FEDERCHIMICA ASCHIMFARMA

Compliance GMP e regolatoria:
novità e aggiornamenti
MILANO – 2 maggio 2018

Dal *Quality by Design* alla *Process Validation* nel processo di sviluppo di un medicinale

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MENARINI

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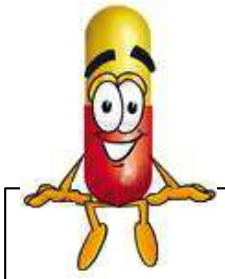


NEW DRUG PRODUCT

- **Development**
  - Quality Target Product Profile
  - Preformulation
  - Formulation
  - Manufacturing Process
- **Validation**

  (Process Performance Qualification)
- **Commercial manufacturing process**

  (Continued Process Verification)

References:

- **ICH PHARMACEUTICAL DEVELOPMENT Q8(R2)**
  Current Step 4 version dated August 2009
- **ICH QUALITY RISK MANAGEMENT Q9**
  Current Step 4 version dated November 2005
- **ICH SPECIFICATIONS:** Test Procedures and Acceptance Criteria for new Drug Sustances and new Drug Products:
  CHEMICAL SUBSTANCES Q6A
  Current Step 4 version dated October 1999
- **ICH PHARMACEUTICAL QUALITY SYSTEM Q10**
  Current Step 4 version dated June 2008
- **FDA Guidance for Industry**
  Process Validation: General Principles and Practices
  January 2011 CGMP - Revision 1
- **EMA Guidelines for GMP for Medicinal Products**
  for Human and Veterinary Use
  Annex 15: Qualification and Validation March 2015
- **FDA PHARMACEUTICAL CGMPS FOR THE 21ST CENTURY**
  A RISK-BASED APPROACH September 2004
- **FDA Guidance for Industry PAT**
  A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance U.S. September 2004

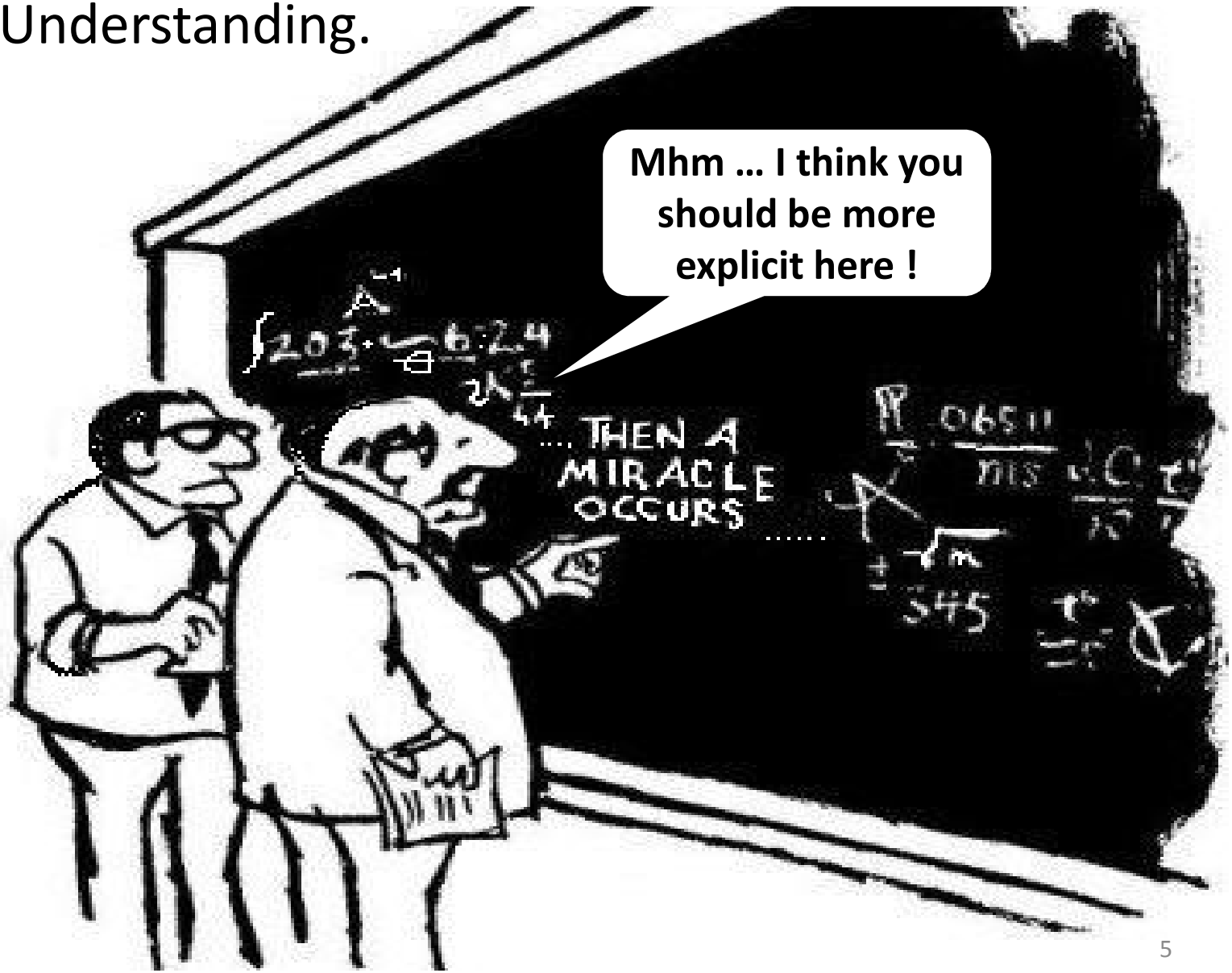
The aim of pharmaceutical development is:

to design a quality product and its manufacturing process to consistently deliver the intended performance of the product.

The information and **knowledge gained from pharmaceutical development** studies and manufacturing experience **provide scientific understanding** to support the establishment of the design space, specifications, and manufacturing controls.

It is important to recognize that
Quality cannot be tested into products.

- Process Knowledge
- Process Understanding.



Pharmaceutical development should include the following elements:

- **Quality Target Product Profile** (QTPP) : it relates to quality, safety and efficacy, considering e.g., the route of administration, dosage form, bioavailability, strength, and stability; drug product quality criteria.

- Identifying potential **Critical Quality Qttributes** (CQAs) of the **drug product**, so that those product characteristics having an impact on product quality can be studied and controlled.

- Determining the **Critical Quality Attributes** of the **drug substance,** excipients etc., and selecting the type and amount of excipients to deliver drug product of the desired quality;

- Link **Material Attributes** and **Process Parameters** of the appropriate manufacturing process, to Drug Product CQAs by using **Risk Assessment** that is a valuable science-based process.

- Defining a **Control Strategy** to ensure that a product of required quality will be produced consistently.

