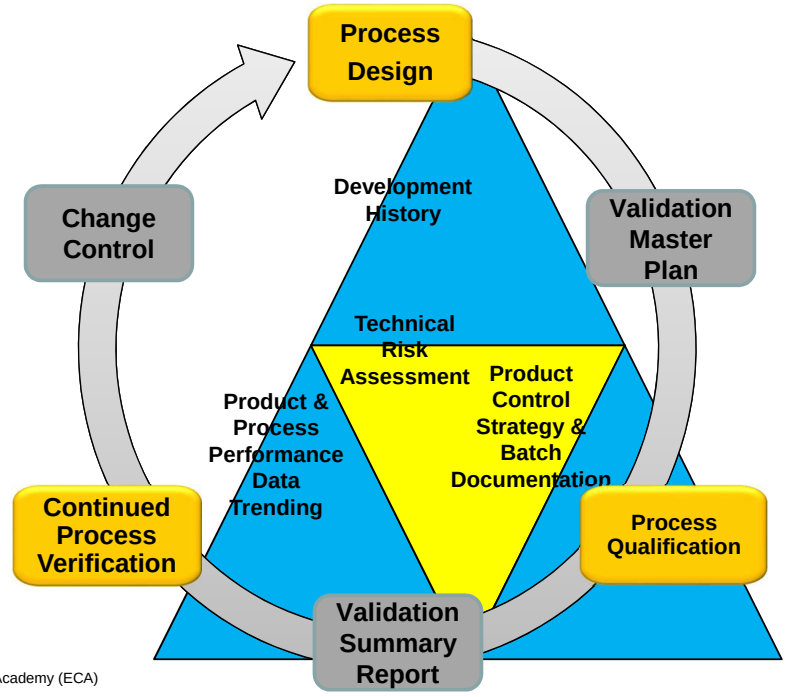
Associate Director
Office of Manufacturing and Product Quality
Office of Compliance

IFPAC Annual Meeting (Baltimore, MD)
January, 22-25, 2013

Product Quality Lifecycle Management



Typical Shift in Risk Assessment & Management

from "design" to "development" to "daily"

Technical Quality Risk Assessment

Early Phase Development	Late Phase Development	Commercial Manufacture/Supply
(product design)	(its process development)	(daily)

area of most focus

Product
e.g. specification

specific product & "generic" process understanding

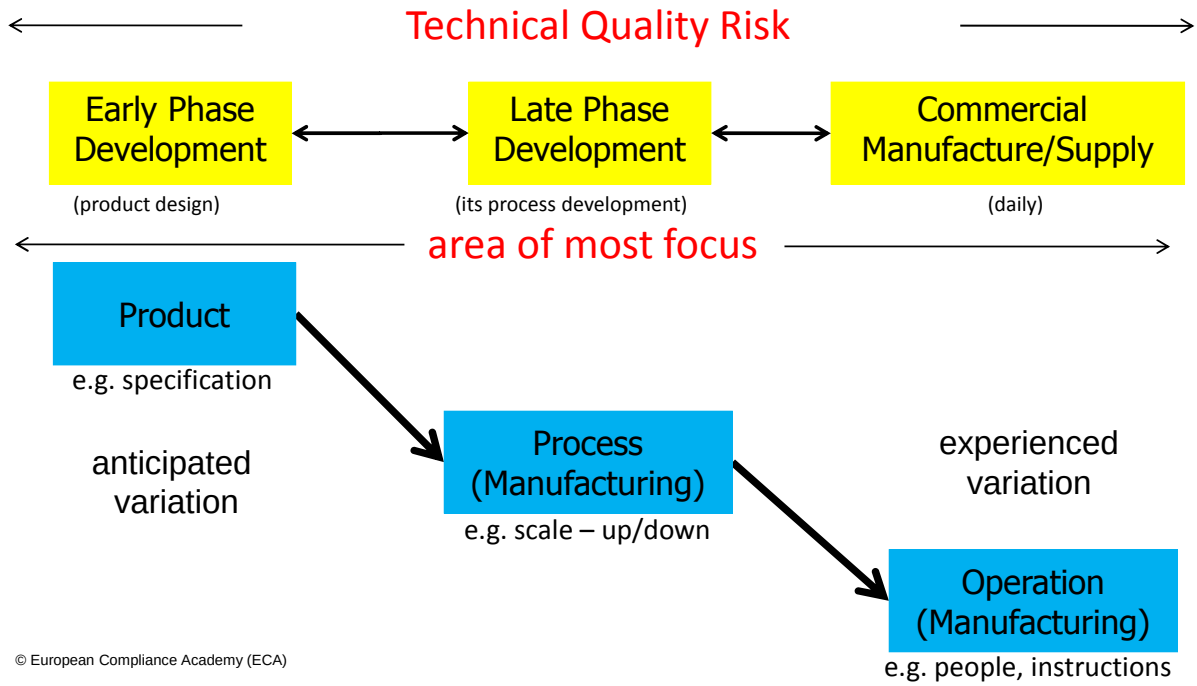
Process (Manufacturing)
e.g. scale – up/down

specific product & process(ing) understanding

Operation (Manufacturing)
e.g. people, instructions

Typical Shift in Product Lifecycle & Management

from “design” to “development” to “daily”



Pharmaceutical compaction

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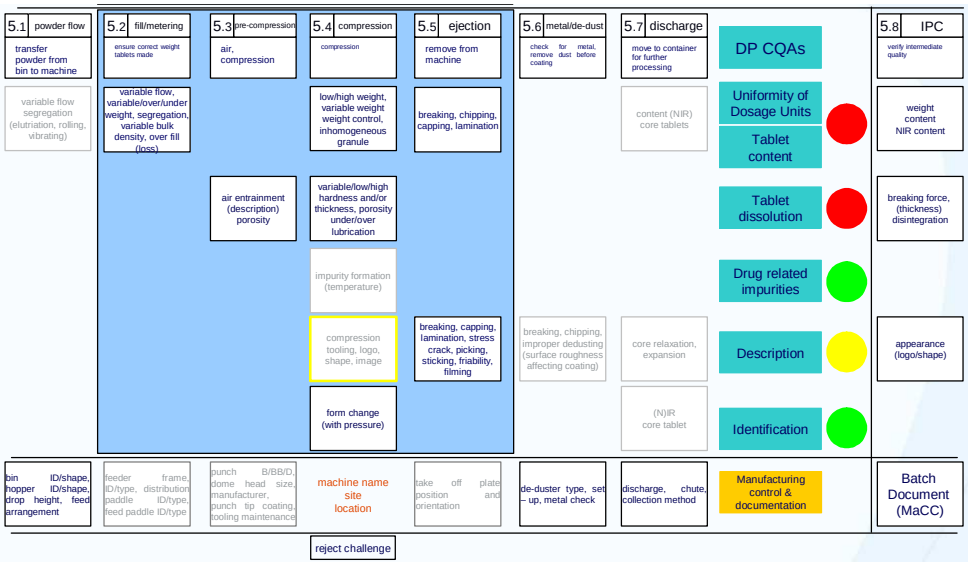
typical technical risk associated with tabletting



- powder flow, potential segregation
- low/high/variable weight
- appearance from compression and/or handling
- low/high/variable hardness, DT, dissolution
- lubrication impacting hardness, dissolution

tablet manufacture

how do we make sure a tablet is fit for purpose?

