Quality by Design in Action:
Improving Product Quality by the Transformational Use of Process Understanding in Design, Development, and Commercial Supply

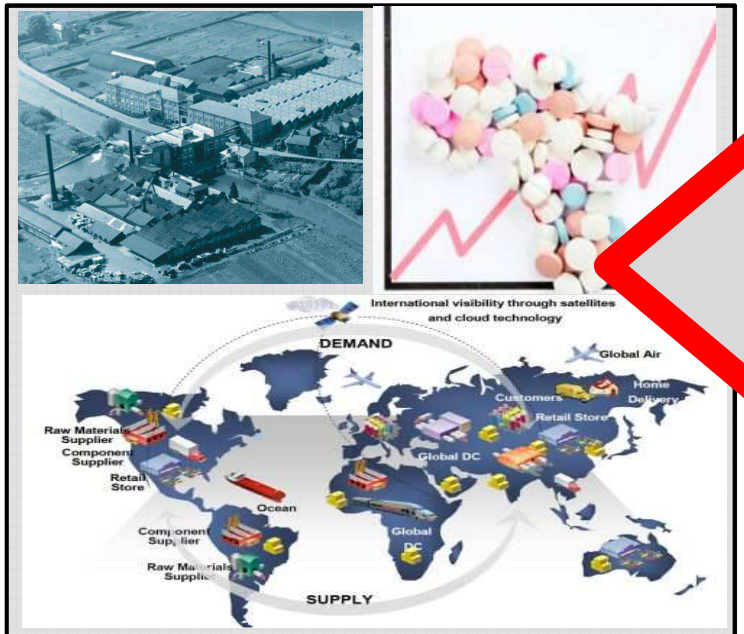
ir Sander van den Ban CEng EurIng MIChemE
Product Lead, Oral Solid Dose Centre of Excellence

Heidelberg October 2014

Drug Product Development : Commercial View

proactively include context of Product Lifecycle & Commercial Drivers

product & product quality design criteria

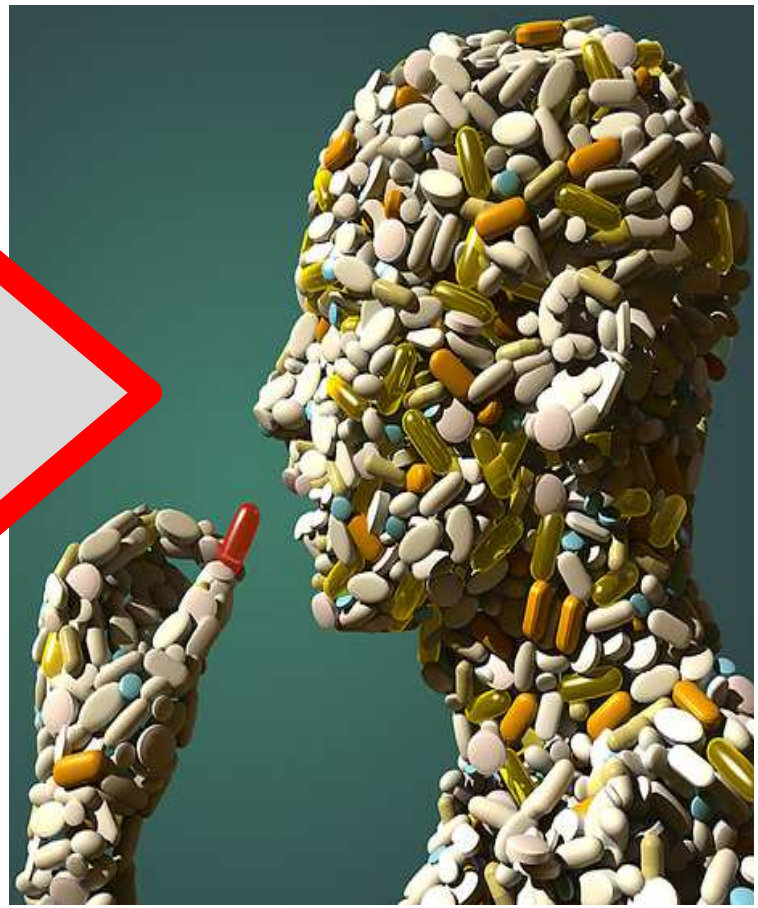


manufacturability (technical) & commercial design criteria

e.g.
efficacy, safety
…

RISK

e.g.
“batch” size
processing route
supply chain
manufacturability



In control ? High Risk ?

In control ? More risk ?

Embrace Risk

… access groundbreaking new possibilities …

Technical Risk Assessment

…excerpts from the PAT Guidance …

built-in quality, science and engineering principles, design, control, …

Using this approach of *building quality into products*, this guidance highlights the necessity for process understanding and opportunities for improving manufacturing efficiencies through innovation and enhanced scientific communication between manufacturers and the Agency. Increased emphasis on *building quality into products* allows more focus to be placed on relevant multi-factorial relationships among material, manufacturing process, environmental variables, and their effects on quality. This enhanced focus provides a basis for identifying and understanding relationships among various critical formulation and process factors and for developing effective risk mitigation strategies (e.g., product specifications, process controls, training). The data and information to help understand these relationships can be leveraged through preformulation programs, development and scale-up studies, as well as from improved analysis of manufacturing data collected over the life of a product.

Pharmaceutical manufacturing continues to evolve with increased emphasis on science and engineering principles. Effective use of the most current pharmaceutical science and engineering principles and knowledge — throughout the life cycle of a product — can improve the efficiencies of both the manufacturing and regulatory processes. This FDA initiative is designed to do just that by using an integrated systems approach to regulating pharmaceutical product quality. The approach is based on science and engineering principles for assessing and mitigating risks related to poor product and process quality. In this regard, the desired state of

IV. PAT FRAMEWORK

The Agency considers PAT to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. It is important to note that the term *analytical* in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner. The goal of PAT is to enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: *quality cannot be tested into products; it should be built-in or should* ***be*** *by design*. Consequently, the tools and principles described in this guidance should be used for gaining process understanding and can also be used to meet the regulatory requirements for validating and controlling the manufacturing process.

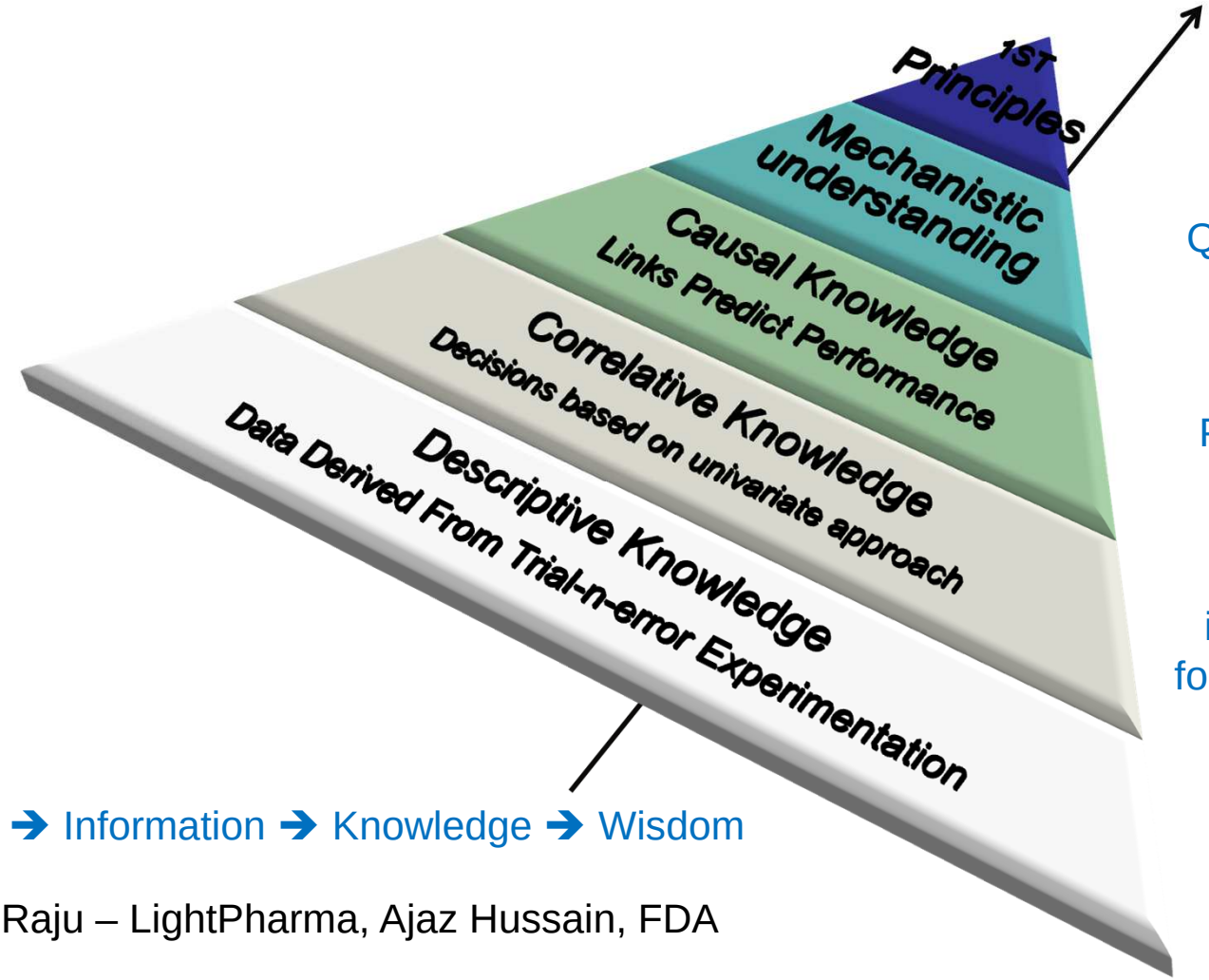
Guidance for Industry

PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

Pharmaceutical CGMPs
September 2004

An enhanced approach to quality risk management
The Knowledge Pyramid*



Strengthen

Quality Risk Assessment

With

Process Understanding

increase transparency
for regulators and industry

Data ➔ Information ➔ Knowledge ➔ Wisdom

*GK Raju – LightPharma, Ajaz Hussain, FDA

Knowledge Pyramid in action:

Empirical to mechanistic modelling in high shear granulation*

Table 1
An overview of different granulation models ranging from pure empirical to more or less mechanistic ones

Empirical

Mechanistic

Method	Characteristics	+/−	Reference
Multivariate process modelling	Statistical models	+ Good results within experimental space − Totally empirical	Miyamoto et al. (1997) Wehrlé et al. (1993)
Relative swept volume	Relative swept volume held constant during scale-up	+ Simple to use − Weak physical relevance	Schaefer (1988)
Tip speed	Tip speed held constant during scale-up	+ Simple to use − Weak physical relevance	Ameye et al. (2002)
Dimensionless numbers	Different dimensionless numbers held constant during scale-up	+ Simple to use − Weak physical relevance	Faure et al. (1999)
Normalized impeller work	Energy/mass = const	+ Theoretical relevance − Calibration required	Sirois and Craig (2000)
Power consumption and/or temperature	Power consumption as end point	+ New, promising − Macroscopic	Betz et al. (2004), Landin et al. (1999)
Integrated power over time	Mixer work as endpoint	+ New, promising − Macroscopic	Bardin et al. (2004)
Solid mechanics models	Friction models	+ Mechanistically derived − Dry powders only	Knight et al. (2001)
Population balances	Coalescence probability Coalescence factors functions of process variables	+ Mechanistically derived − Some empirical fitting required	Iveson (2002), Jansson et al. (2004), Sanders et al. (2003), Verkoeijen et al. (2002)
DEM models	Flow patterns	+ Mechanistically derived − Few particles in models	Kuo et al. (2002)

*I. Niklasson Bjorn et al. Chemical Engineering Science 60 (14) (2005)

The Challenge

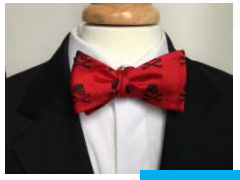
- Apply enhanced approach to quality risk assessment based on process understanding

  - Can we provide a scientific 1st principles basis for identifying CQA/CPPs ?