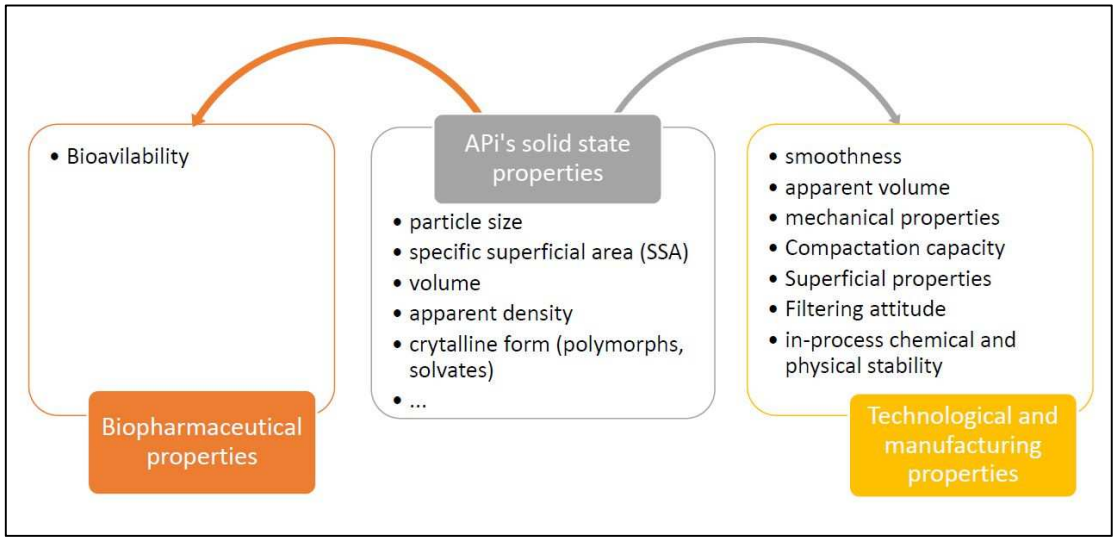
Quality Target Product Profile

			Justification
Dosage form		Tablet	Pharmaceutical equivalence requirement: same dosage form
Dosage design		Immediate release tablet without a score or coating	Immediate release design needed to meet label claims
Route of administration		Oral	Pharmaceutical equivalence requirement: same route of administration
Dosage strength		20 mg	Pharmaceutical equivalence requirement: same strength
Pharmacokinetics		Immediate release enabling T_{max} in 2.5 hours or less; Bioequivalent to RLD	Bioequivalence requirement Needed to ensure rapid onset and efficacy
Stability		At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life
Drug product quality attributes	Physical Attributes	Pharmaceutical equivalence requirement: Must meet the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality).	
	Identification		
	Assay		
	Content Uniformity		
	Dissolution		
	Degradation Products		
	Residual Solvents		
	Water Content		
	Microbial Limits		
Container closure system		Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf-life and to ensure tablet integrity during shipping
Administration/Concurrence with labeling		Similar food effect as RLD	RLD labeling indicates that a high fat meal increases the AUC and C_{max} by 8-12%. The product can be taken without regard to food.
Alternative methods of administration		None	None are listed in the RLD label.

PHARMACEUTICAL DEVELOPMENT

- Components of the Drug Product
  - **Drug Substance**
  - Excipients
- Drug Product
  - Formulation Development
  - Manufacturing Process Development

The physicochemical and biological properties of the drug substance can influence the **performance** and **manufacturability** of the drug product



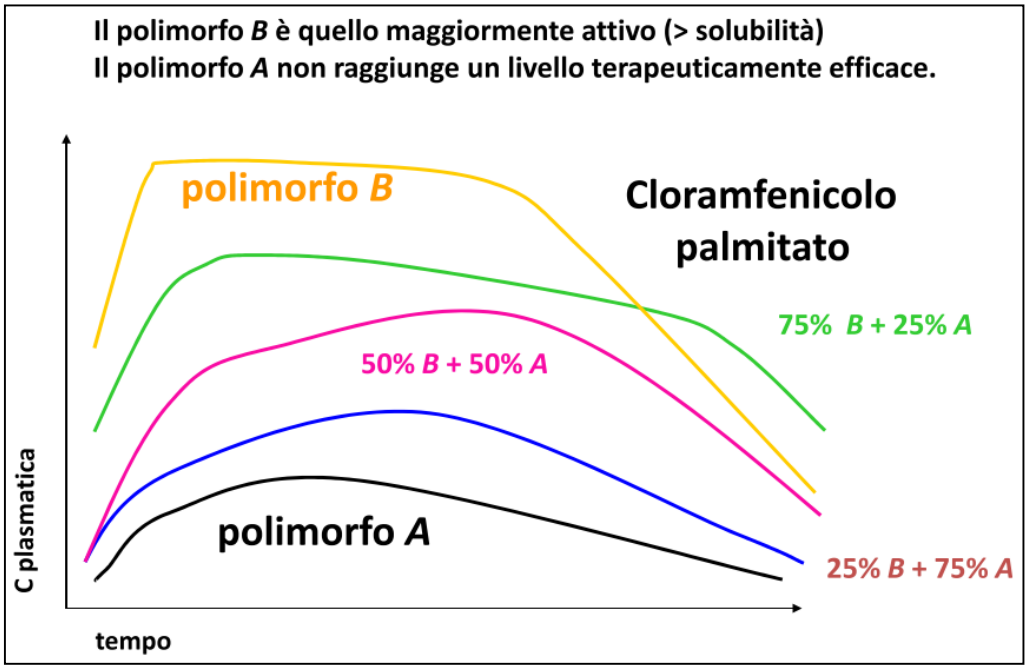
Solid state's properties (Fonte: Aschimfarma, adapted from A. Gazzaniga)

- **Polymorphism**
  - Stability
  - Dissolution
  - Compaction (high amount)
- **Particle size**
  - Distribution (CU)
  - Dissolution
- **Particle shape**
  - Compaction
  - Segregation (CU)

The potential effect of drug substance properties on drug product can be used to justify the drug substance specification.

EXAMPLES FROM THE SCIENTIFIC LITERATURE ,DESCRIBING NON-EQUIVALENCE OF THE FORMULATIONS DUE TO A ***DIFFERENT PHYSISCAL FORM OF THE ACTIVE INGREDIENT*** *(AMORFOUS FORMS, POLYMORPHISM, SOLVATES)*

- Novobiocin (1960)
- CAF palmitate (1967, 1980)
- Ampicillin (1968, 1981)
- Chlortetracycline (1974)
- Amobarbital (1981)
- 6-mercaptopurine (1981)
- Phenylbutazone (1984)
- Indomethacin (1987)
- Cimetidine (1987)
- Carbamazepine (1992, 2000, 2003)
- Oxytetracycline chlorhydate (1999)



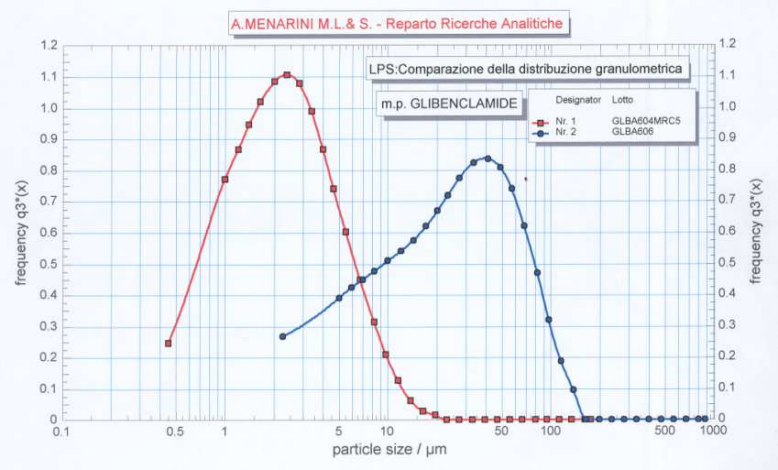
Particle Size

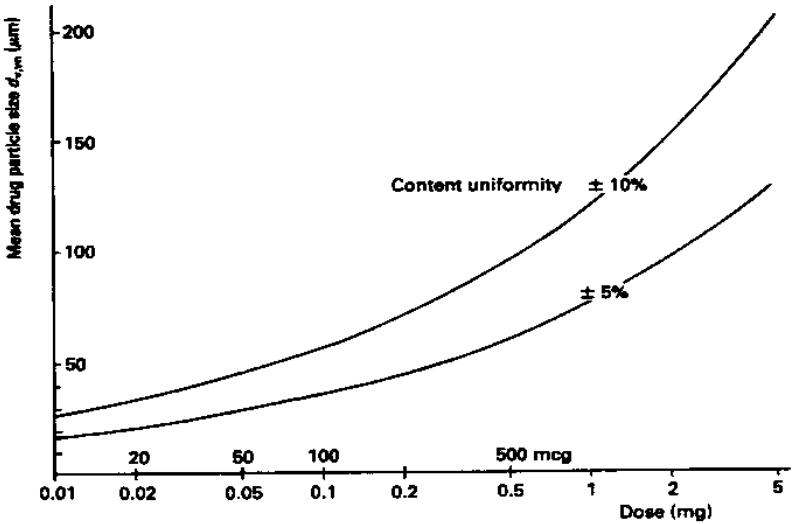
For the drug substance, the International Conference on Harmonization (ICH) guideline Q6A provides guidance (decision tree #3) on when a particle size specification should be considered [5].