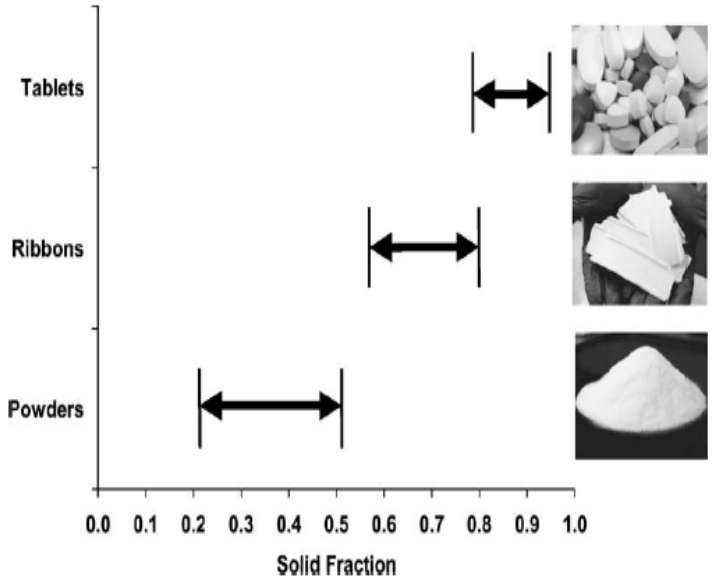
- Strong enough to be handled
  - Adequate Tensile strength (Hardness)
- Weak enough to disintegrate in the body
  - Low Disintegration time (Typically < 15mins)
- Manufacturable and Elegant
  - High throughput
  - Defect free
- Safe and efficacious
  - Quality by Design and PAT
  - End testing

tablet assessment

evaluation of commercial scale performance in development

- Initial tablet assessment on 3 areas:
  - Tensile Strength (USP <1217>)
  - Solid Fraction (tablet density (m/vol)/true granule density)
  - Compaction Pressure (force / die area)
  - (Ejection Stress) (ejection force / tablet belly band area)
  - all of the above can be obtained from at – line measurements

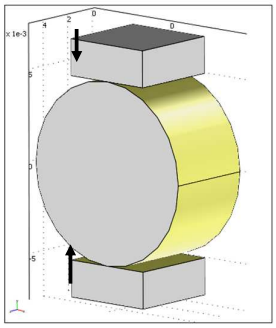
solid fraction
transformation during processing

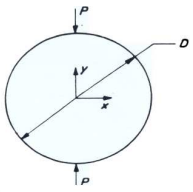


After Zinchuk et al 2004

Tensile strength

- Flat faced disc tablet





$$\sigma = \frac{2P}{\pi D t}$$

σ = tensile strength (MPa)
P = fracture load (N)
t = thickness (mm)
D = diameter (mm)

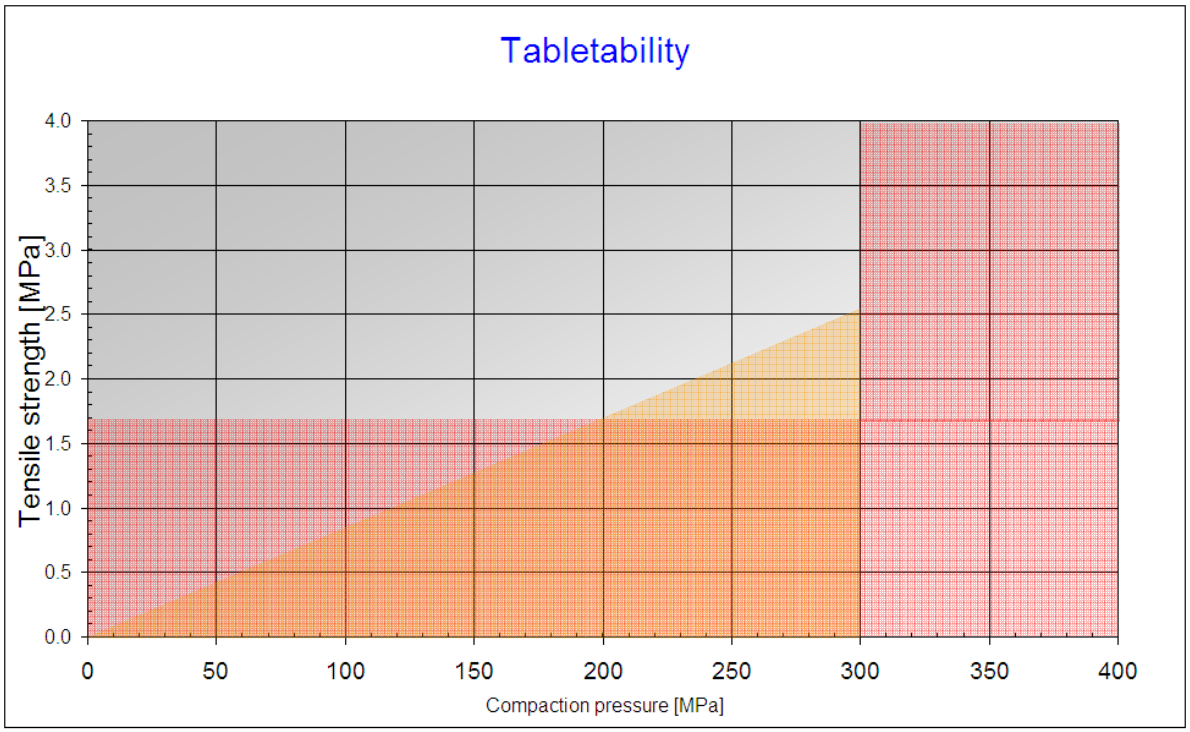
- Shaped round tablet (USP nomograph 1217)

$$\sigma = \frac{10P}{\pi D^2}(2.84\frac{t}{D} - 0.126\frac{t}{W} + 3.15\frac{W}{D} + 0.01)^{-1}$$