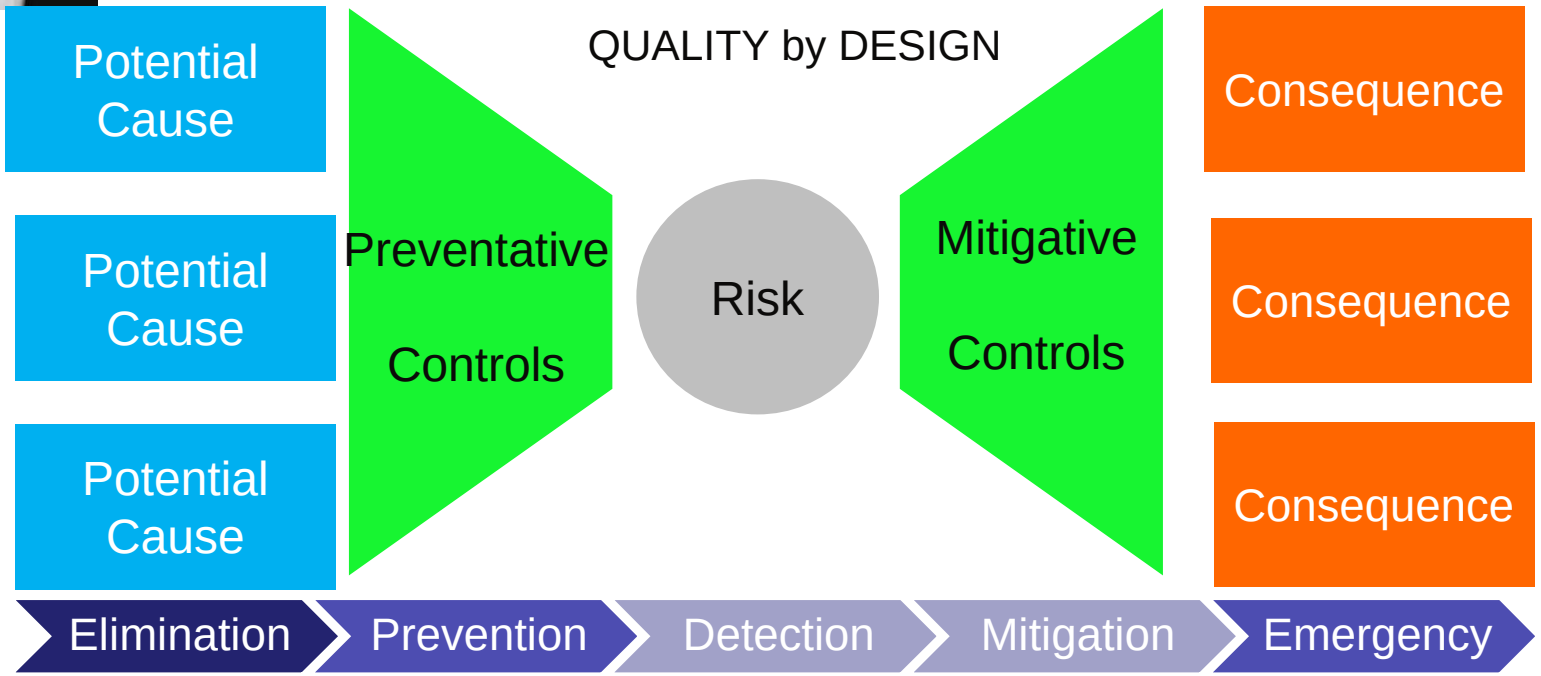
  - If possible, can we apply “generic” criteria as an “*indirect*” risk assessment ?

- In GSK, science based manufacturability criteria* are used to more effectively apply and utilise prior knowledge in (early phase) risk management

  *In the UK a “*manufacturability classification system (MCS)*” is in development with the *Academy of Pharmaceutical Sciences – Great Britain*



Risk Bowtie, the Quality Maturity Model, and Economics of Quality



- Quality system will drive quality/cost for a “best-in-class quality system” (see Quality Maturity Model, ANSI/ISO/ASQ Q9004 – 2000)

- A “2- σ stat”: CoPQ ~15-25% of total production cost, visible part of COPQ is 5-8% of total production cost

Quality System Maturity (ANSI/ISO/ASQ Q9004-2000)

Maturity level	Performance level	Guidance
1	No formal approach	No systematic approach evident, no results, poor results or unpredictable results
2	Reactive approach	Problem- or corrective-based systematic approach; minimum data or improvement results available
3	Stable formal system approach	Systematic process-based approach, early stage of systematic improvements; data available on conformance to objectives and existence of improvement trends
4	Continual improvement emphasized	Improvement process in use; good results and sustained improvement trends
5	Best-in-class performance	Strongly integrated improvement process; best-in-class benchmarked results demonstrated

Source: American Society for Quality (2000, p. A8)

BS6143: Guide to the Economics of Quality

part 1: process cost model, part 2, prevention, appraisal and failure model

TOTAL PRODUCTION COST

=

COST-OF-CONFORMANCE (PROCESS COST)

intrinsic cost of product mfg'd to specified standard process in 100% effective manner
– does not imply efficiency or necessity –

innovation
new technology

EXAMPLE:
basic cost of process (yield, cycle time, inventory)
design & development cost
design review, validation and verification
staff training & compliance

+

COST OF NON - CONFORMANCE (QUALITY COST)

cost of inefficiency with specified process
i.e. time, materials and capacity (resources)
- these are non – essential costs -

continuous improvement

EXAMPLE:
deviations, customer complaints, PIRCs / recalls, product liability

troubleshooting, slow running, expediting, non-complying RMs, disrupted schedule

buffer inventory, stock-outs, premium freight, lost sales, morale loss

*broader definition of poor quality enables access to "hidden factory"

Quality Maturity Model (and Economics of Quality)

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

LESS LIKE ⟷ ***MORE LIKE***

reactive/corrective

Quality Management System used to comply

produce "product A/B/C"

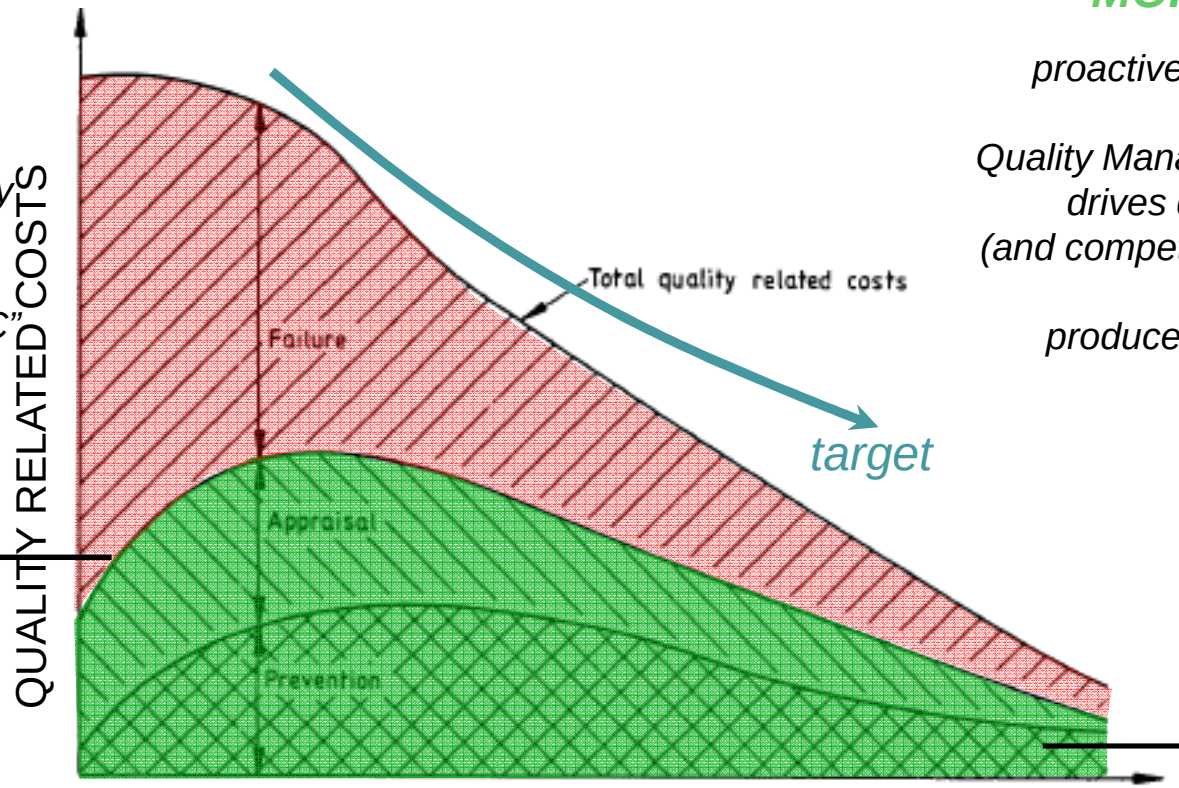
…

proactive/preventative

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

produce "medicines"

…



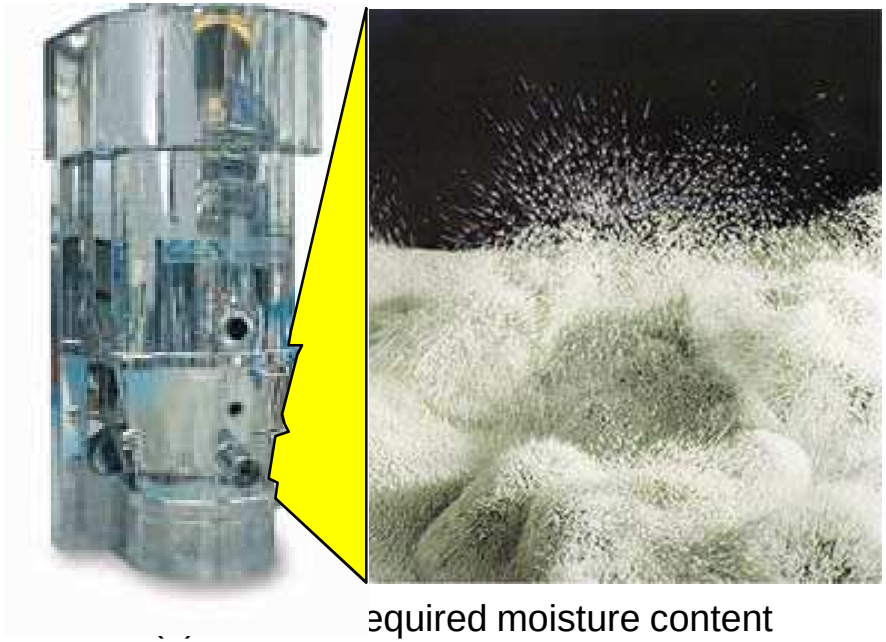
COST of NON – CONFORMANCE *(CoPQ)*

COST OF CONFORMANCE (DESIGN COST)

QUALITY AWARENESS AND IMPROVEMENT

Example 1: Fluid Bed Drying

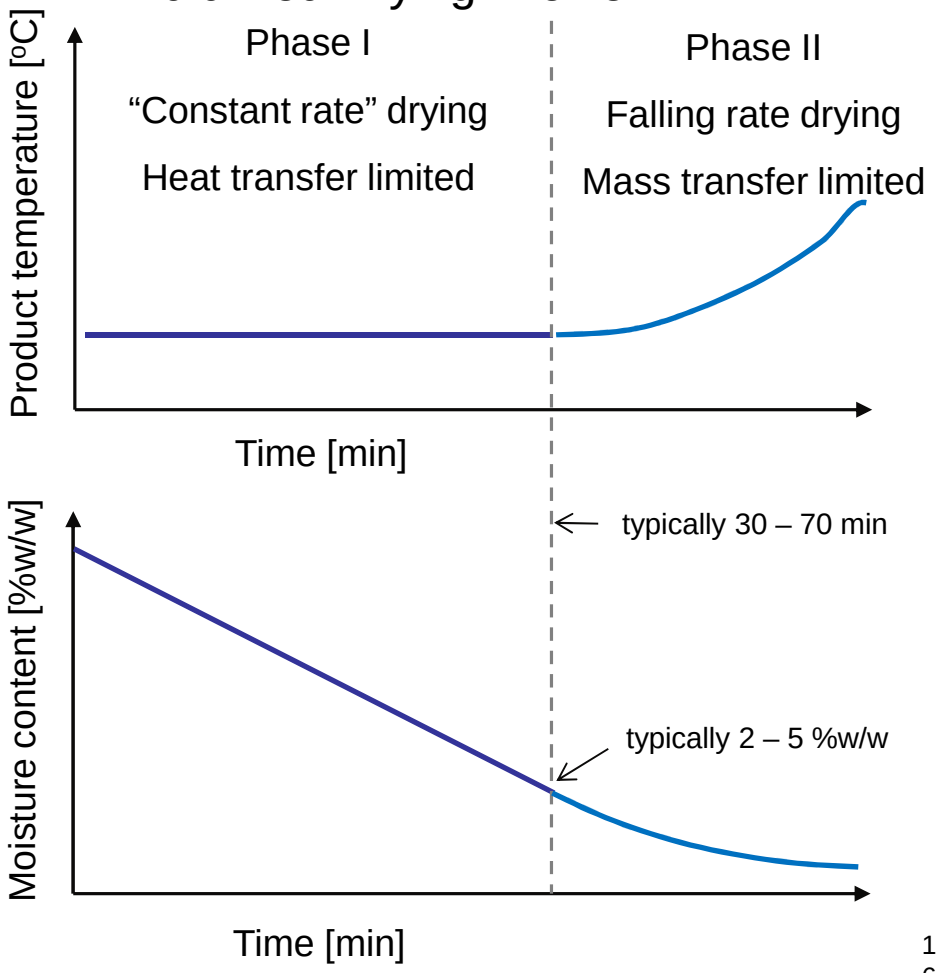
- Fluid Bed Dryer Processor



equired moisture content

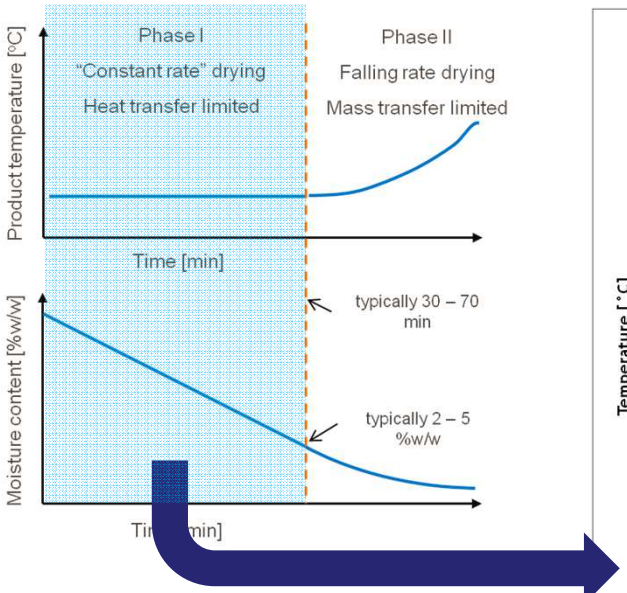
(e.g. for onward processing or product stability)