A particle size specification of the drug substance is required if it is critical for drug product performance (i.e., **dissolution**, solubility, bioavailability, **content uniformity**, stability, or product appearance) or manufacturability (i.e. **processability, flowability**, **blend uniformity**, and **compactibility**, etc.).

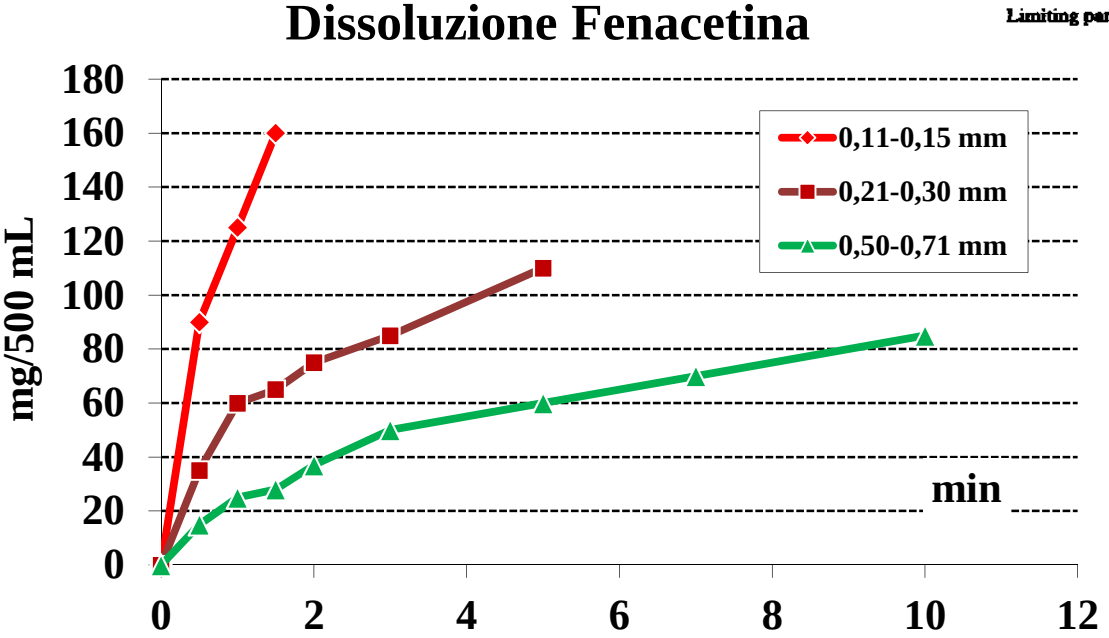
Direct compression is a process by which the tablets are compressed directly from powder blends of the active pharmaceutical ingredient (API) and suitable excipients,.

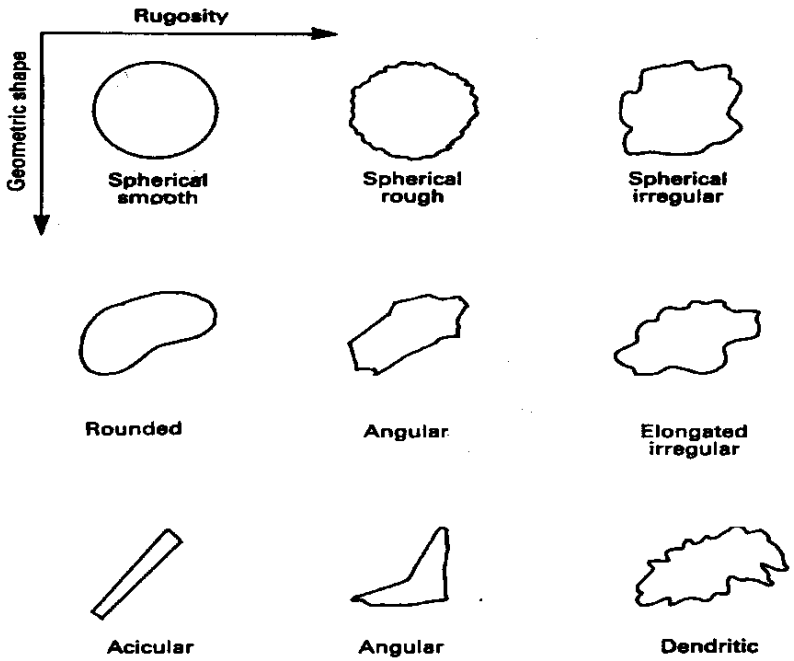
For these different components (e.g., API, fillers, disintegrants, lubricants, etc.), if the differences in the **particle size**, **shape**, or **density** are significant, the powder blend (i.e., the mixture) may have a tendency to segregate, which will result in failure of **blend uniformity**.



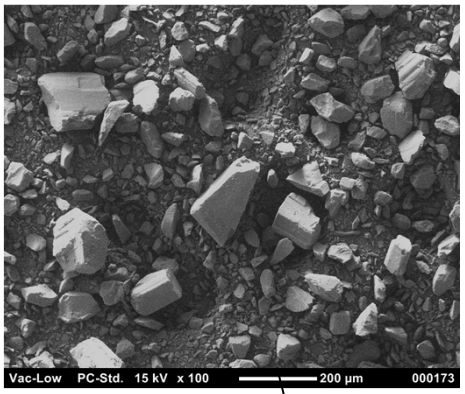


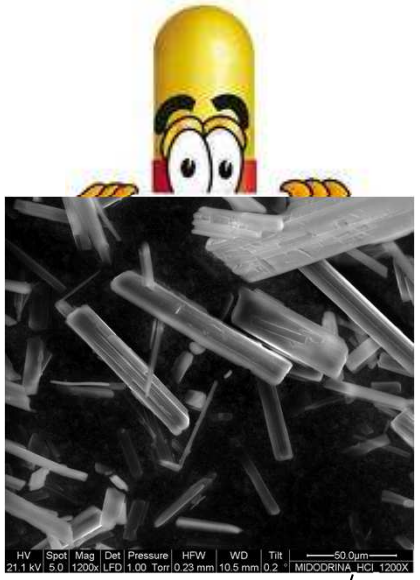
Limiting particle sizes consistent with content uniformity and increasing drug doses (0.01–5 mg).

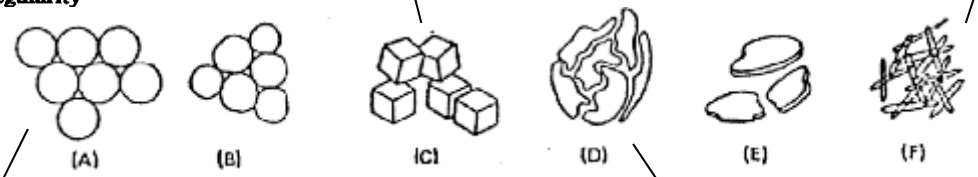




Characteristic particle shapes related to geometric shape and surface irregularity