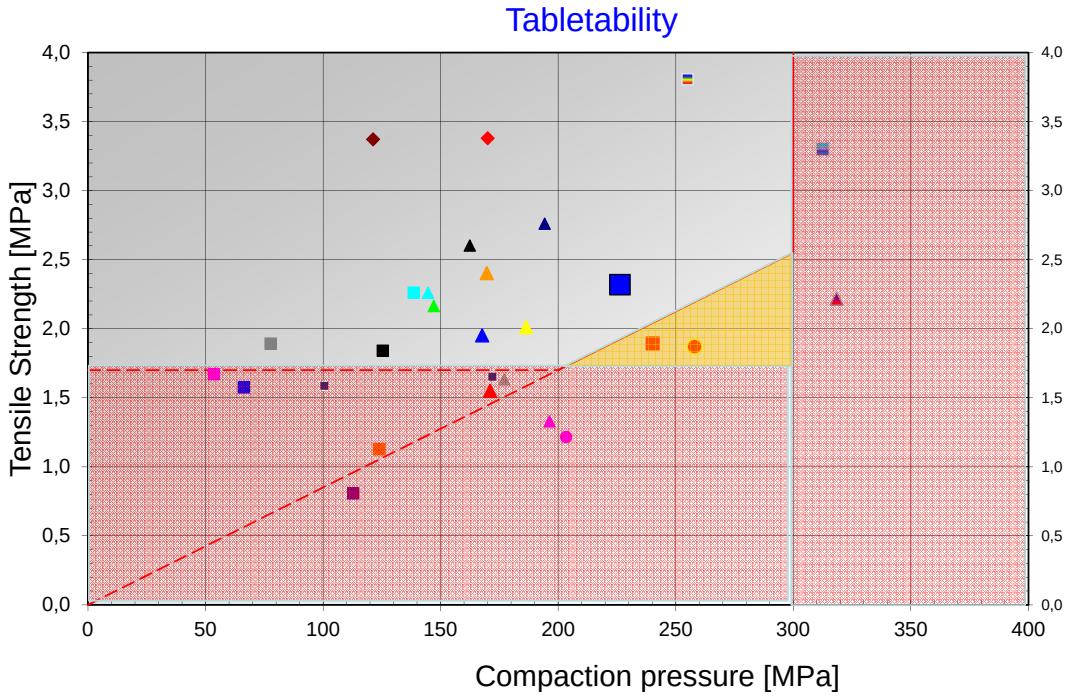
- Shaped oval tablet*

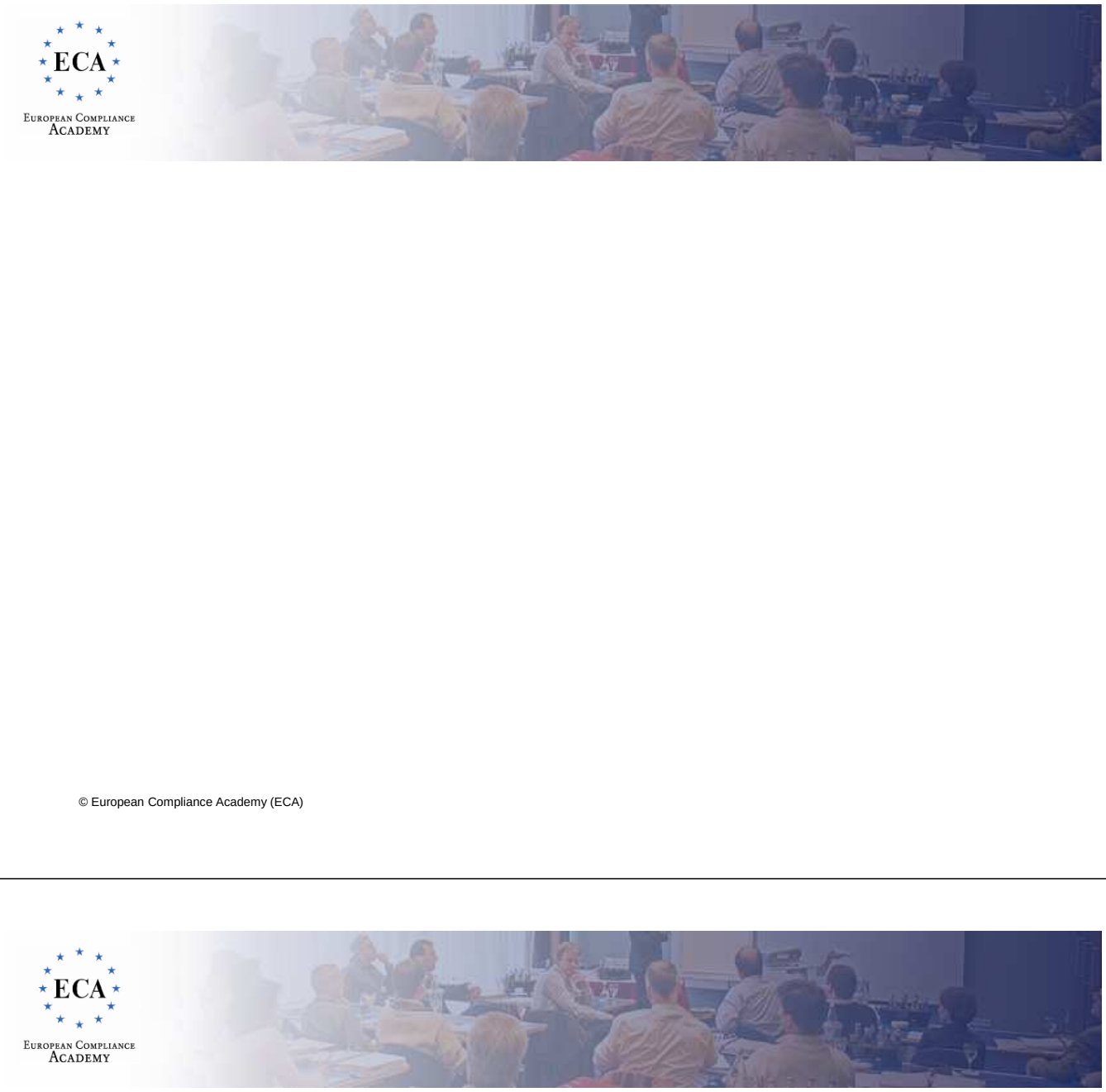
$$\sigma = 2/3\{\frac{10P}{\pi D^2}(2.84\frac{t}{D} - 0.126\frac{t}{W} + 3.15\frac{W}{D} + 0.01)^{-1}\}$$