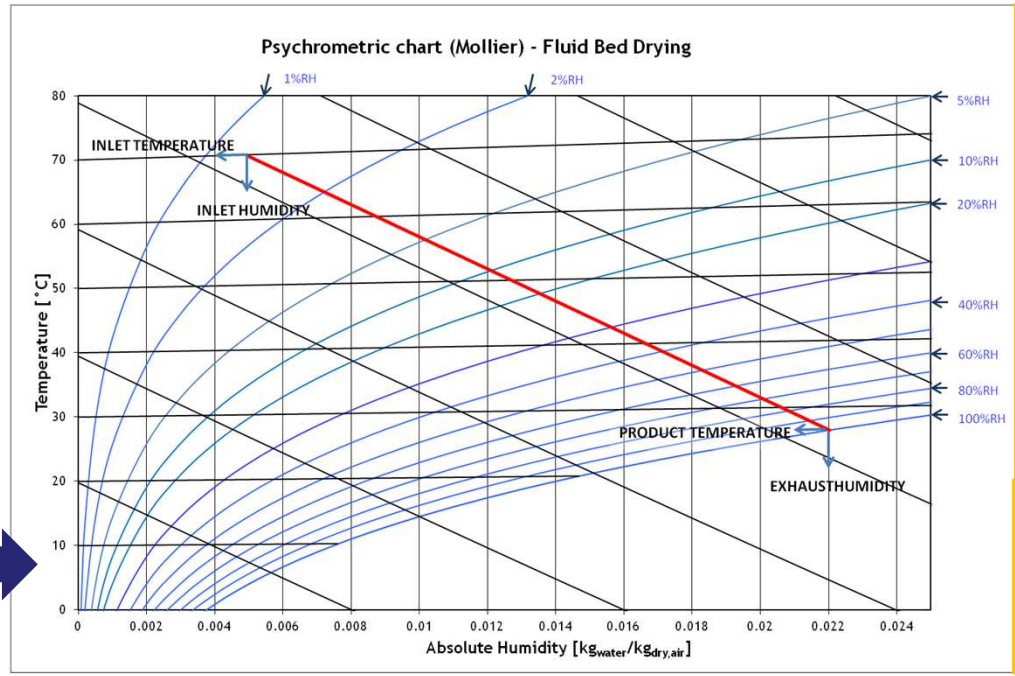
- Fluid Bed Drying Profile



Psychrometry

- Fluid Bed Drying Profile





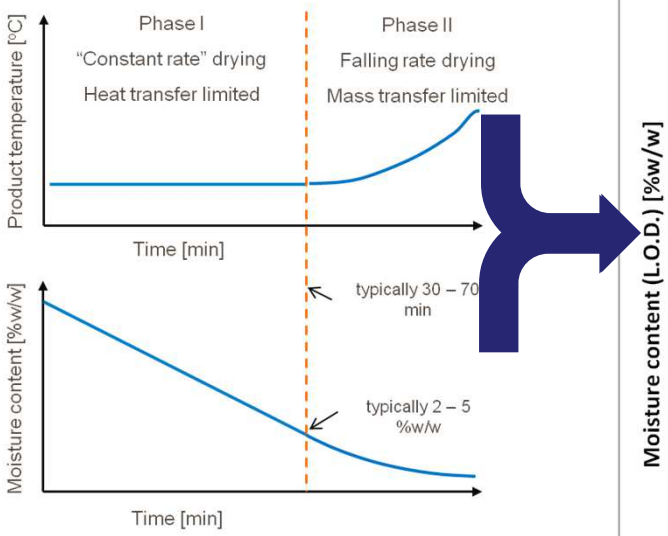
inlet temperature [C]	product temperature* [C]	drying rate* g/m3
60	24	15
70	27	17
80	29	20

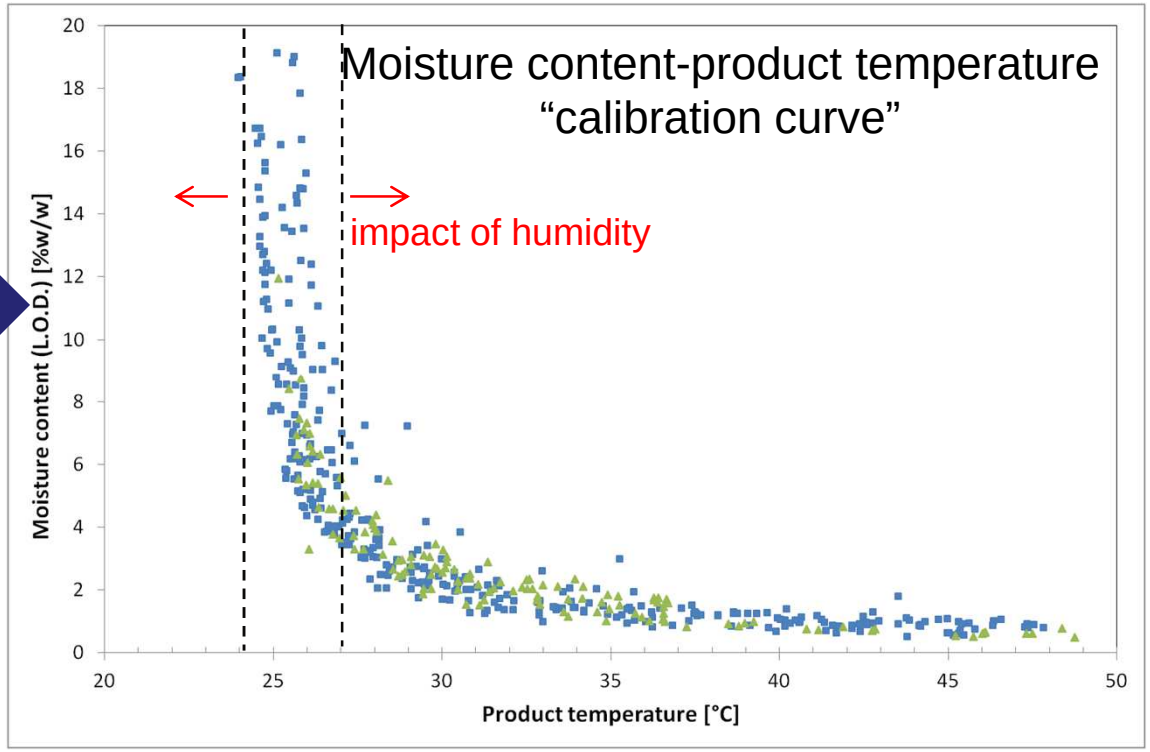
*inlet humidity 5 g/kg

- "Constant rate" drying predictable by 1st principles science
- Time of this period proportional to **ratio** of water amount to air mass flow rate

Drying Curve*

- Fluid Bed Drying Profile





- Moisture content is a statistical distribution for each product temperature endpoint
- Variation in moisture content reduces for increasing product temperature endpoints
- Based on standard instrumentation and control (a.k.a "delta – T" method in other industries)

*T. Lipsanen et al., International Journal of Pharmaceutics 357 (2008)

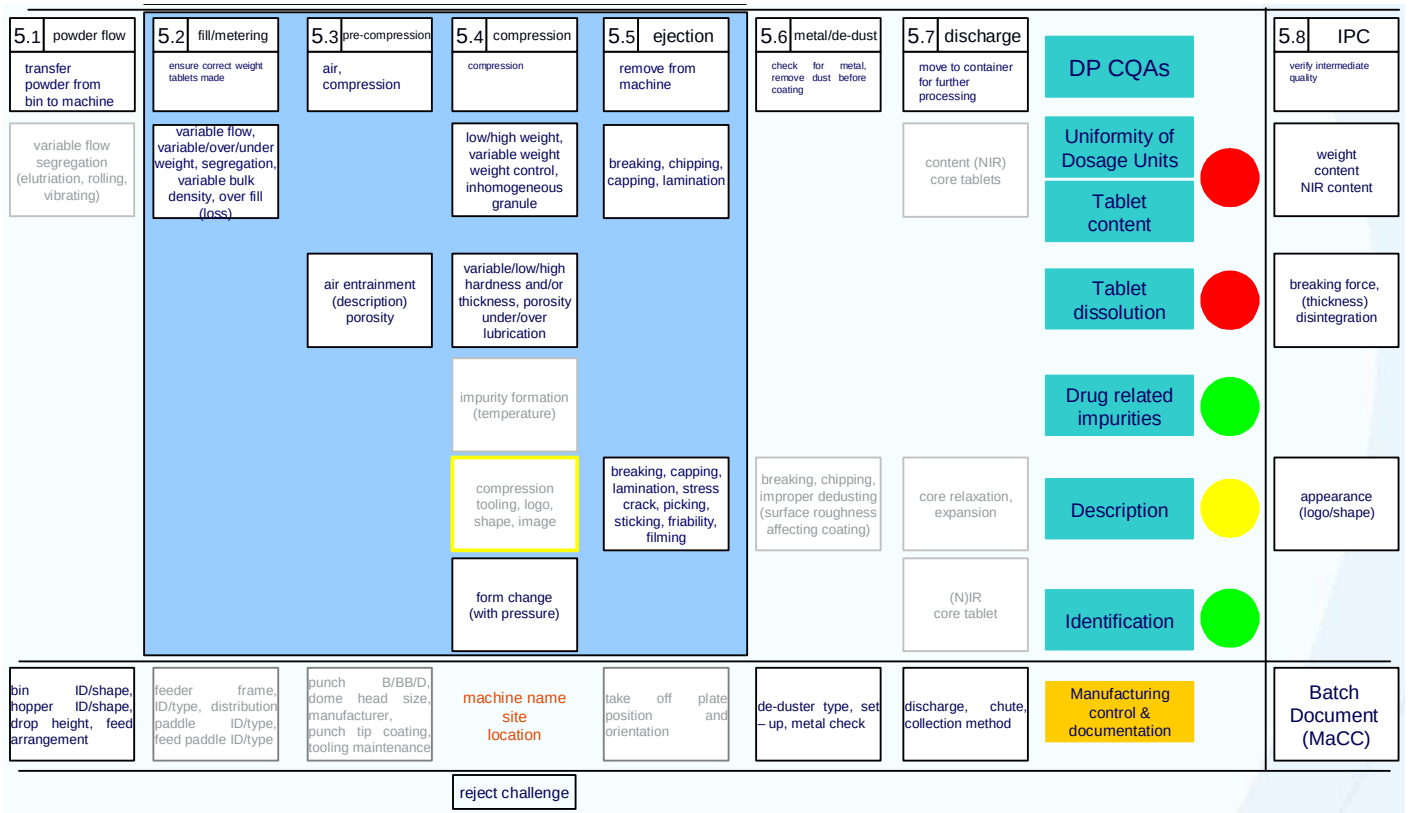
Example 2: Tablet Compaction

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

- Strong enough to be handled
  - Adequate Tensile Strength

  (breaking force, crushing strength, hardness)
- Weak enough to disintegrate in the body
  - Low Disintegration time (typ.< 15mins)
- Manufacturable and Elegant
  - High throughput
  - Defect free
- Safe and efficacious
  - Quality by Design and PAT
  - End testing