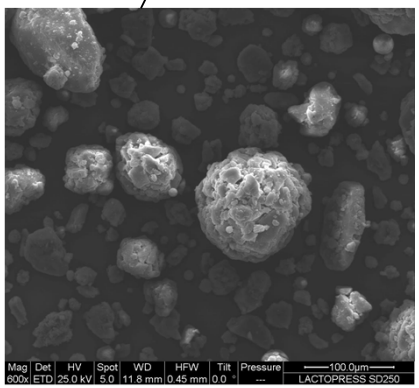


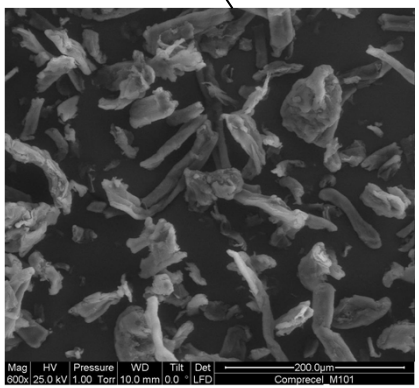


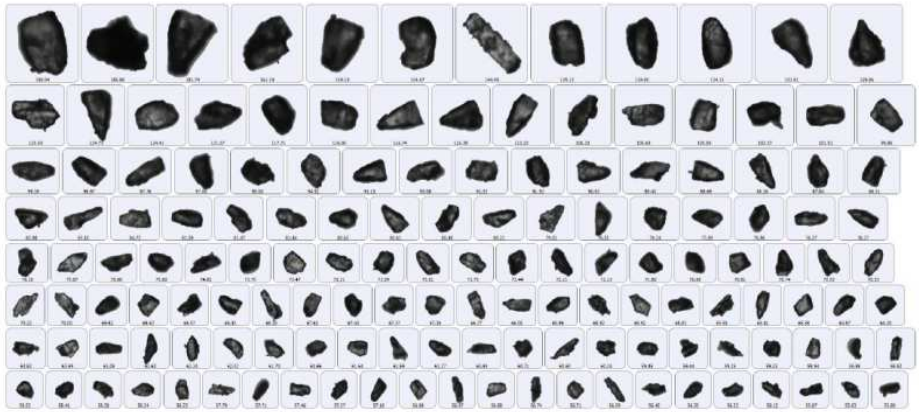


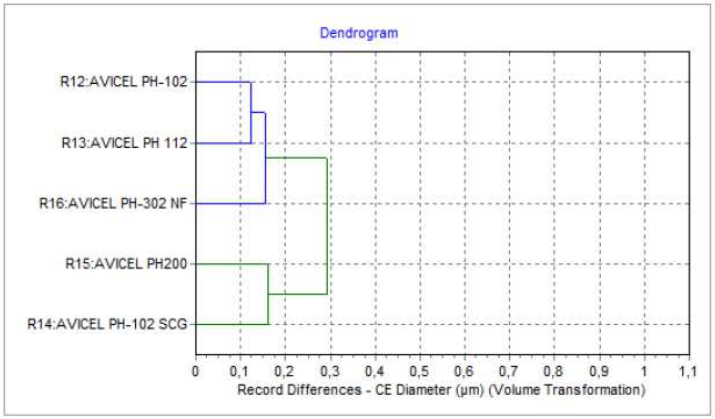
Particle shape

information may be required if it have significant influence on mixing and flow properties of final powder blends.

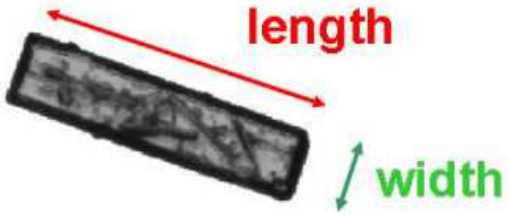




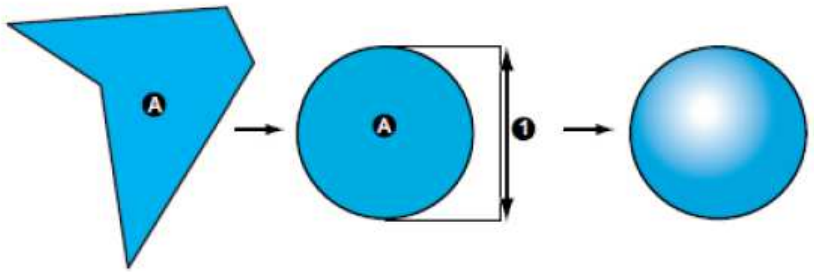




$$Aspect\ ratio = \frac{Larghezza}{lunghezza} \qquad Elongation = 1 - \frac{Larghezza}{lunghezza}$$



$$Circularity = \frac{2 \times \sqrt{\pi \times Area}}{Perimeter} \qquad Convexity = \frac{Perimeter\ di\ A + B}{Perimeter\ di\ A}$$



$$Volume = \frac{\pi \times\ Diametro\ CE^2}{6}$$

CE Diameter [Diametro del cerchio equivalente] - il diametro ❶ di un cerchio con la stessa area (A) di quella dell'immagine della particella, come mostrato di seguito:

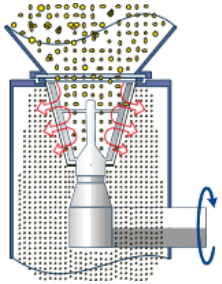
POLVERI

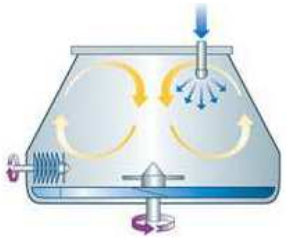
La possibilità di misurare alcune proprietà consente di ottenere informazioni complete e definitive su ingredienti farmaceutici e di migliorare la conoscenza e l'efficienza dei processi produttivi.

Granulometria :
Granulometria a diffrazione Laser: USP 429, EP 2.9.31, JP 10, ISO 13320.
Morfologia
Analisi automatizzata di immagine: USP 776, EP 2.9.37, JP 3.04, ISO 13322
Microscopia Elettronica a Scansione SEM: USP 1181.
Area superficiale BET
Area Superficiale Specifica BET: USP 846.
Densità
Densità reale di solidi e polveri – picnometria a gas: USP 699.
Porosità
Porosimetria ad intrusione di Mercurio: USP 267
Assorbimento di acqua
Dynamic Vapor Sorption DVS: USP 1241

Manufacturing phases

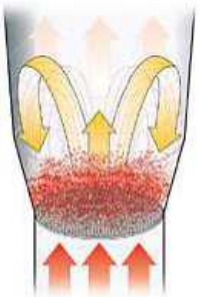
Milling

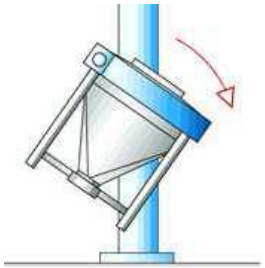




Granulation
(Wet/Dry)

Drying





Blending

Tabletting/Filling

Coating

Process Validation is:

the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

(ICH Q7 - EMA)

Process Validation is:

the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality product

(FDA)

FDA Guidance for Industry
Process Validation: General Principles and Practices
January 2011 Current Good Manufacturing Practices (CGMP)- Revision 1

B. Stage 1 — Process Design 8

1. Building and Capturing Process Knowledge and Understanding 8
2. Establishing a Strategy for Process Control 9

C. Stage 2 — Process Qualification 10

1. Design of a Facility and Qualification of Utilities and Equipment 10
2. Process Performance Qualification 11
3. PPQ Protocol 12
4. PPQ Protocol Execution and Report 13

D. Stage 3 — Continued Process Verification 14

FDA encourages the use of modern pharmaceutical development concepts, quality risk management, and quality systems at all stages of the manufacturing process lifecycle.

Stage 1 – Process Design:

The commercial manufacturing process is defined during this stage based on knowledge **gained through development** and scale-up activities.

A successful validation program depends upon information and knowledge from product and process development.

This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process that results in products with the desired quality attributes. Manufacturers should:

- **Understand the sources of variation**
- **Detect the presence and degree of variation**
- **Understand the impact of variation on the process and on product attributes**
- **Control the variation in a manner commensurate with the risk**

Product development activities provide key inputs to the process design stage, such as the intended dosage form, the quality attributes, and a general **manufacturing pathway.**

Stage 2 _ Process qualification: Confirming that the manufacturing process as designed is capable of reproducible commercial manufacturing.

5.21. A **process validation** should be **defines the critical process parameters (CPP), critical quality attributes (CQA)** and the associated **acceptance criteria which should be based on development data or documented process knowledge**.

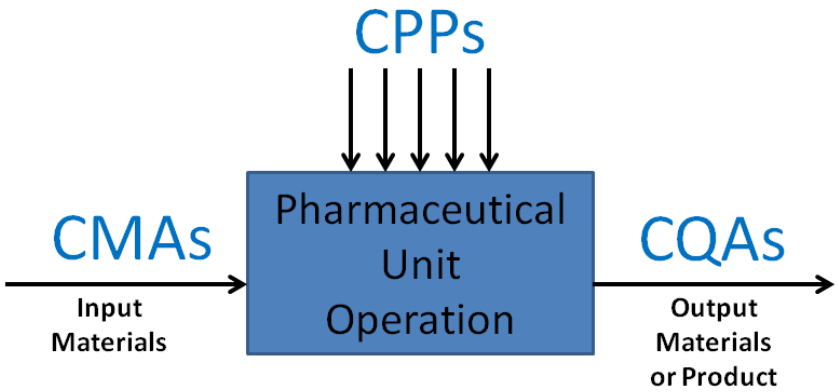
a robust product development process
is in place to enable successful process validation.