K. Pitt, http://dx.doi.org/10.1016/j.powtec.2011.12.060



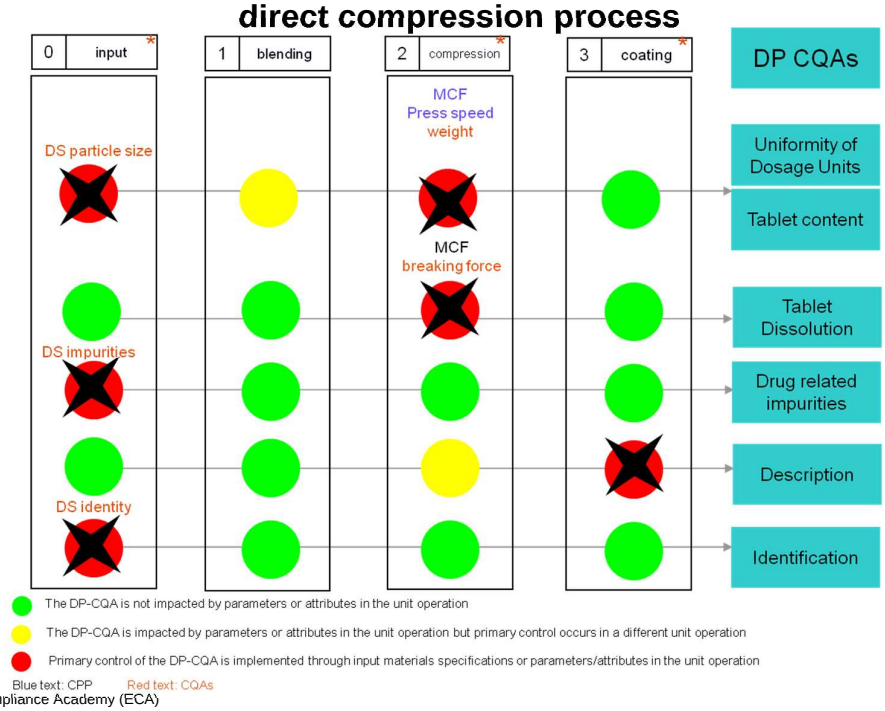
Tabletability - marketed and in development products





summary of a control strategy

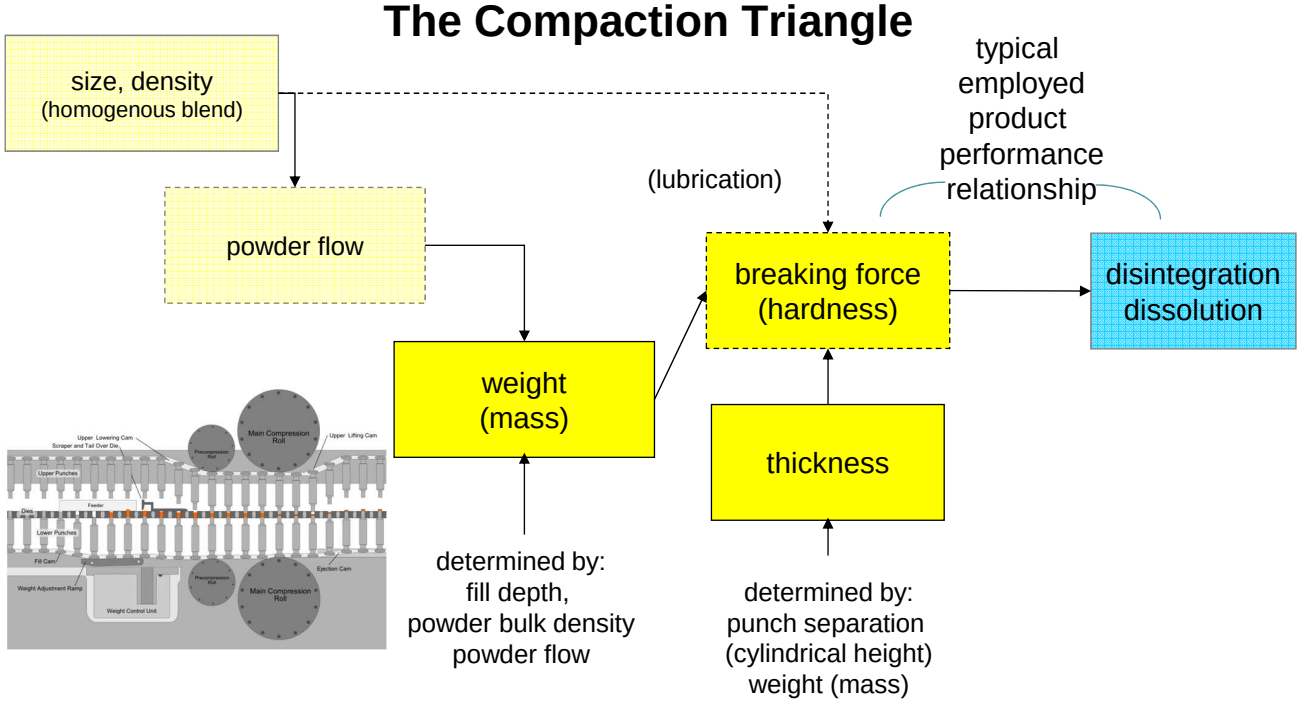
direct compression process



Process Validation

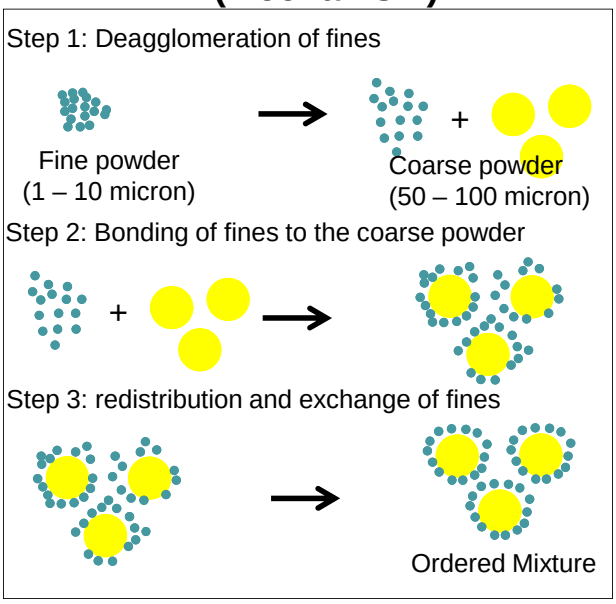
- Direct Compression Process – Content Uniformity