typical technical risk associated with tabletting



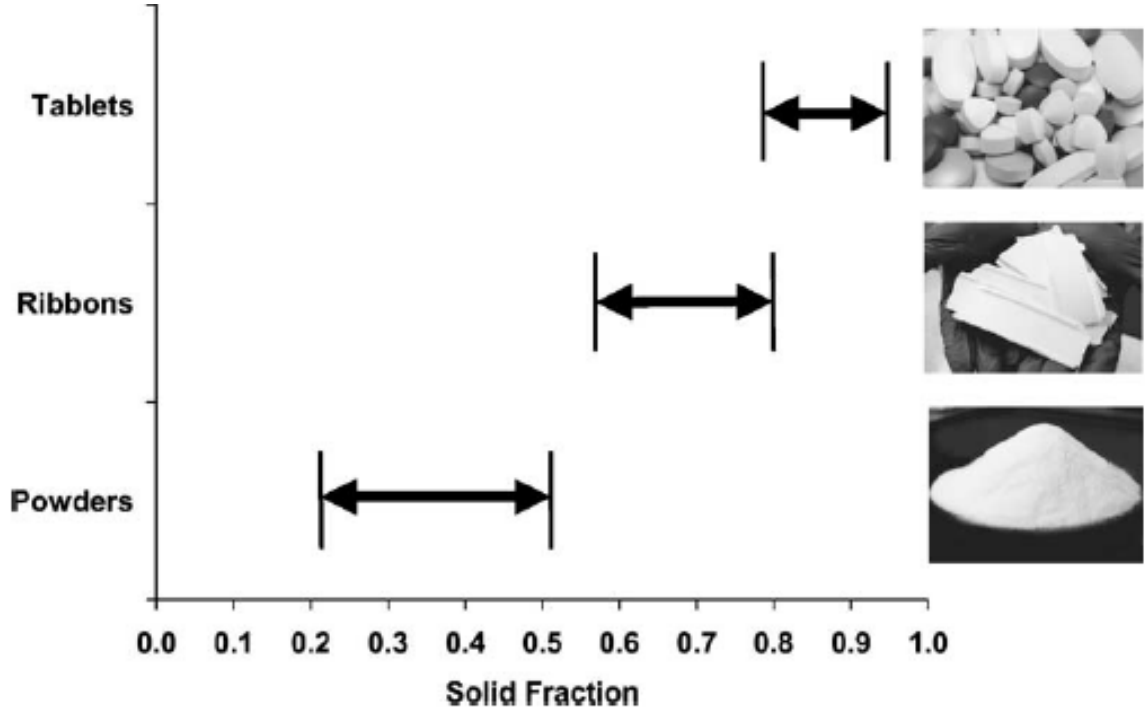
- powder flow, potential segregation
- low/high/variable weight
- appearance from compression and/or handling
- low/high/variable hardness, DT, dissolution
- lubrication impacting hardness, dissolution

Tablet assessment:

evaluate anticipated 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)
- All of the above can be obtained from at – line measurements

Solid fraction: transformation during compression*



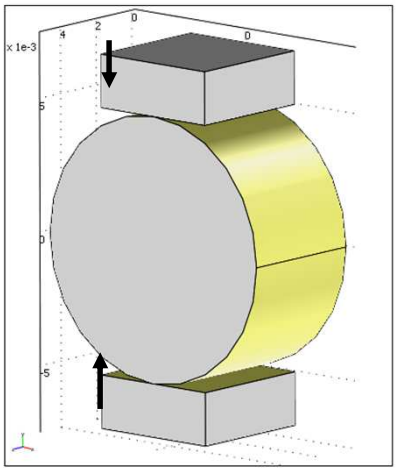
typical tablet solid fraction (SF) is 0.85 ± 0.05

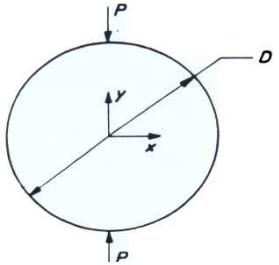
- Compressing to a solid fraction of greater than 0.9 – 0.95 may lead to stress cracking, capping, lamination etc

*A.V. Zinchuk et al. International Journal of Pharmaceutics 269 (2004)

Tensile strength

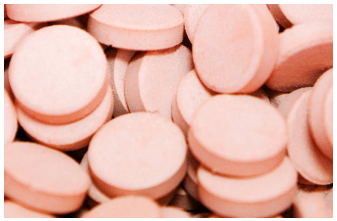
- Flat faced disc tablet





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

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



- Shaped round tablet (USP nomograph 1217)

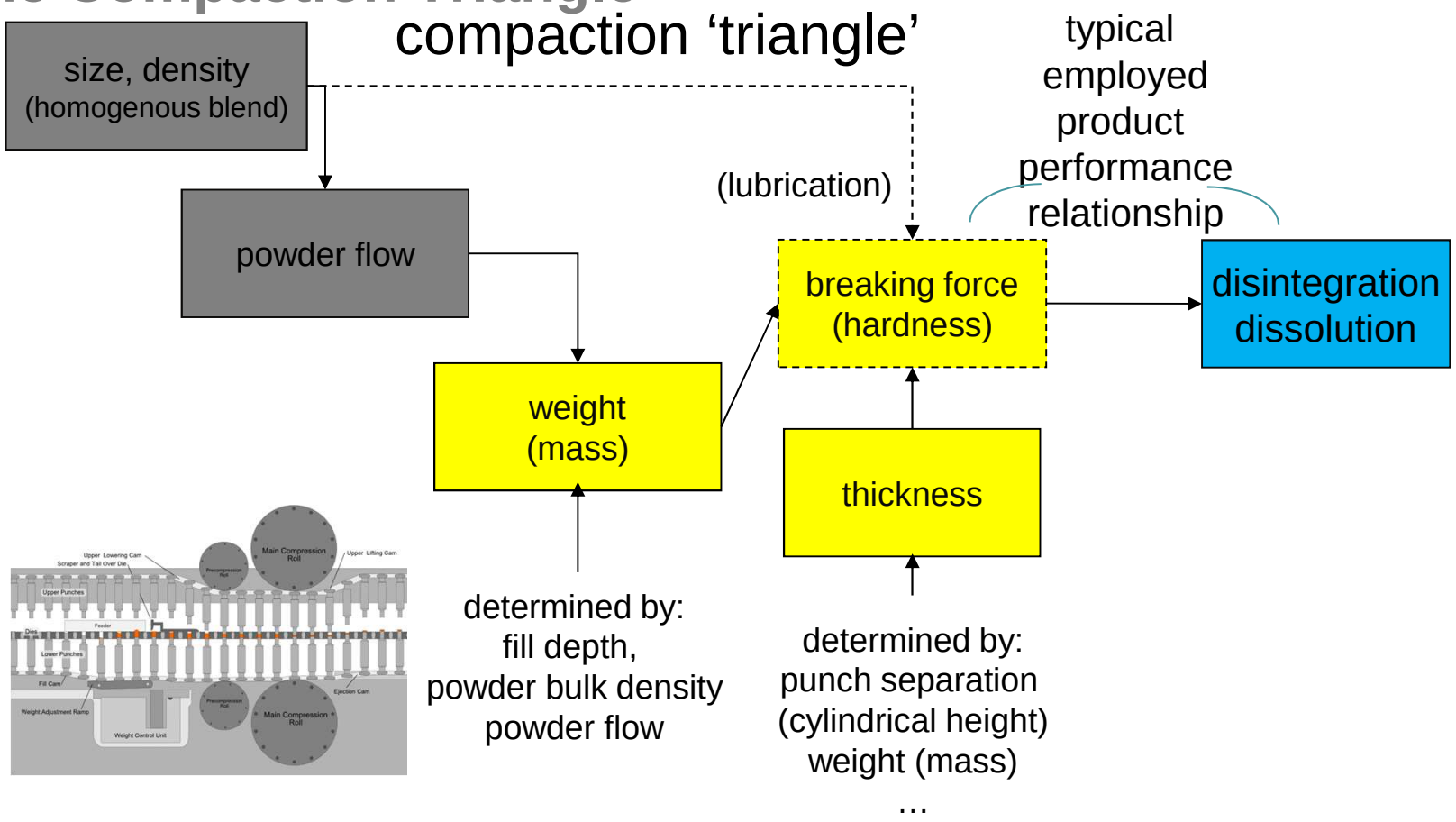
$$\sigma = \frac{10P}{\pi D^2}\left(2.84\frac{t}{D} - 0.126\frac{t}{W} + 3.15\frac{W}{D} + 0.01\right)^{-1}$$

- Shaped oval tablet*

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

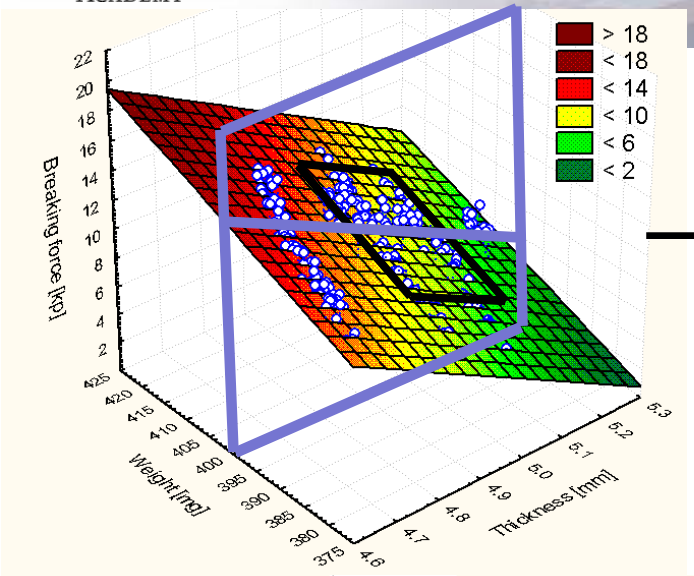
K. Pitt, http://dx.doi.org/10.1016/j.powtec.2011.12.060

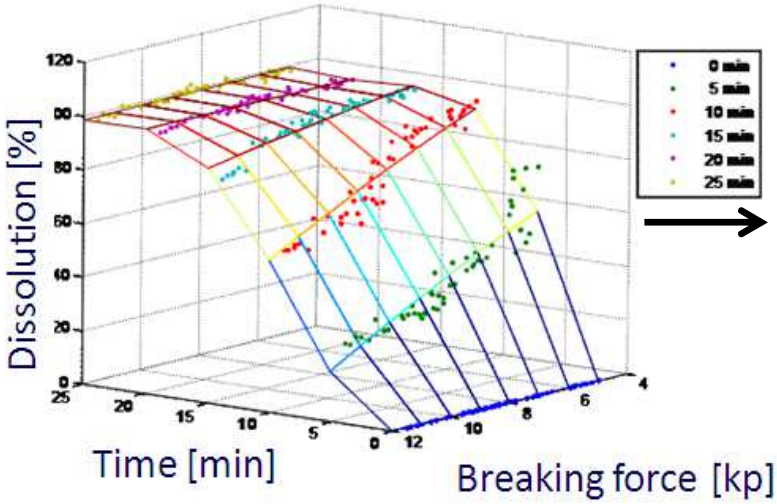
The Compaction Triangle



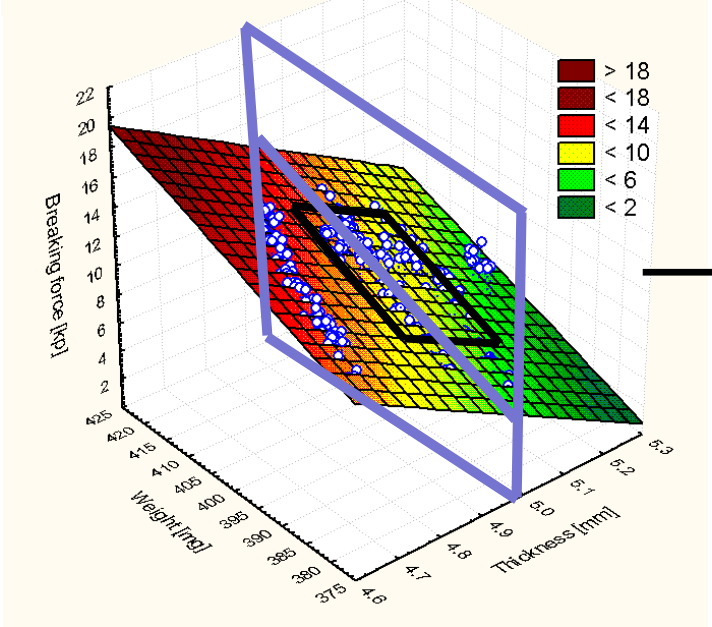
- Powder Flow: Carr’s index <20% excellent, 20 – 30% acceptable, > 30% …
- Granule density NLT 0.3g/cc based on standard tablet dimensions & equipment