The sampling plan.
The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches. The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination.

Criteria and **process performance indicators** that allow for a science- and risk-based decision about the ability of the process to consistently produce quality products.
A description of the **statistical methods to be used in analyzing all collected data** (e.g., statistical metrics defining both intra-batch and inter-batch variability).

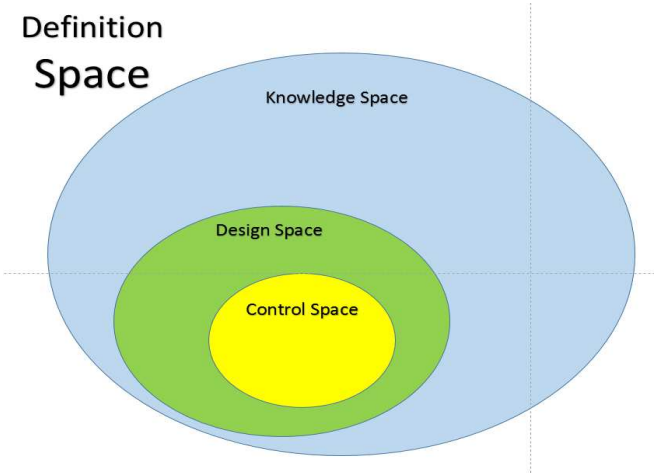

Process Qualification is not quite complete ….. we still have a few bugs into !

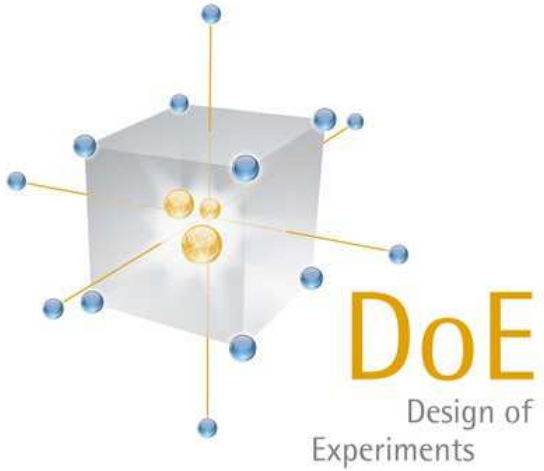
Critical process parameters (CPP) and Critical quality attributes (CQA)



Design Of Experiments (**DOE**) is a structured, organized method for determining the relationship between factors affecting a process and the output of that process

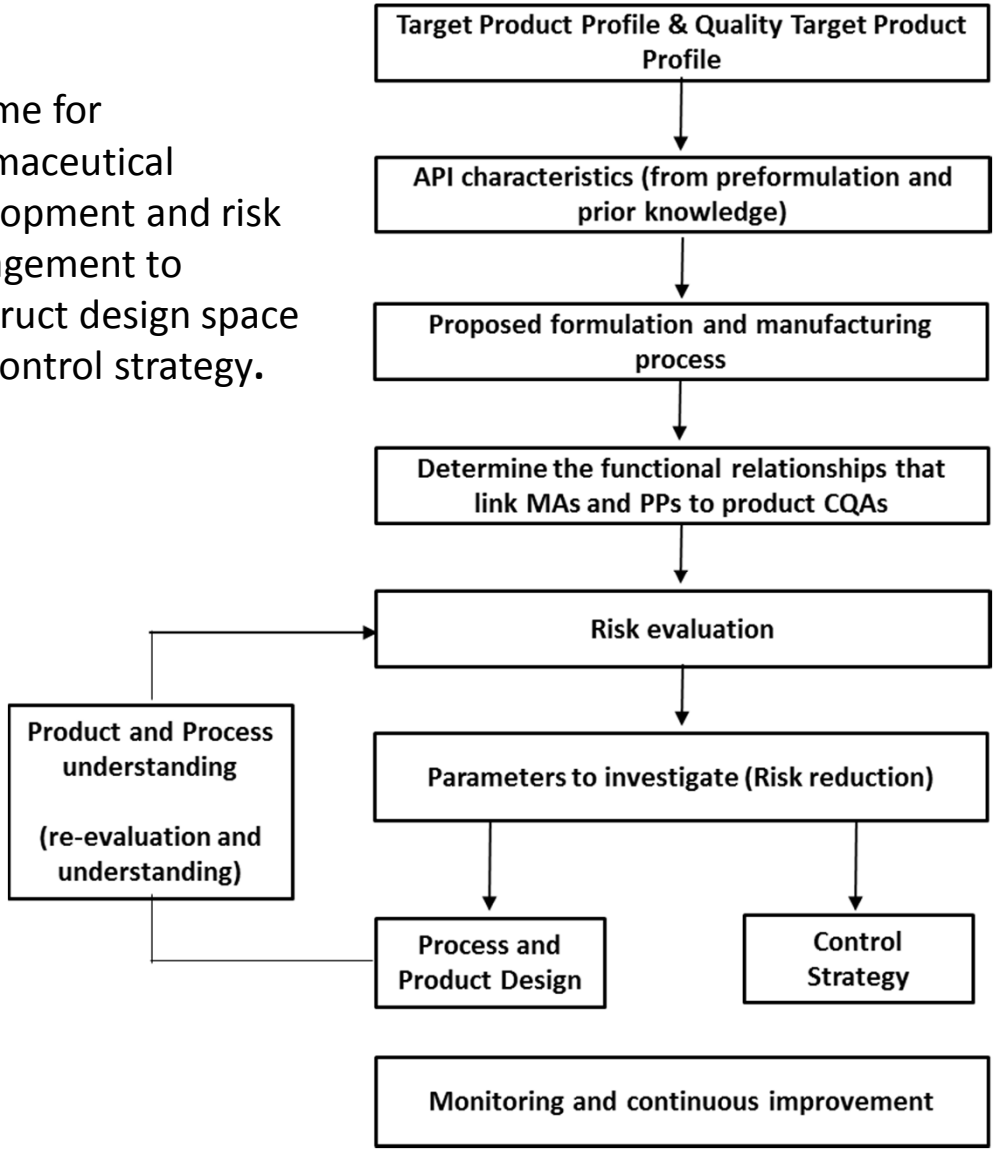
$$CQAs = f\,(CPP_1, CPP_2, CPP_3 \ldots CMA_1, CMA_2, CMA_3 \ldots)$$