The Compaction Triangle

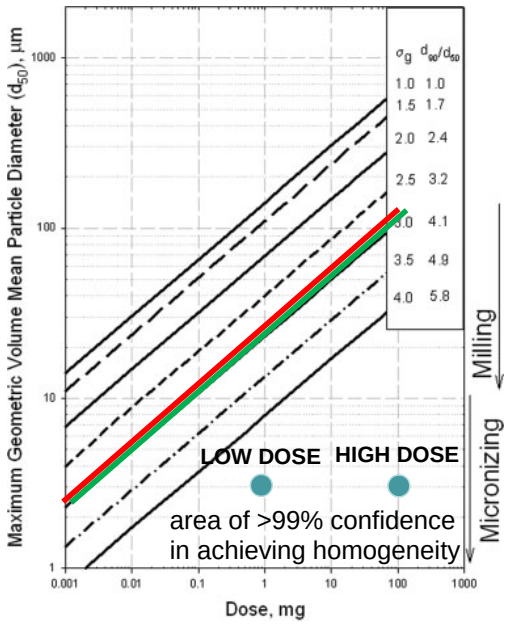


Direct Blending - Low dose products

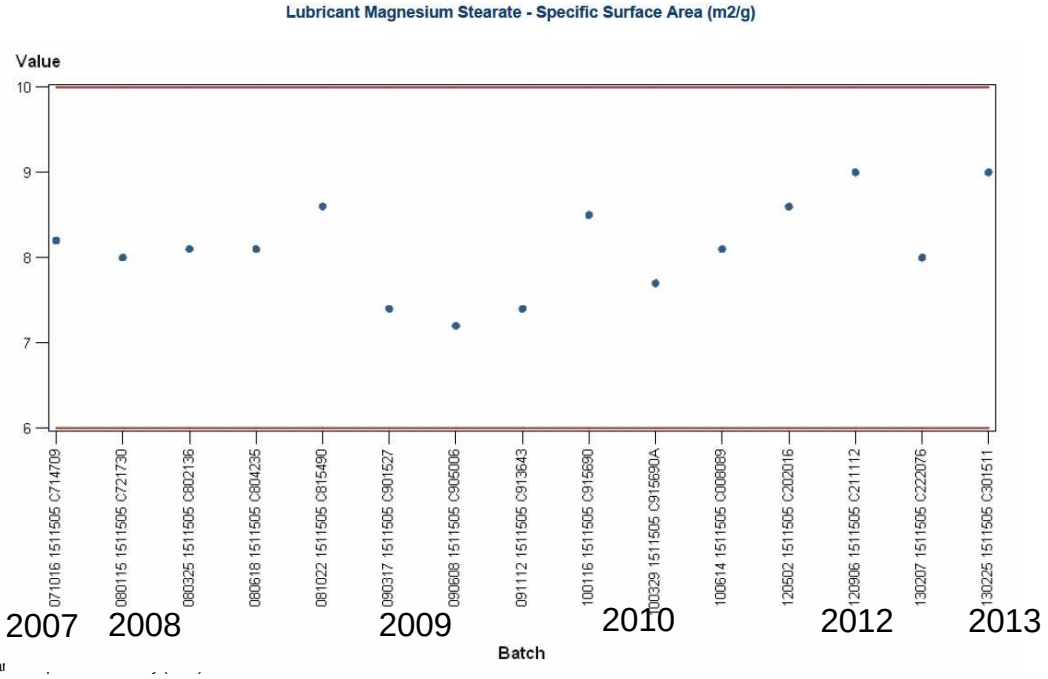
Ordered Mixing (Mechanism)



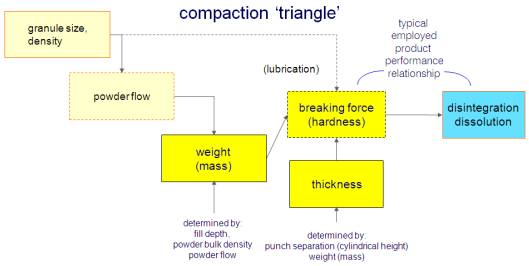
Particle Size Limits to Meet Content Uniformity Criteria

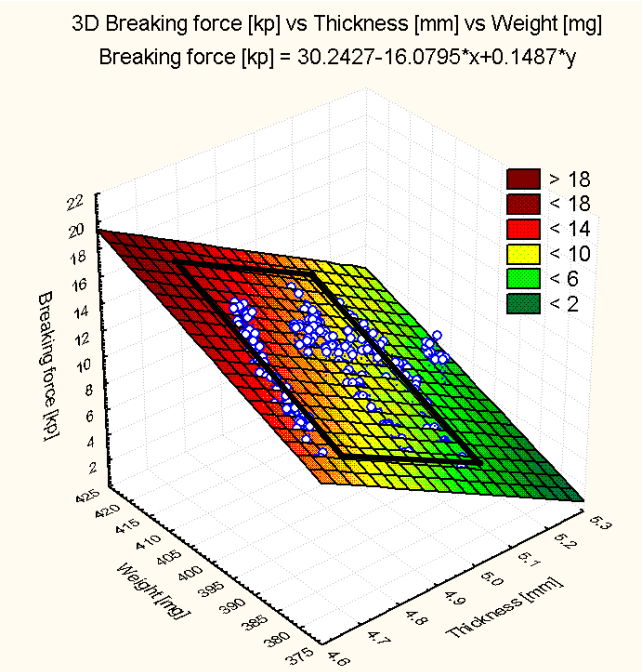


Formulation robustness to excipient variation



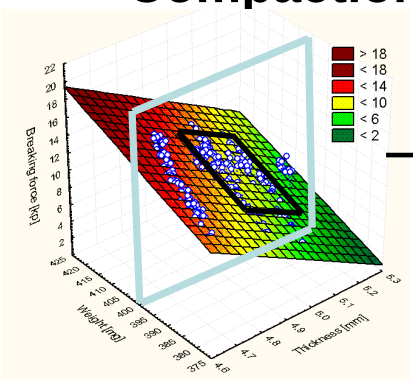
Compression Assessment: Data

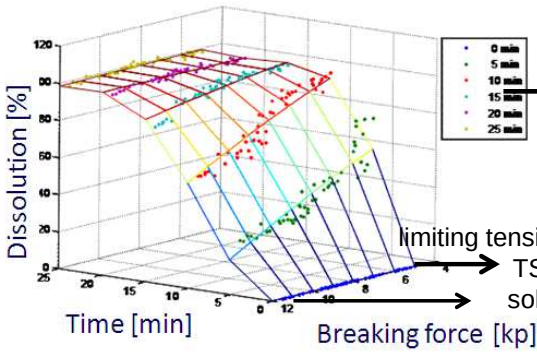




weight/thickness varied as "double H – gearbox pattern"