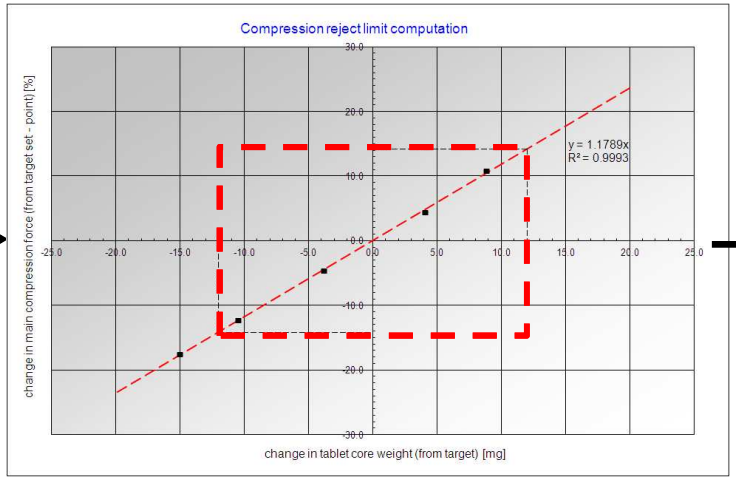
Compaction – Design Space Development





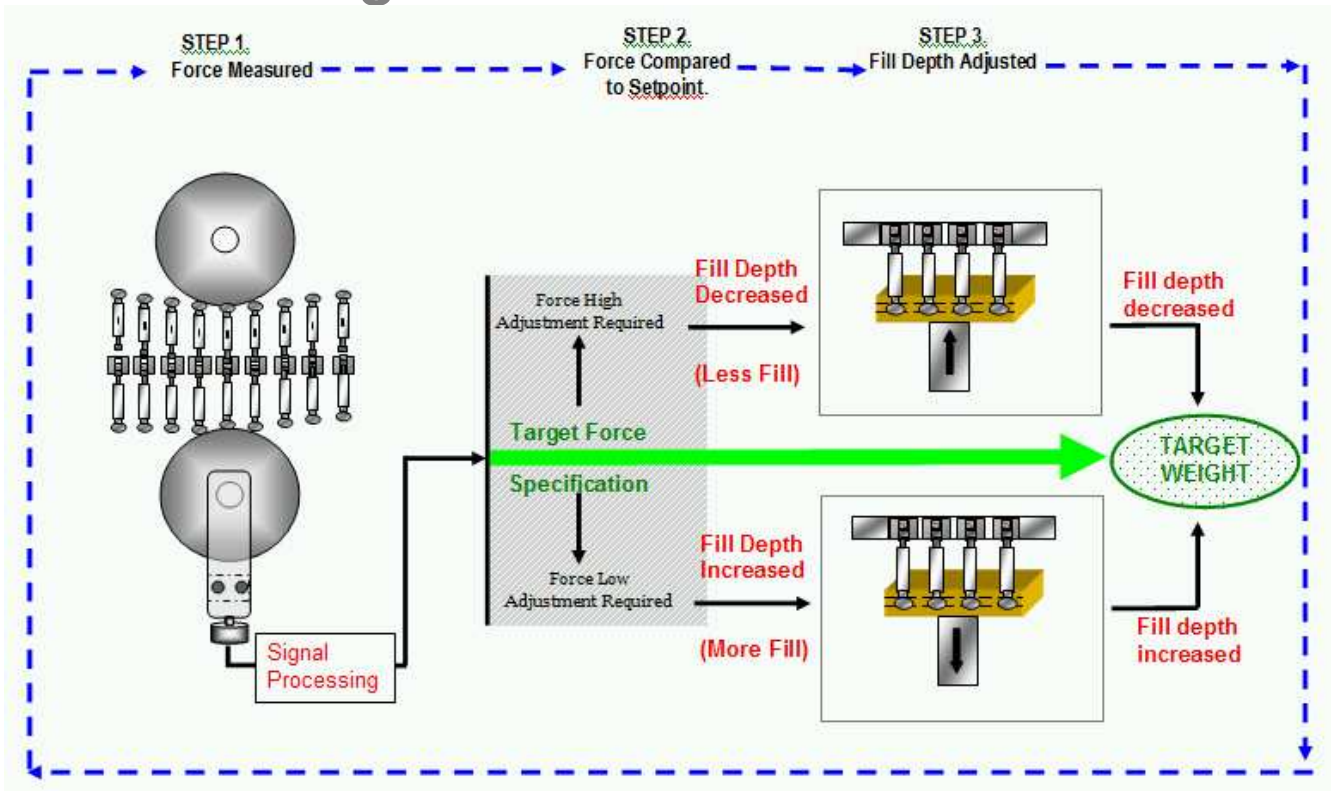
IPC limits breaking force to assure dissolution





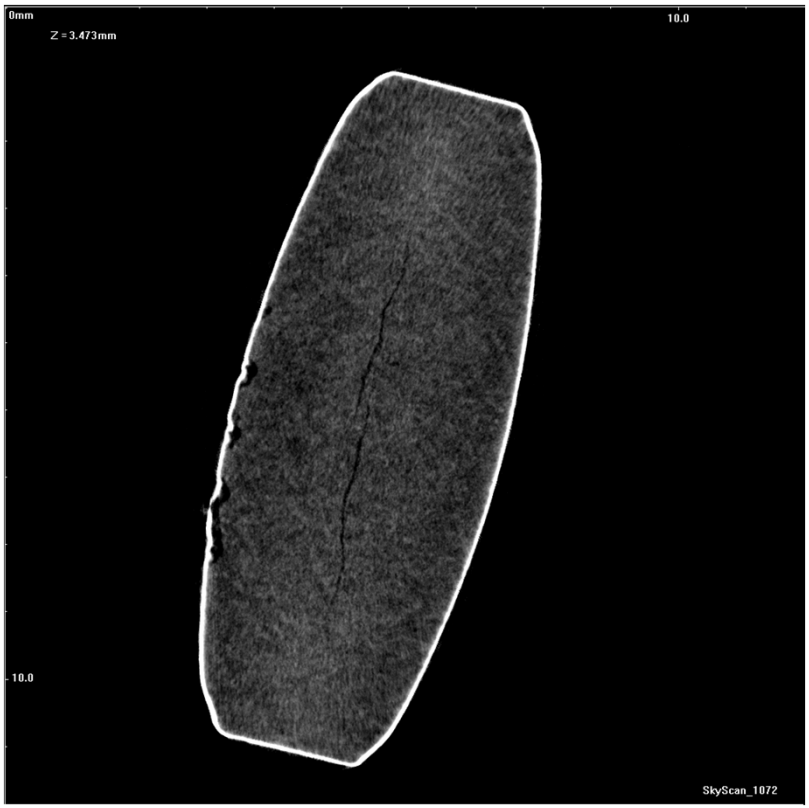
compression force control to assure weight (uniformity)

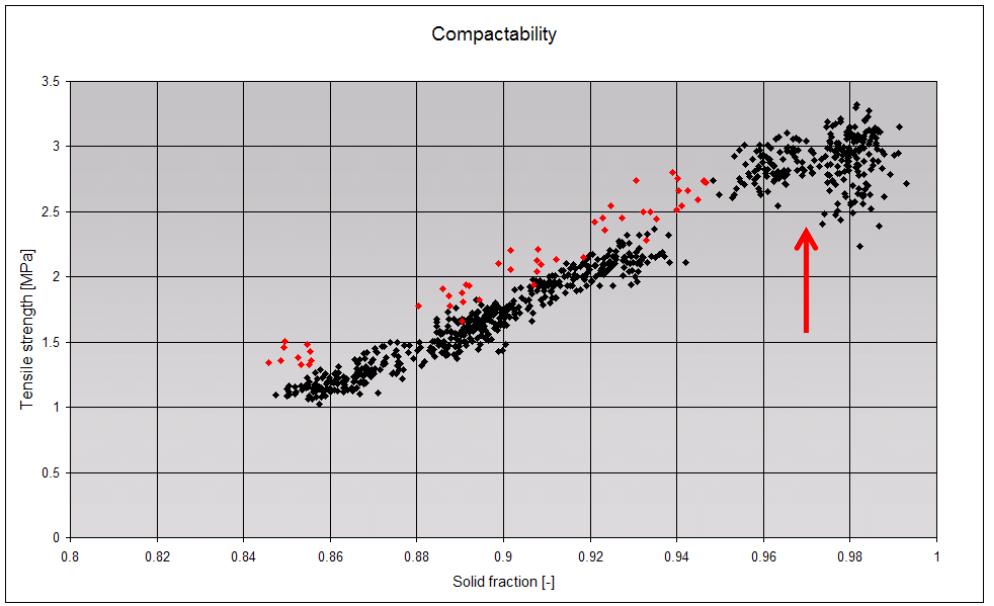
Compaction: Weight Control



- In constant volume operation, main compression force may be used as surrogate for weight
- Rejection of tablets outside a predetermined range of main compression force (surrogate for tablet weight) Contributes to control strategy for tablet Content and Uniformity of Dosage Units.
  - Sample size now expanded to include every manufactured tablet.