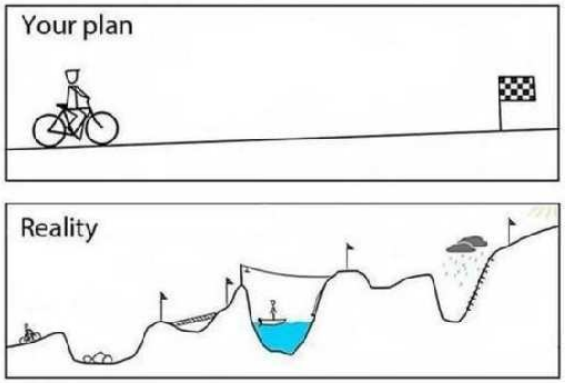




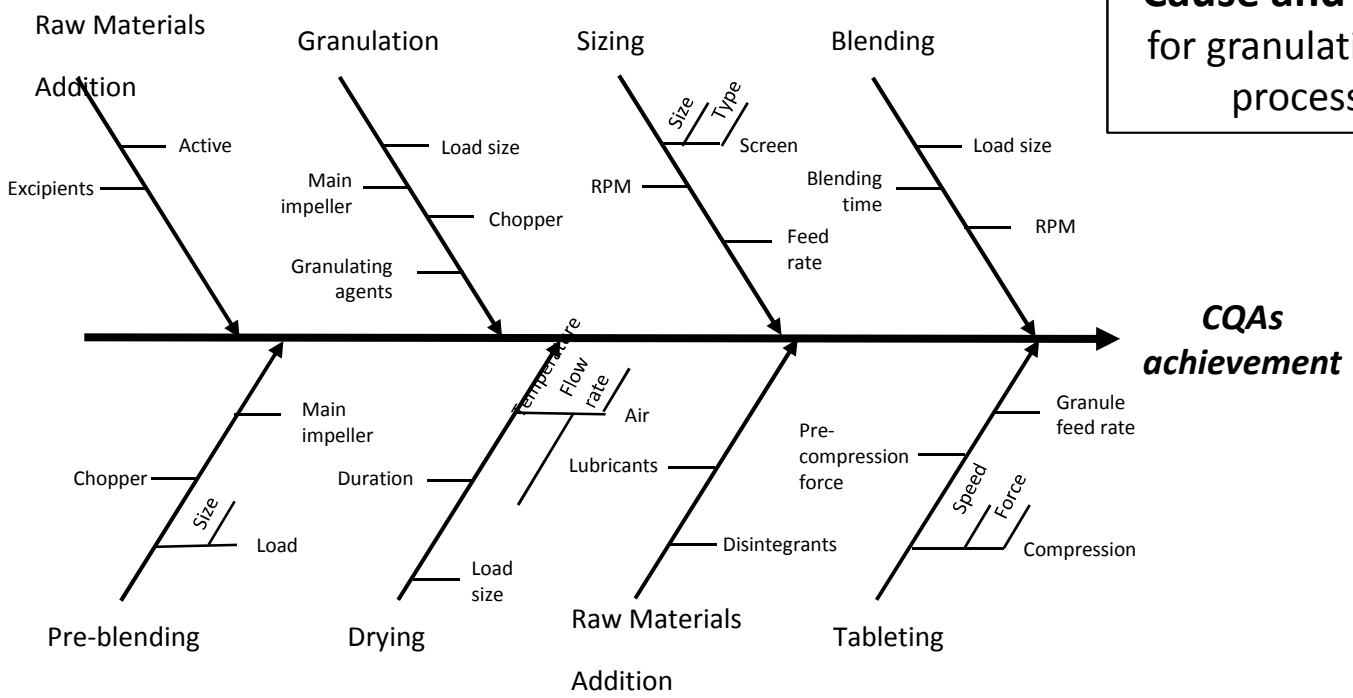
Design Space: The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

Scheme for pharmaceutical development and risk management to construct design space and control strategy.



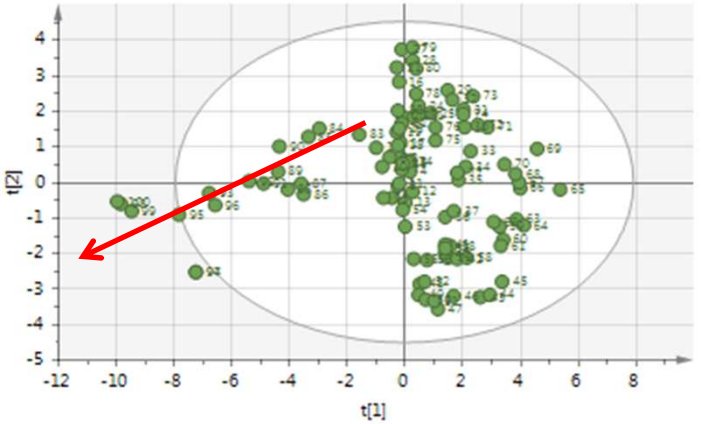


Cause and Effect Diagram
for granulation and tableting process (Ishigawa)



Multivariate Analysis

PCA Score plot.
Warning limit (the ellipse) is displayed. The arrow shows the process drift direction



Stage 3 — Continued Process Verification (Ongoing Process Verification)

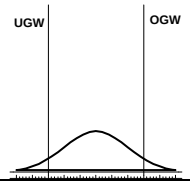
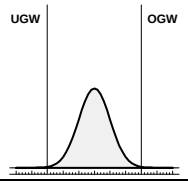
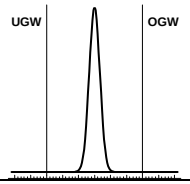
*Documented evidence that the process remains in a **state of control** during commercial manufacture.*

State of control. *A condition in which the set of controls consistently provides assurance of acceptable process performance and product quality.*

Good process design and development should anticipate significant sources of variability and establish appropriate detection, control, and/or mitigation strategies, as well as appropriate alert and action limits.

Process Capability Analysis

Estimate the potential percent of defective product

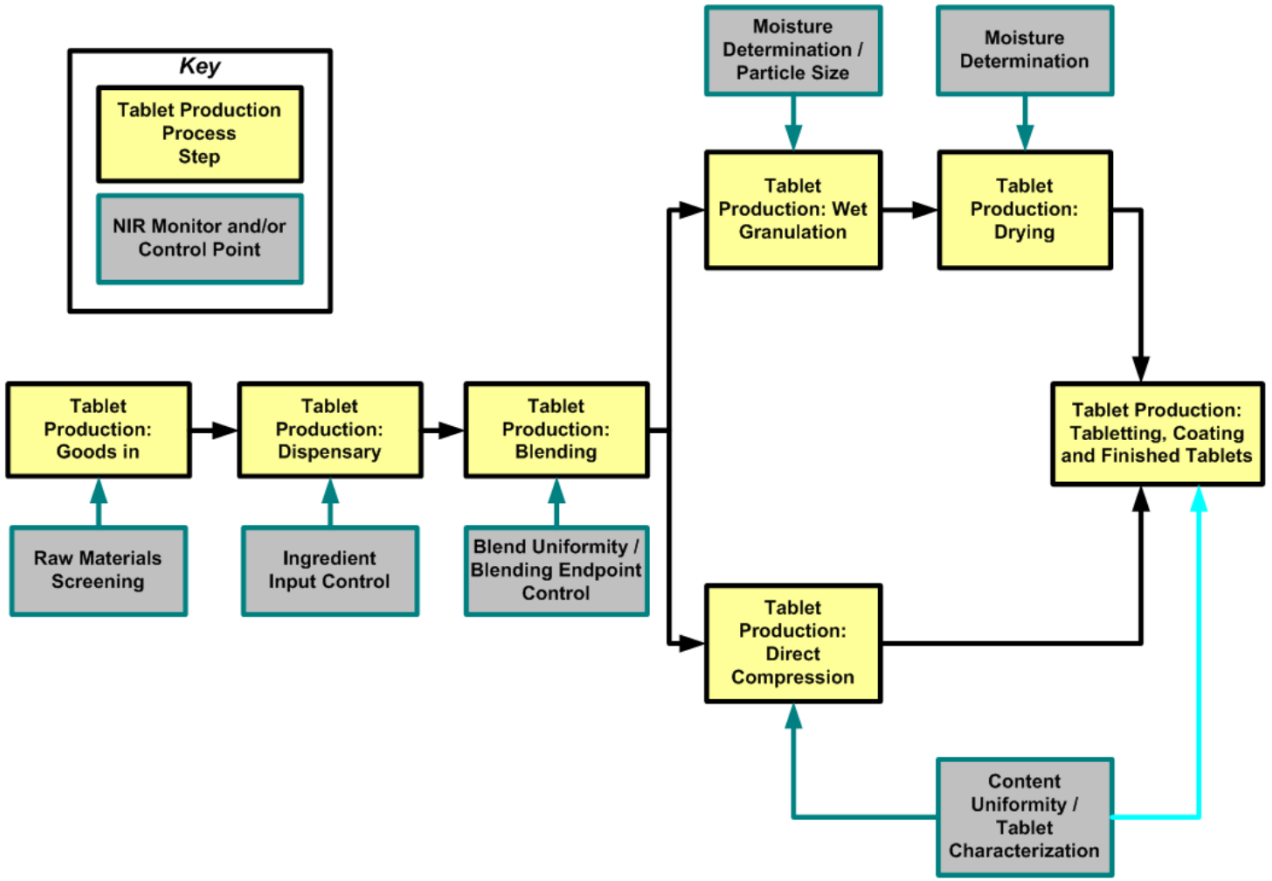
Cp value	cp=0.5	cp=1	cp=3
graphical view of different cp values			
values statistically out of limit	13,58 %	0,27 %	approx. 0
values in the limit	86,42 %	99,73 %	> 99,999999 %
Result:	process statistically out of control	**process statisticaly under control**	