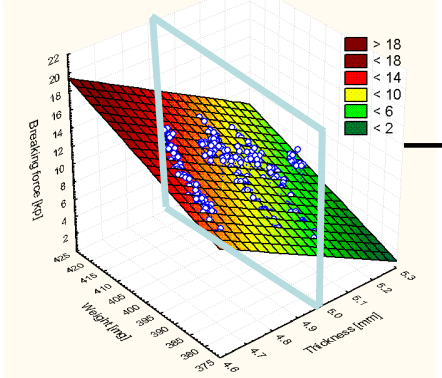
Compaction – Design Space Development

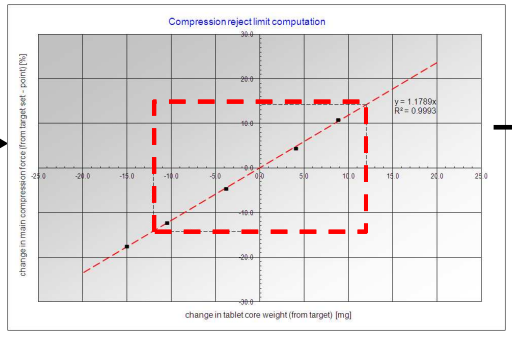




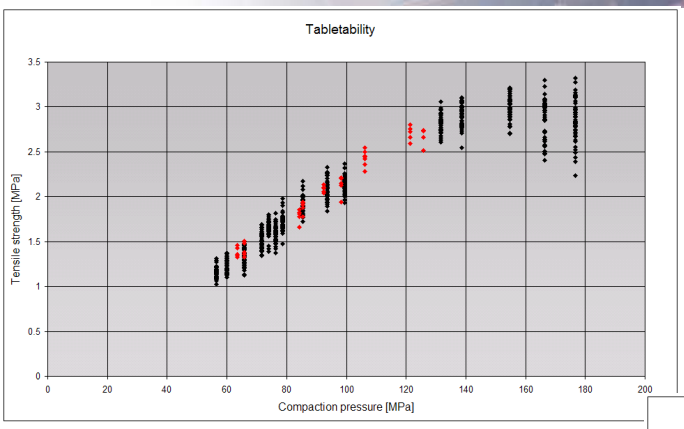
IPC limits breaking force to assure dissolution

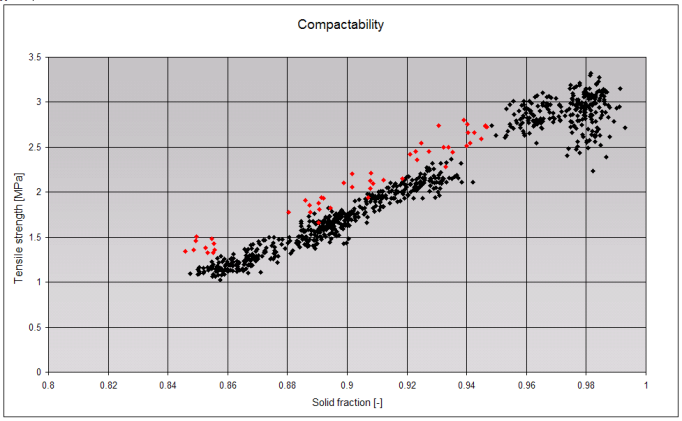
limiting tensile strength ~ 1.7 MPa
TS = 1.6 MPa
solid fraction ~ 0.95
SF = 0.93



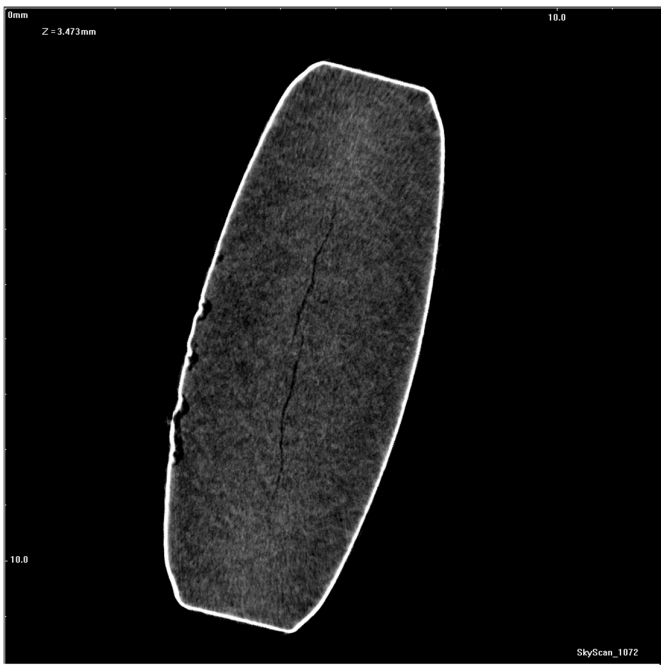


compression force control to assure weight (uniformity)