… not all mechanical failure is visible to the naked eye

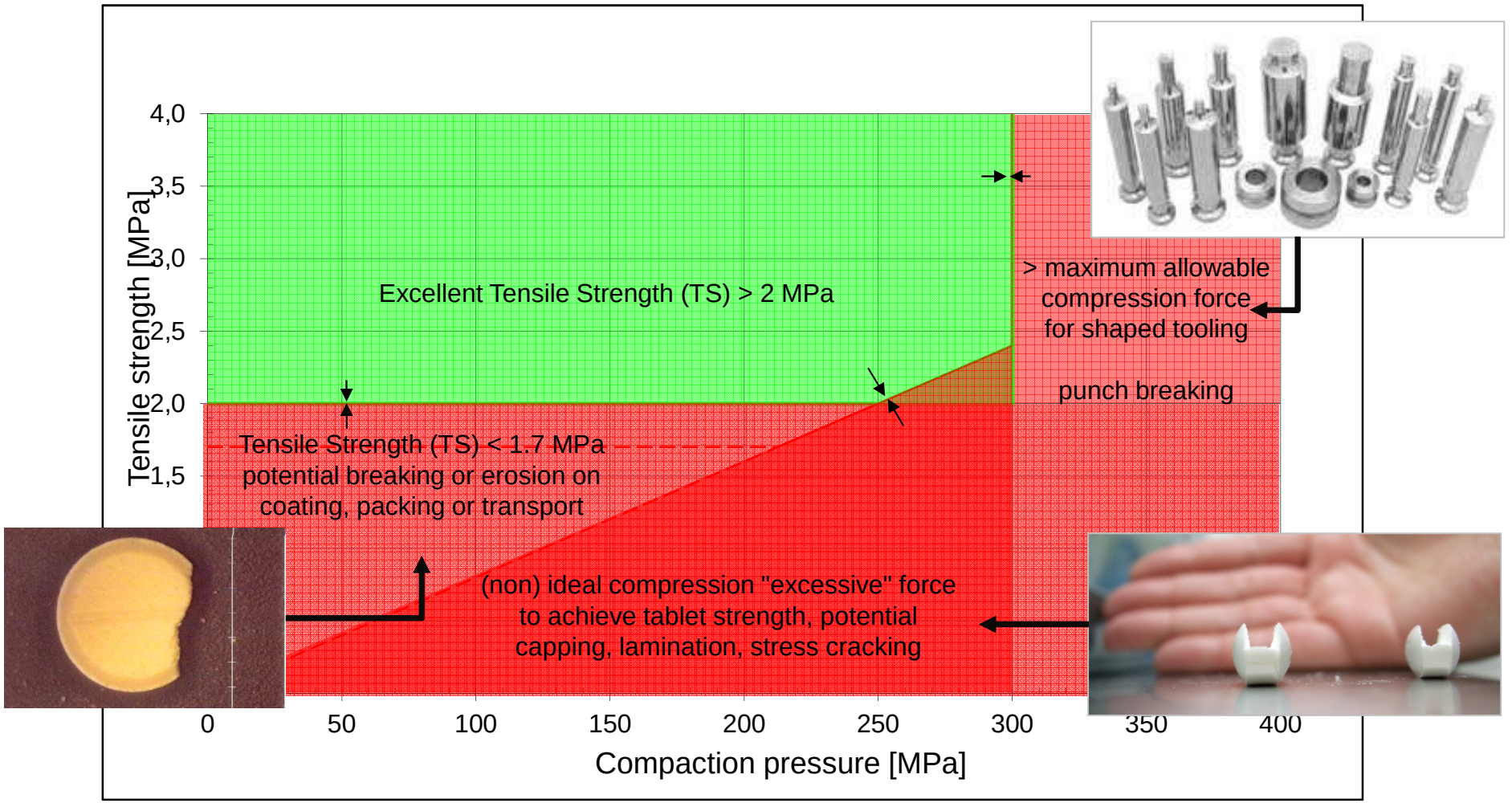




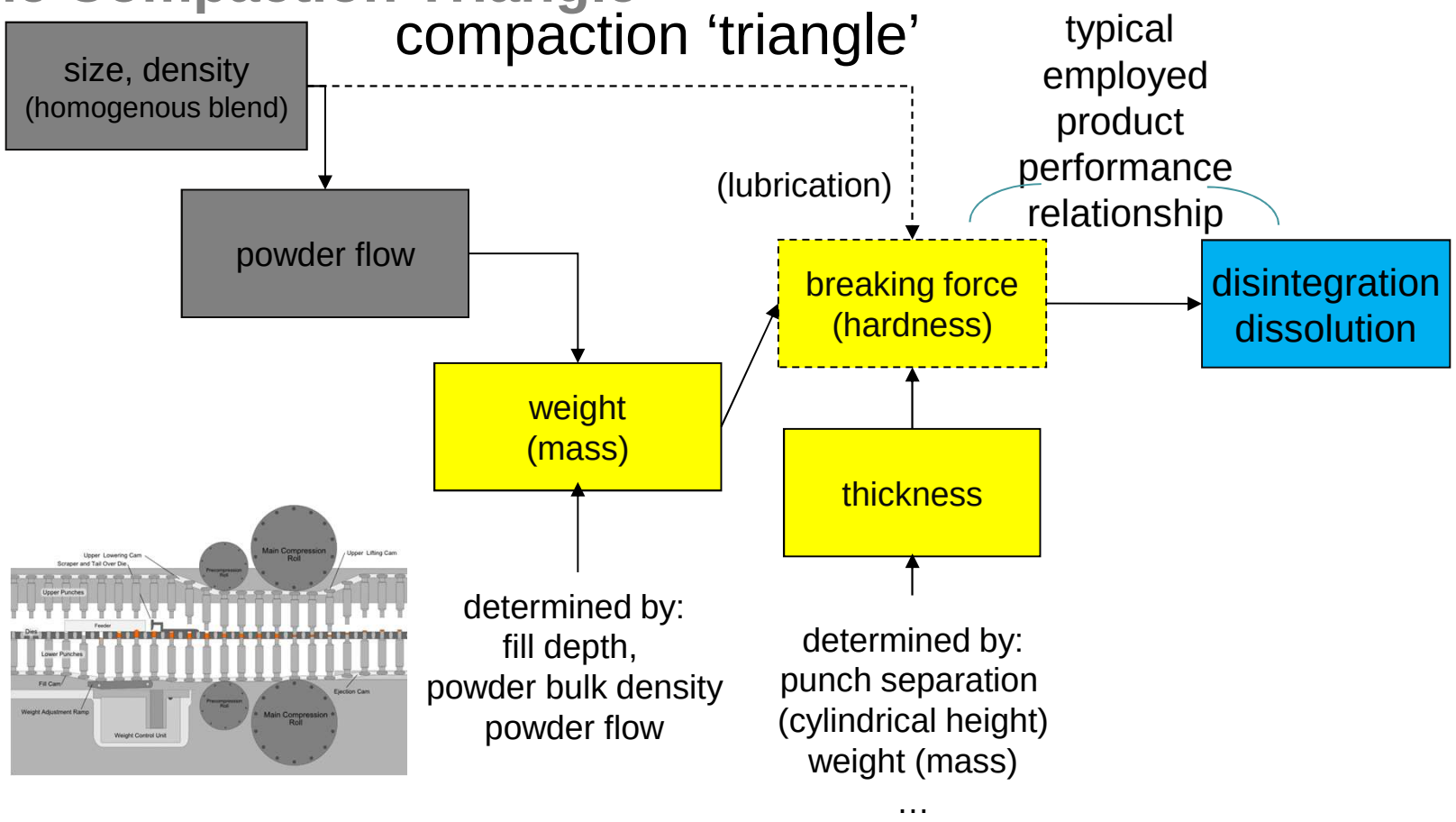
*Tablet debossing ~ 180 µm

- Expect increased variability in breaking force, porosity (disintegration), SF > 0.95

Tabletability with manufacturability criteria

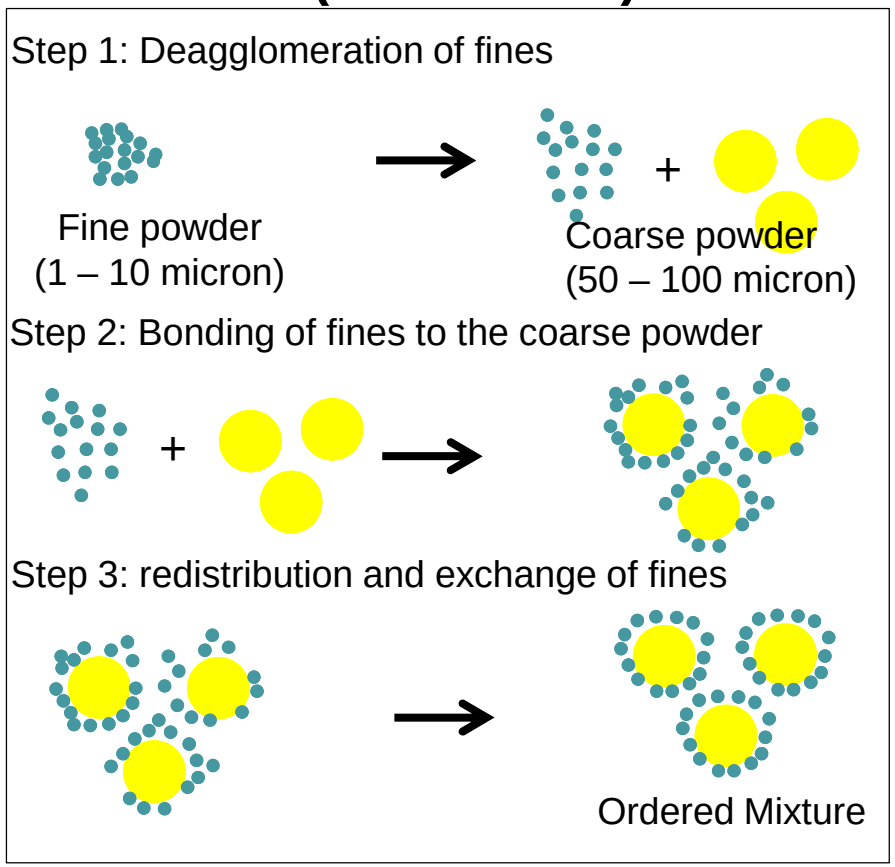


The Compaction Triangle



- Powder Flow: Carr’s index <20% excellent, 20 – 30% acceptable, > 30% …
- Granule density NLT 0.3g/cc based on standard tablet dimensions & equipment

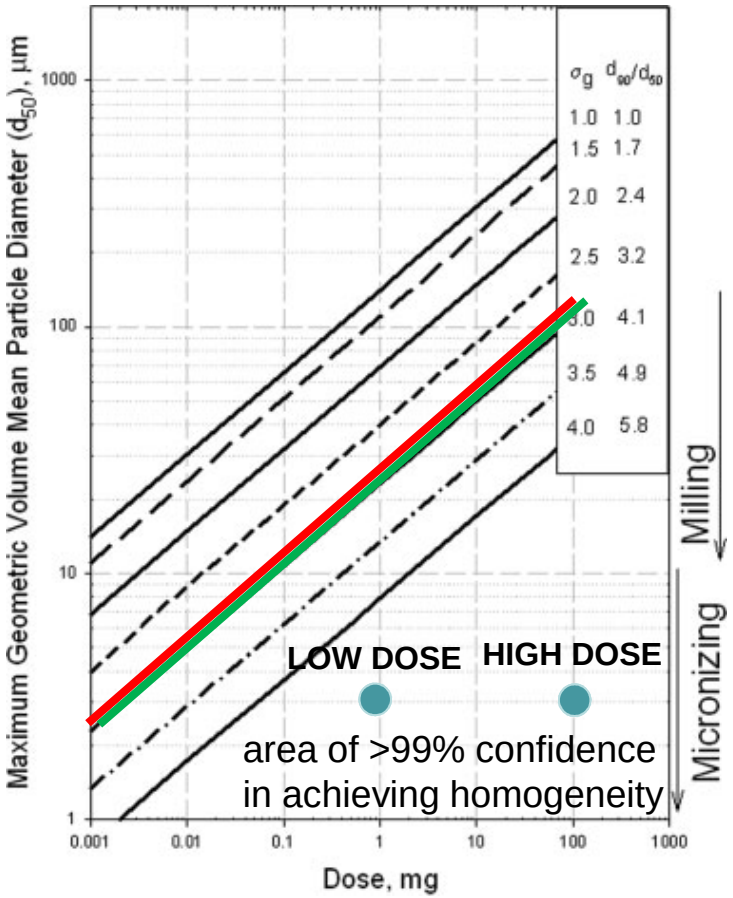
Ordered Mixing (Mechanism)



Ordered Mixing: mechanism, process and applications in pharmaceutical applications, Asian J. Pharm. Sci. 3 (6), Oct 2008

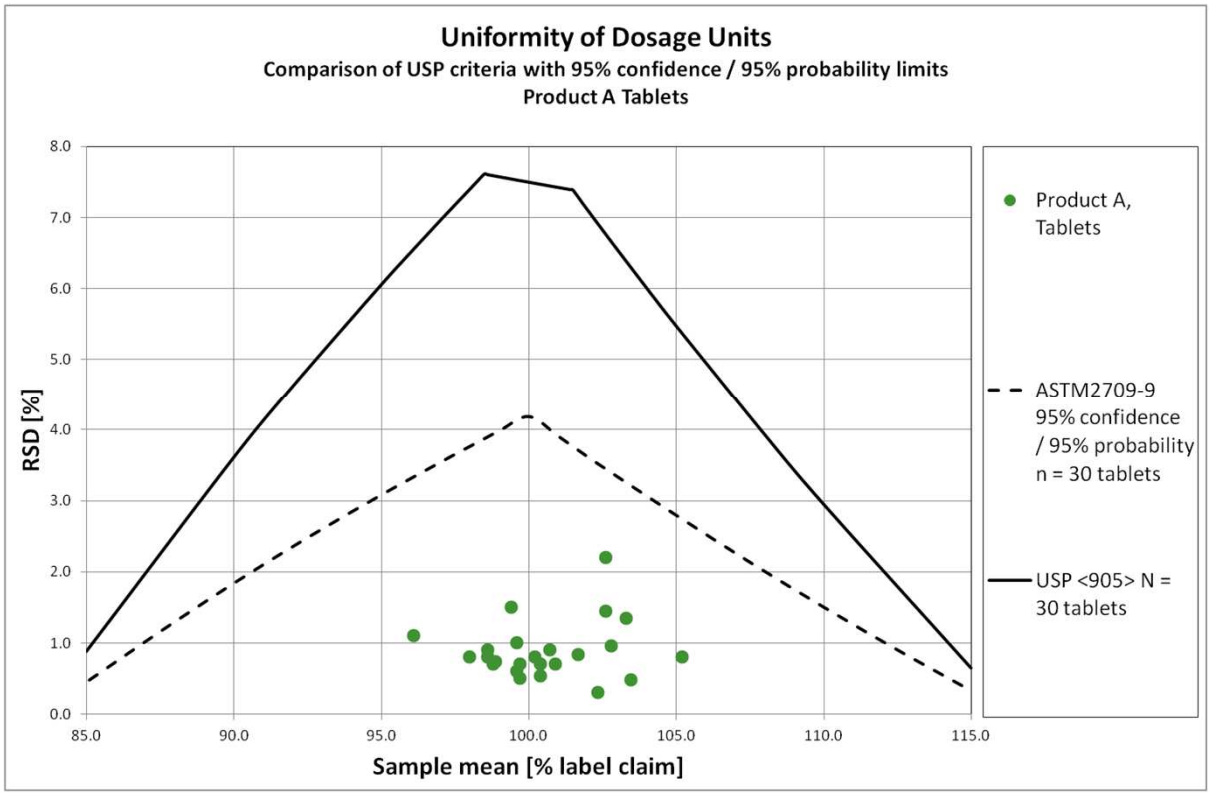
Possibility of achieving an interactive mixture with high dose homogeneity containing an extremely low proportion of drug, European J. Pharm. Sci. 12 , Sep 2000

Particle Size Limits to Meet Content Uniformity Criteria

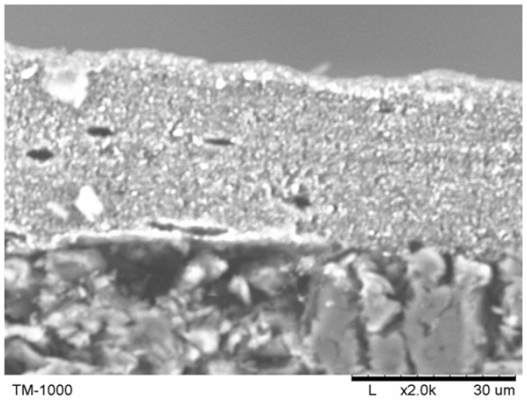


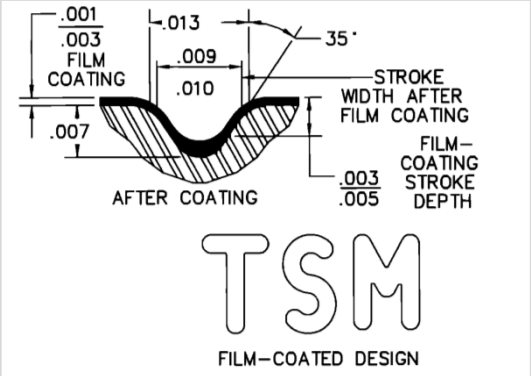
Particle Size Limits to Meet Content Uniformity Criteria for Tablets and Capsules, J. Pharm. Sci. 95 (5), MAY 2006