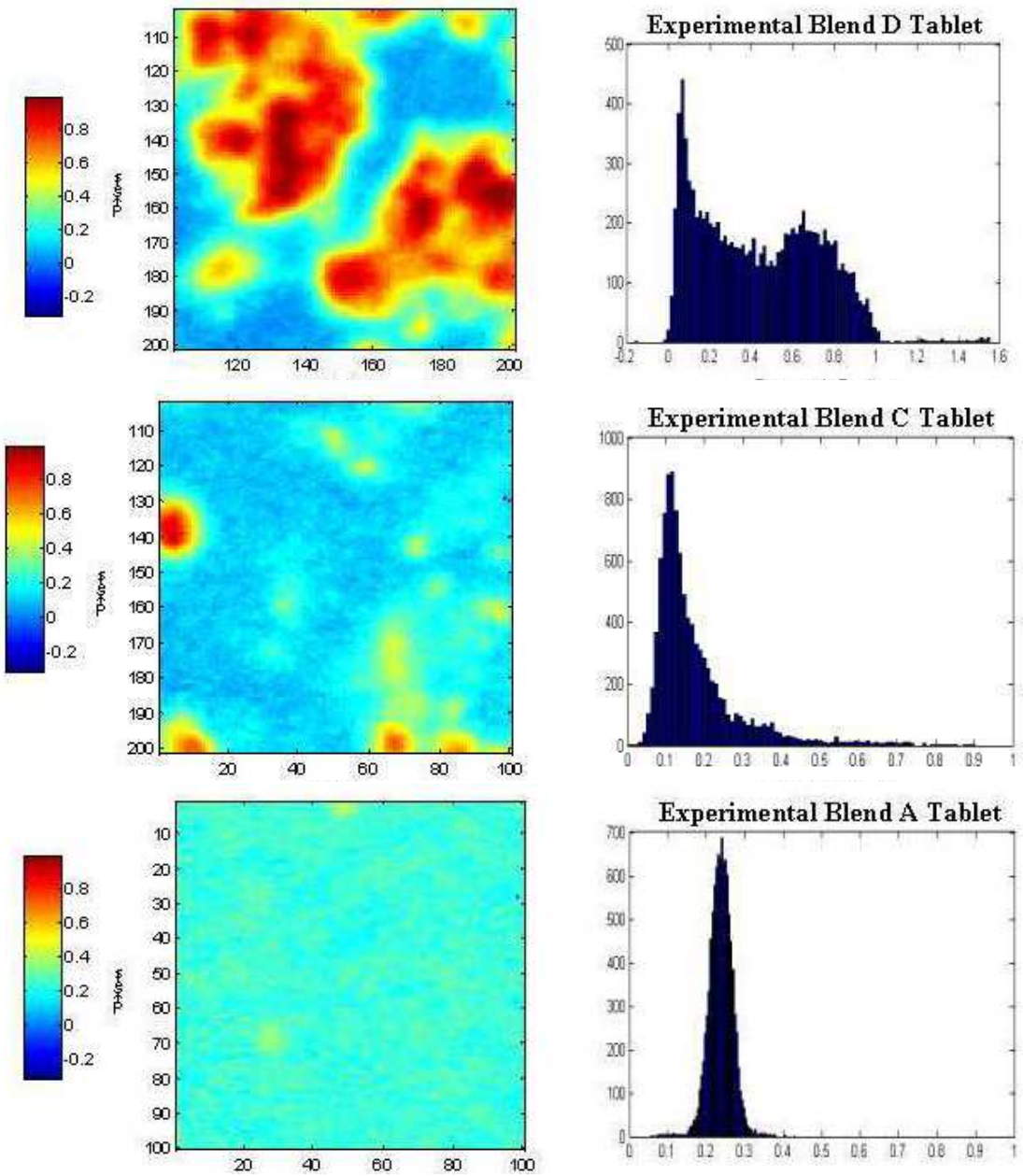
More advanced strategies, which may involve the use of **Process Analytical Technology** (PAT), can include timely analysis and control loops to adjust the processing conditions so that the output remains constant.

Manufacturing systems of this type can provide a higher degree of process control than non-PAT systems.

Process Analytical Technology

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.



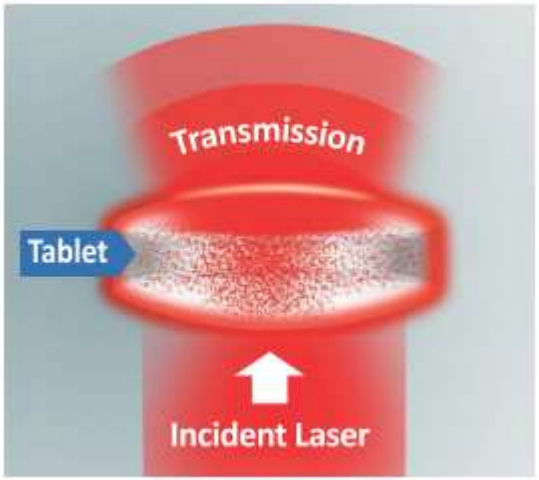


NIR Spectral Imaging

Analysis of Tablets to Assess Powder Blend Homogeneity

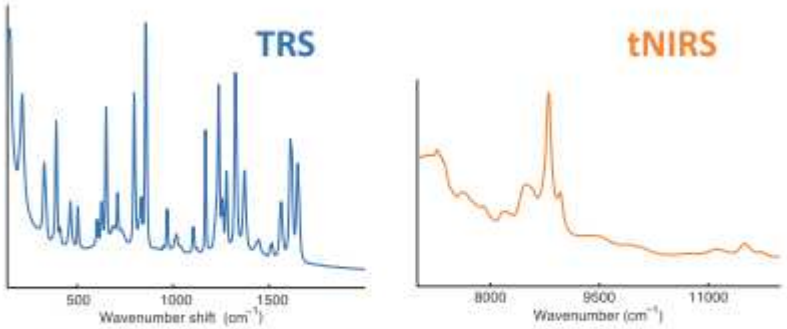
AAPS PharmSciTech 2002; 3 (3) article 17

Transmission Raman Spectroscopy



- ✓ Low or no sensitivity to moisture, particle size and thickness variation
- ✓ Easy-to-interpret sharp spectral features
- ✓ Low LOQ: <1% is often possible
- ✓ Sensitivity to the sample bulk

- **HIGH-THROUGHPUT**
- **NON-DESTRUCTIVE**
- **NON-INVASIVE**
- **NO SAMPLE PREPARATION**



TRS spectrum with discrete API and excipient features, compared with transmission NIR for the same 3-API product

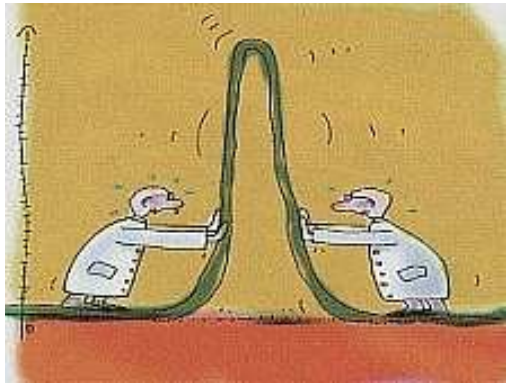
Measuring Low Dose APIs and Polymorph Content

Content Uniformity • Assay • ID • Polymorph Quantification • Formulation Development

Statistical tools

Statistical tool	Intra Batch		Batch to batch	
	Considerations	Acceptance criteria	Considerations	Acceptance criteria
Descriptive statistic (e.g. mean, median, standard deviation, coefficient of variation, range, etc.)	Basis for evaluation that must be integrated with other tools	Results within specification. Generally, CV% between samples is used to evaluate data	Basis for evaluation that must be integrated with other tools	Results within specification. Generally, CV% between batches is used to evaluate data
Histograms	Possibility to evaluate distribution shape, process centering and process variation (suggested link with capability evaluation). Consider if enough data are available for intra batch evaluation	Output should be normal distributed and centered around the mean of the specification	Possibility to evaluate distribution shape, process centering and process variation (suggested link with capability evaluation). To have sufficient data suggested to group all samples result from all batches	Output should be normal distributed and centered around the mean of the specification
Process capability (Cpk)	Possibility to evaluate ability of a process to provide stable outcome within established limits. Appropriate population and normal distribution must be taken into account. Consider if enough data are available for intra batch evaluation.	Depending on criticality of process different limits can be set, however, if Cpk ≥ 1.33, the process is generally considered centered and under control	Possibility to evaluate ability of a process to provide stable outcome within established limits. Appropriate population (at least 30 data points) and normal distribution must be taken into account. To have sufficient data suggested to group all samples result from all batches	Depending on criticality of process different limits can be set, however, if Cpk ≥ 1.33, the process is generally considered centered and under control
Control charts, trends and shifts	Generally, it is not applicable in PPQ (not enough batches)			
ANOVA (Nested Anova)	Generally, it is not applicable intra batch		Possibility to compare means and variance, between batches	Depending on the selected confidence level

Suitable for traditional approach PPQ data analysis.