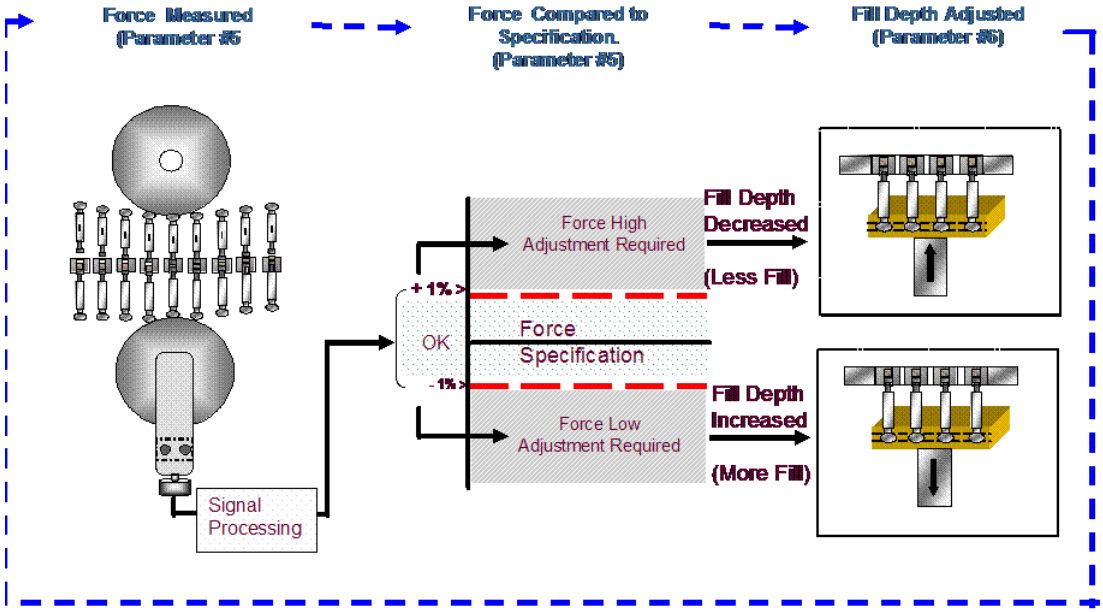


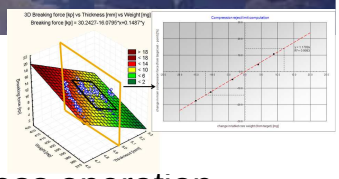
not all mechanical failure is visible to the naked eye



- Tablet debossing = 150 µm

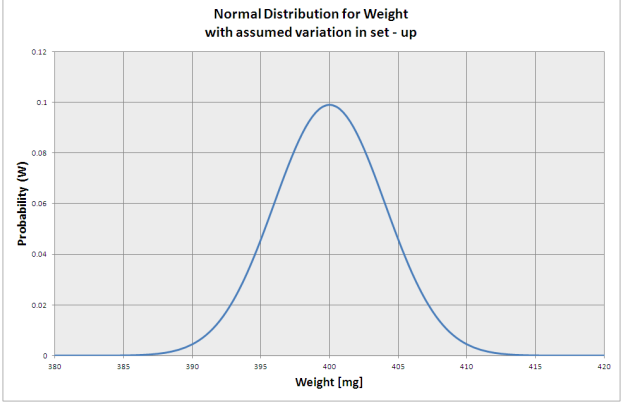
Compression Force – weight control mechanism mean and individual weight (uniformity)





Weight variation - anticipated

- Method of estimating weight distribution in normal process operation
  - commercial manufacturing ~ 4% relative standard deviation in MCF
  - assumed variation in ability to meet target weight



Key “metrics”:

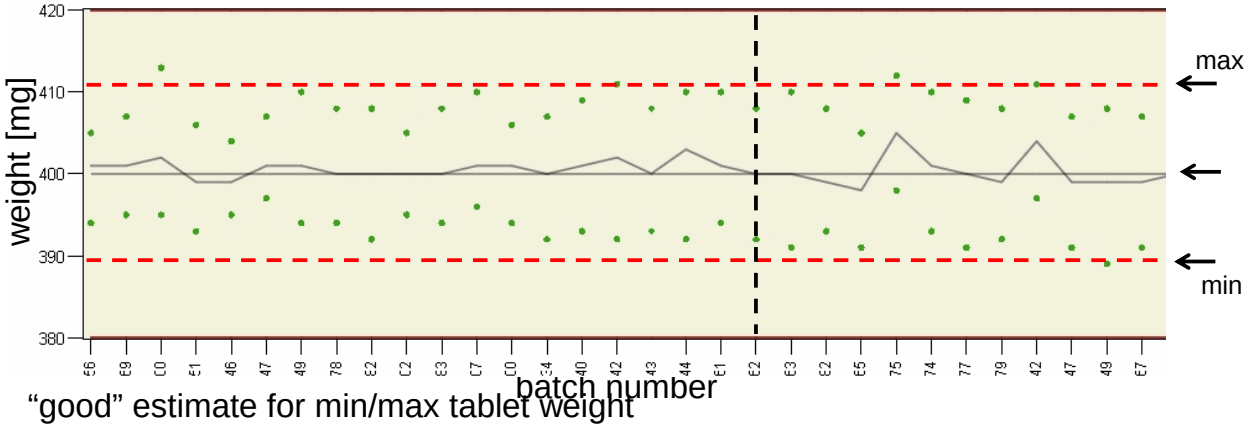
standard deviation ~ 3.9 mg

min/max 389 – 411 mg

sigma level ~ 5

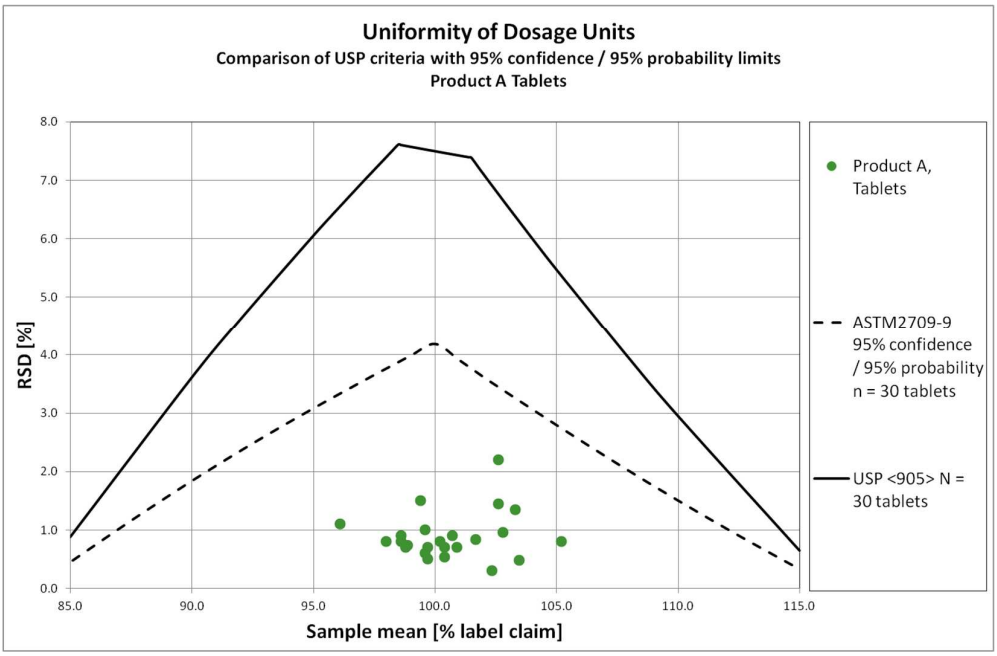
Weight variation – actual variability

- product performance 2009 – 2012 (min/max and average)