Quality Assurance: Use of Statistics



Example 3: Tablet Film Coating

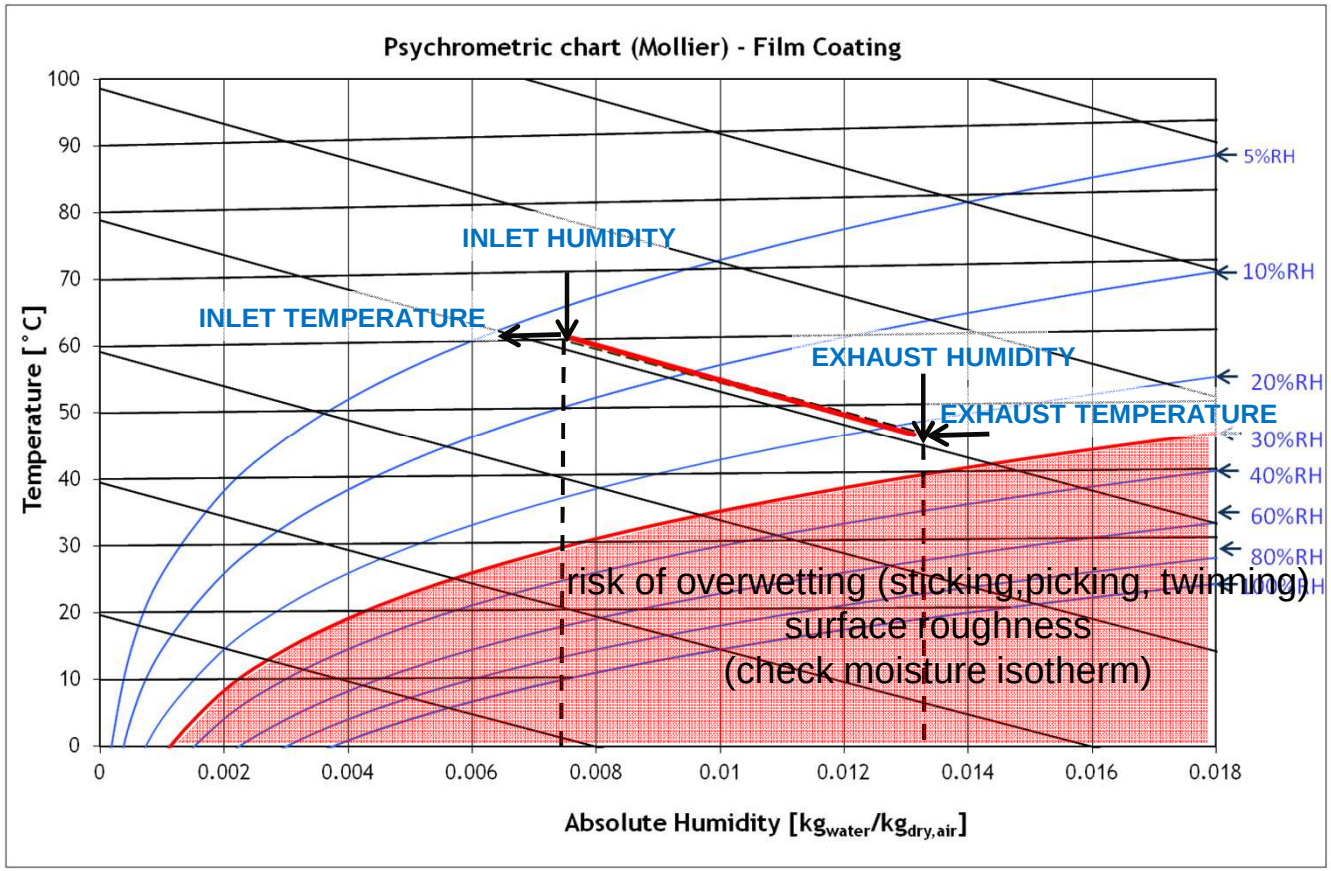




- Quality impacted by:
  - (1) tablet design (“standard” dimensions based on ratio’s and “standard” lettering),
  - (2) film coat formulation (substrate) & film coat amount
  - (3) **environmental conditions for film coat formation**

Psychrometry

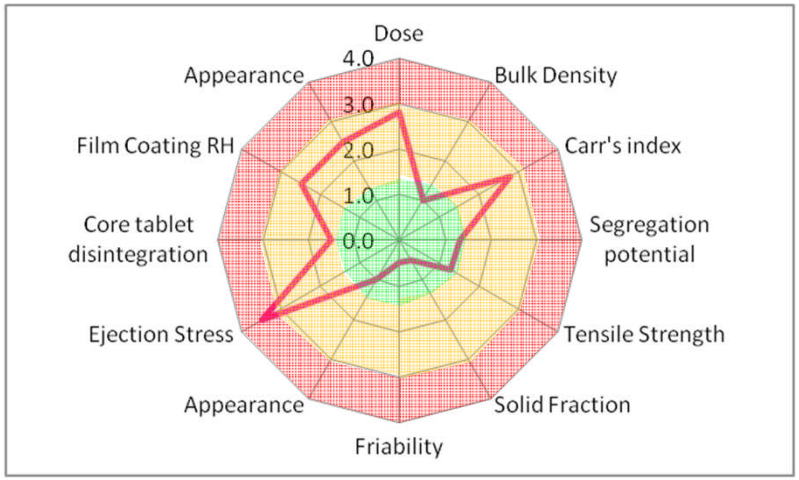
Environmental condition for film coat formation depicted on a psychrometric chart



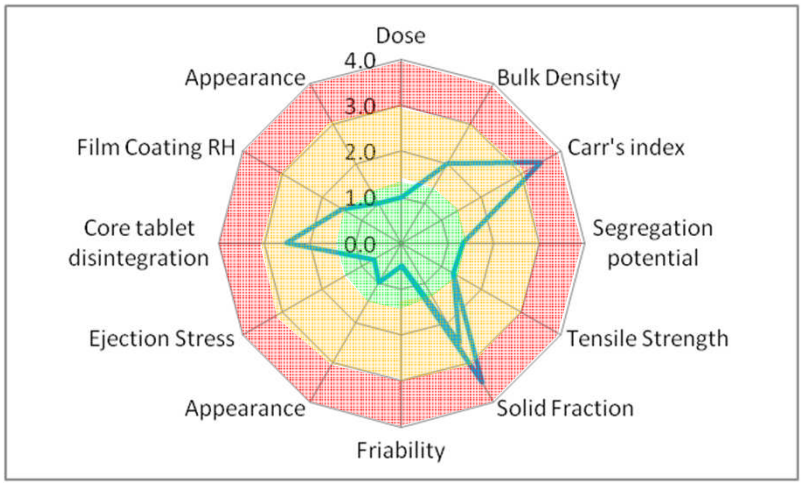
- Film coat to a RH < 30% to avoid risk of overwetting (visual defects, other)

Manufacturability Classification

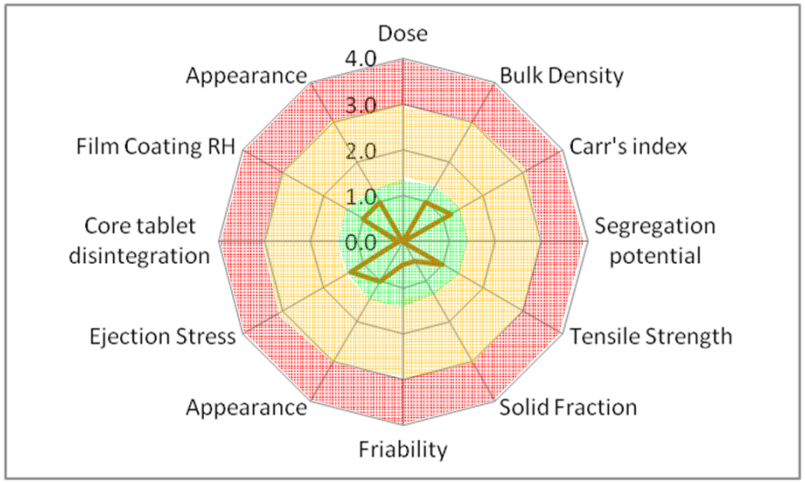
Example representation



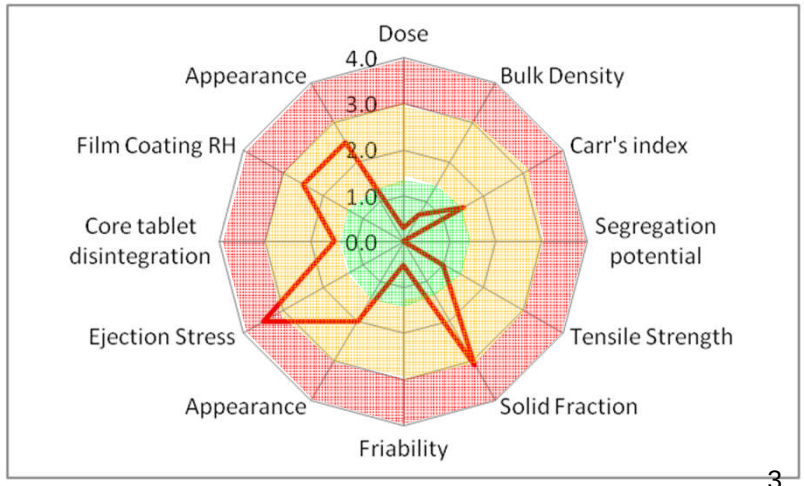
Capping in film coater



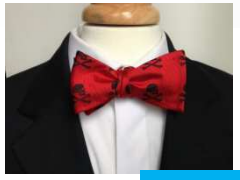
Powder flow, variable density and dissolution



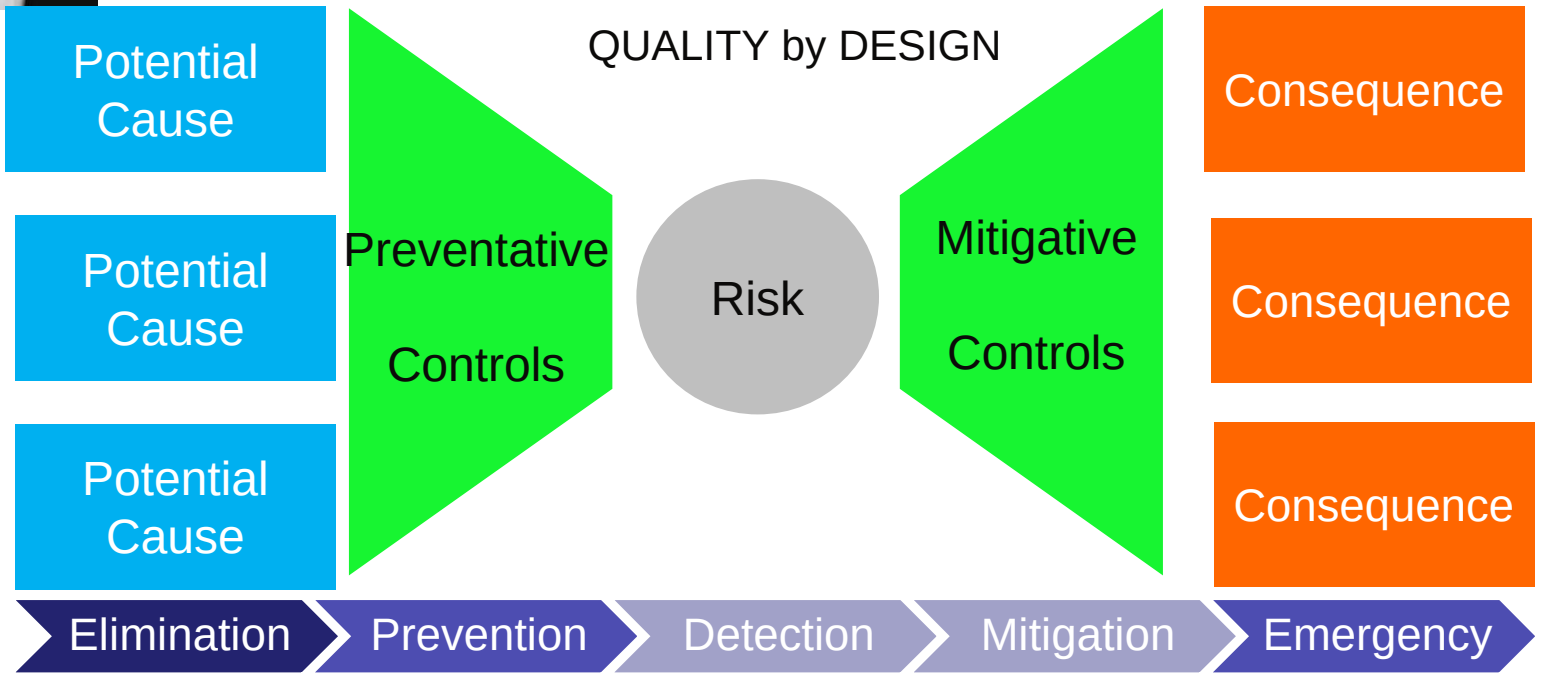
No issues



Capping and in-filling



Risk Bowtie, the Quality Maturity Model, and Economics of Quality

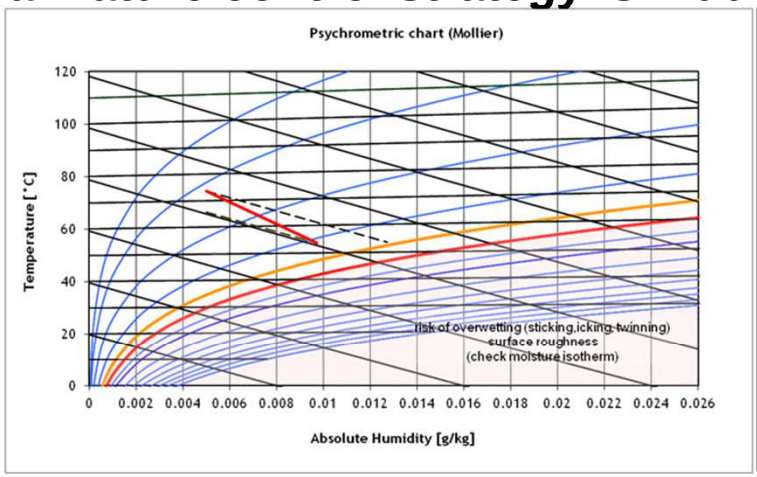


- Quality system will drive quality/cost for a “best-in-class quality system” (see Quality Maturity Model, ANSI/ISO/ASQ Q9004 – 2000)