Statistical Analysis

Tolerance Intervals

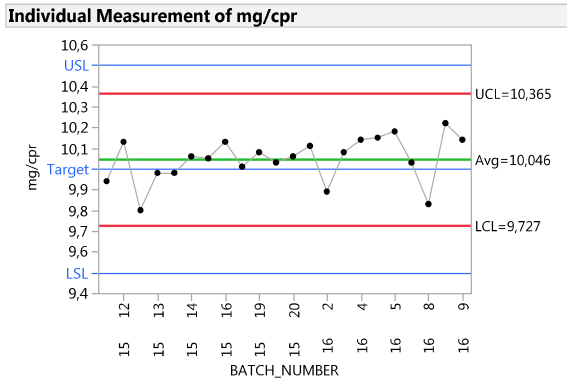
Proportion	Lower TI	Upper TI	1-Alpha
0,990	9,658432	10,4343	0,950

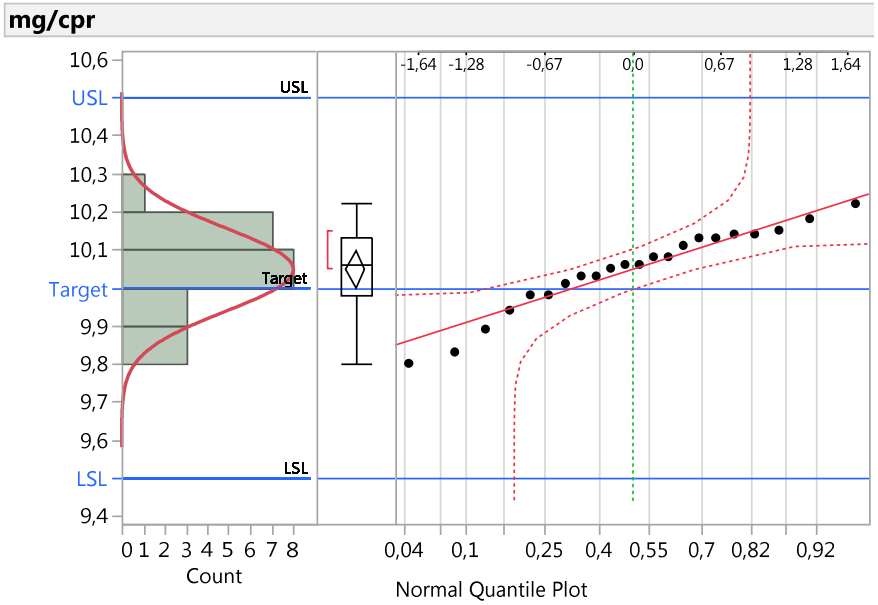
Dixon Outlier Test

Upper or Lower Outlier

Statistic	Estimate
Q0	0,34
Q	0,09524
α	0,05

No outlier detected





Goodness-of-Fit Test

Shapiro-Wilk W Test

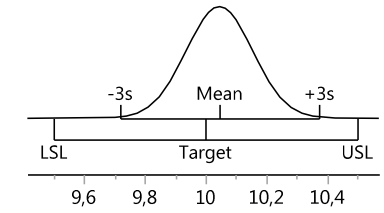
W	Prob<W
0,947759	0,2849

Note: Ho = The data is from the Normal distribution. Small p-values reject Ho.

Capability Analysis

Specification	Value	Portion	% Actual
Lower Spec Limit	9,5	Below LSL	0,0000
Spec Target	10	Above USL	0,0000
Upper Spec Limit	10,5	Total Outside	0,0000

Long Term Sigma



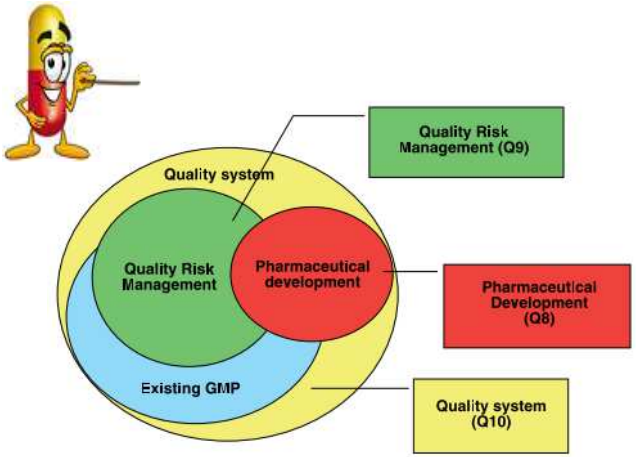
Sigma = 0,10931

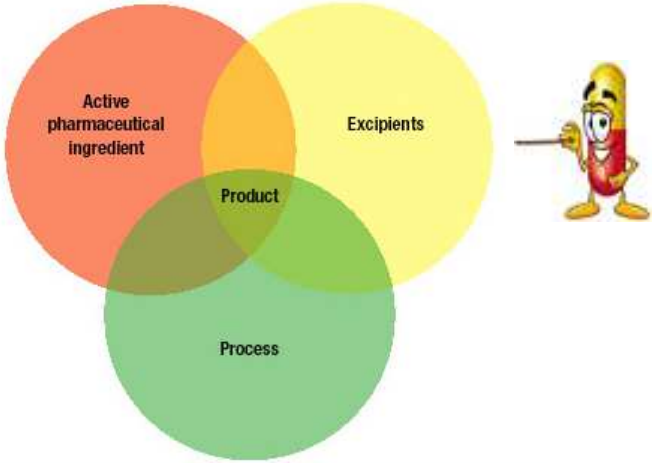
Capability	Index	Lower CI	Upper CI
PP	1,525	1,067	1,982
PPK	1,383	0,942	1,824
CPM	1,404	1,016	1,846
PPL	1,666	1,145	2,183
PPU	1,383	0,944	1,819

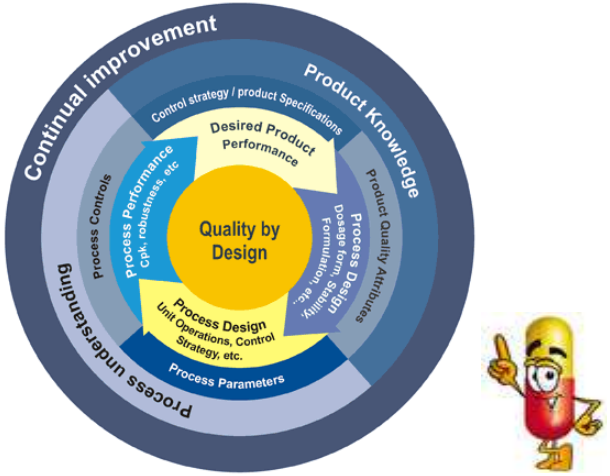
Portion	Percent	PPM	Sigma Quality
Below LSL	0,0000	0,2890	6,498
Above USL	0,0017	16,6160	5,650
Total Outside	0,0017	16,9050	5,646

A critical point of the process is the ability to ensure a **productive dialogue** between:

- chemical development
- formulation development
- manufacturing







Quality By Design

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.(ICH Q8)

Grazie per l’attenzione