- "good" estimate for min/max tablet weight
  - estimated min/max 389 – 411 based on 4% rsd force variation
- "good" estimate for weight variation compared to measured variation 3.6 mg
- observed ~ 200 "defects" per 0.8M tablets as weight rejects, or sigma level of 5
  - estimated sigma level ~ 5

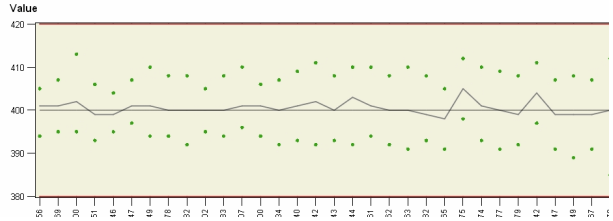
Justified sampling as per Bergum method ASTM2709-9

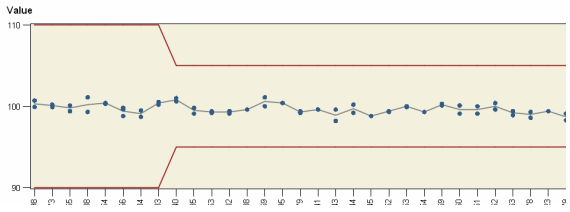


Routine trending of product data

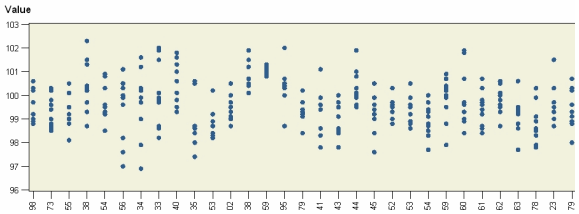
intending to apply Statistical Process Control

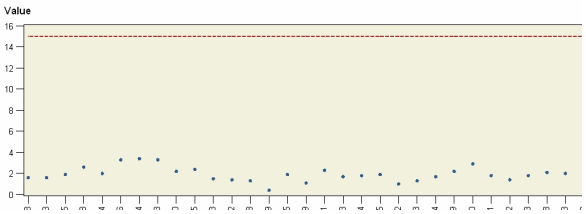
- Individual weight (min/max/mean) Content (min/mean/max) in % LC



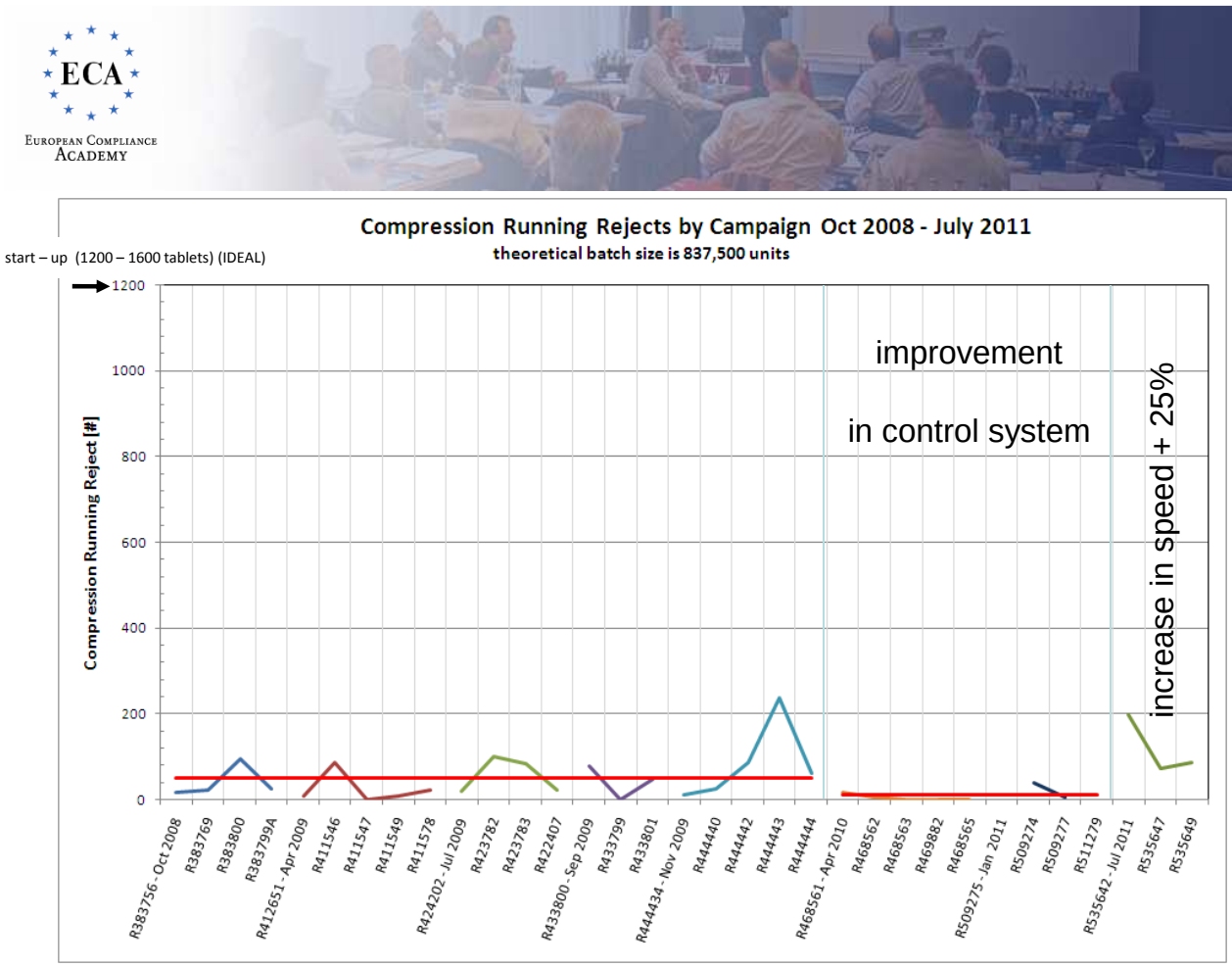


- Individual content in % LC Acceptance value, k





2012 London Olympic Games
“performance of the aggregation of marginal gains”



Conclusion

- Technical + Quality Framework based on ICH/PV guidance will drive design & operation of robust and effective manufacturing processes of quality product

- An effective control strategy is industrialised and translated to the “shop floor”
  - e.g. sampling, data trending & review, batch mfg instructions, …

- Unlock its value via the “performance of the aggregation of marginal gains”