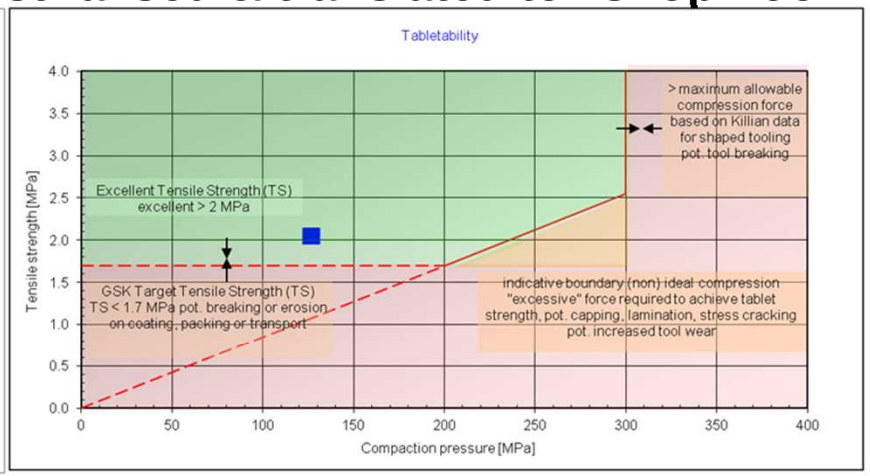
- A “2- σ stat”: CoPQ ~15-25% of total production cost, visible part of COPQ is 5-8% of total production cost

… “technology” as a key quality differentiator … ?

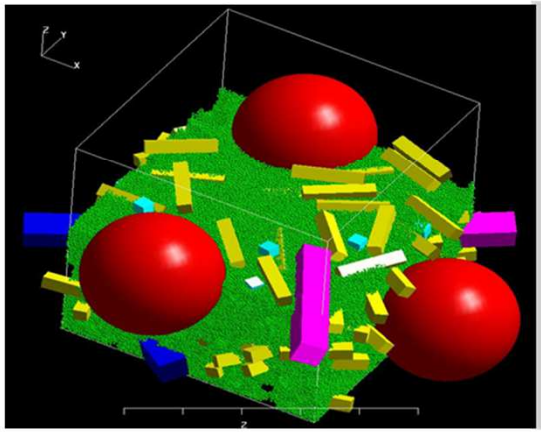
a mature control strategy is industrialised & translated to “shop floor”

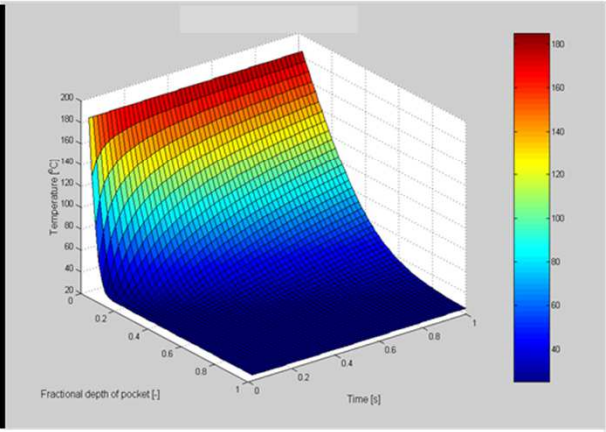


PREDICTIVE MODEL:SPRAY DRYING & FILM COATING

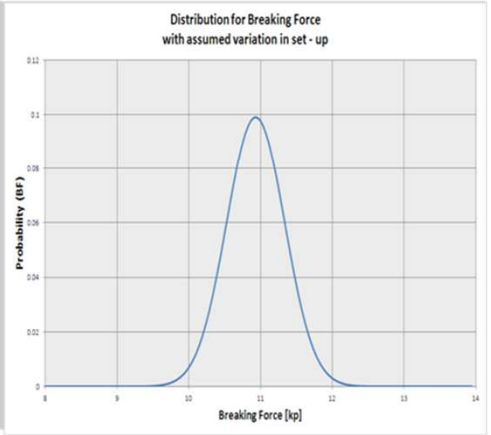


COMPRESSION PERFORMANCE



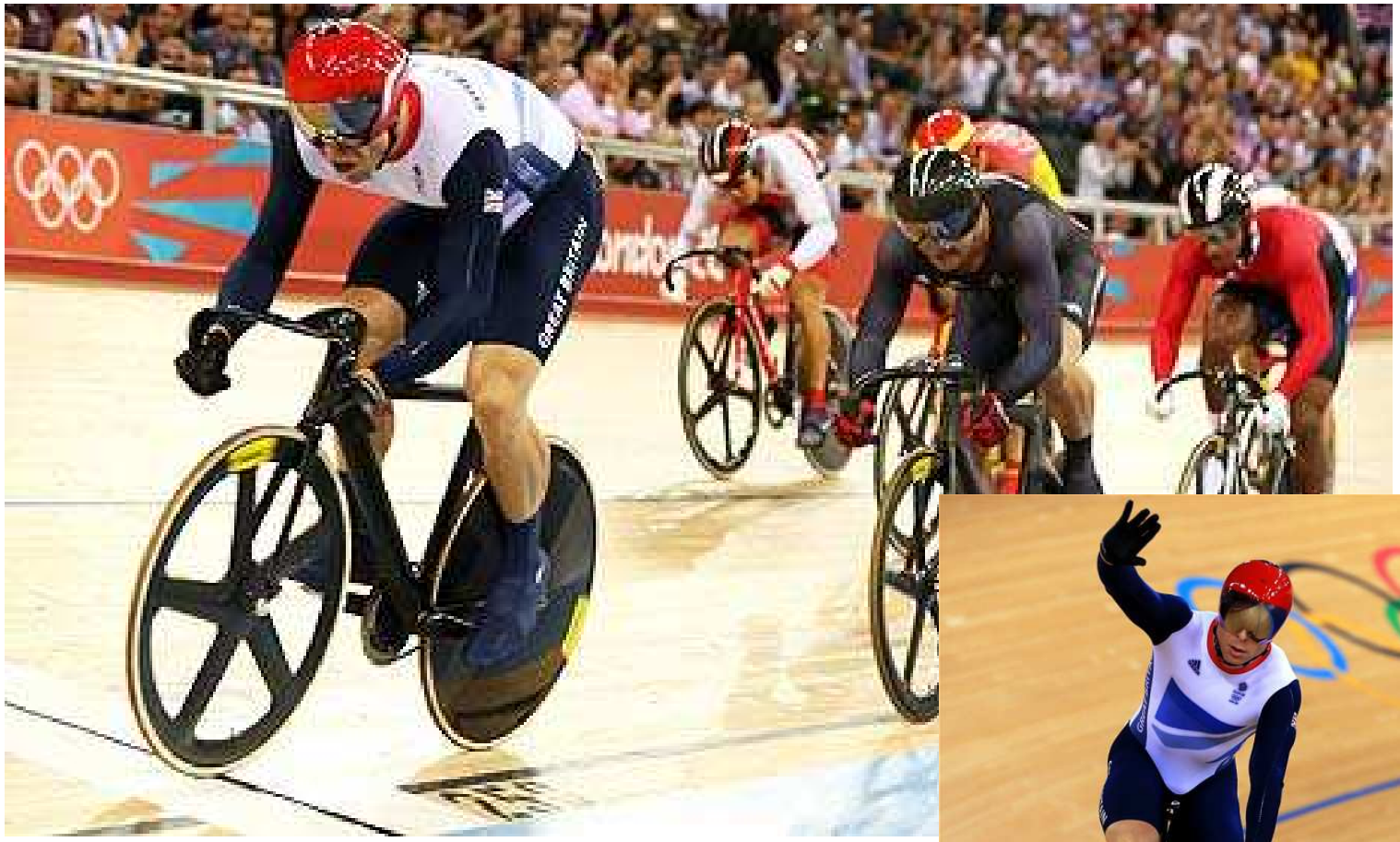


FORMULATION:STRUCTURE-PERFORMANCE

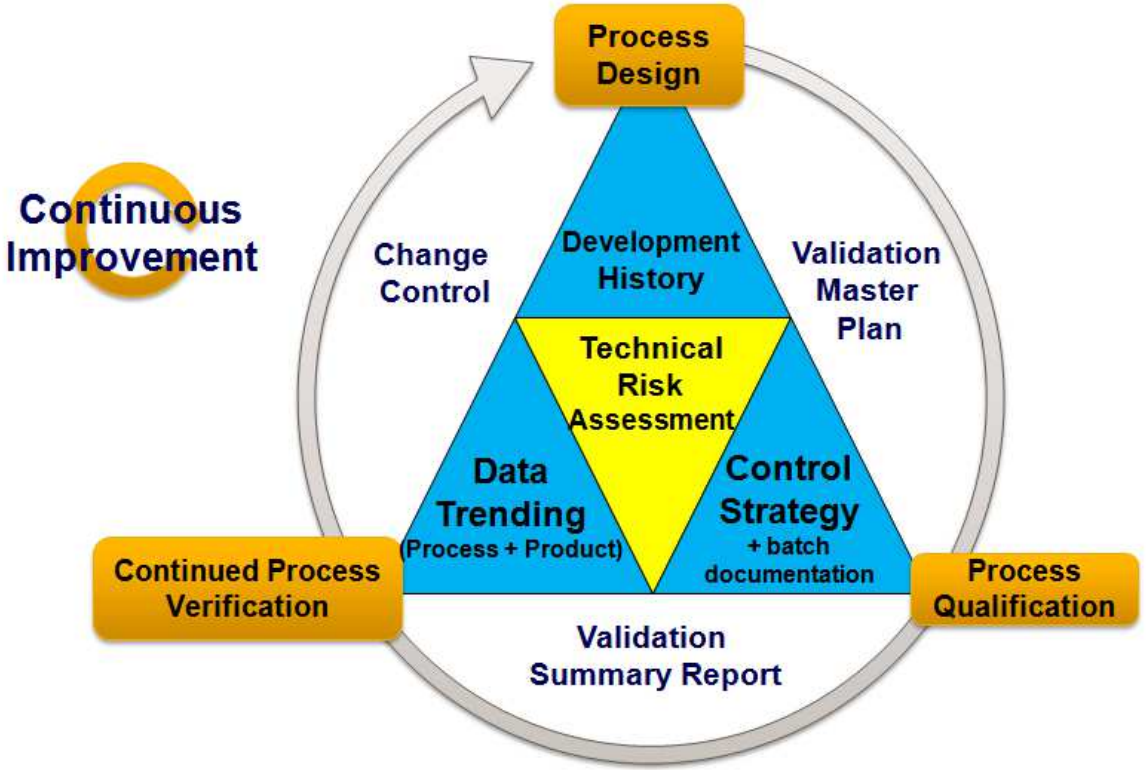


MONTE CARLO: PRODUCT QUALITY

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



Product Lifecycle Management



• An enhanced approach to product control strategies based on process understanding is possible and will increase transparency

• An effective control strategy to manage risk is industrialised, translated to the “shop floor”, and must be pro-actively managed

Acknowledgements

- Gordon Muirhead
- Bernadette Doyle
- Kendal Pitt

Thank you