Manufacturing Pharmaceutical Granules: Is the Granulation End-Point a Myth?

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Moist agglomeration is a wide spread but critical unit operation

- Process
  - wet massing,
  - screening,
  - subsequent drying.
- Correct “end-point” of this important process
  - when do you need to stop massing
  - or stop with the addition of granulating liquid?
  - what is the correct amount of granulating liquid?

A similar situation exists in case of the moist agglomeration in fluidized bed equipment.

The SIGMA Concept I

FDA pushes forward the PAT Initiative for very good reasons:

- The variability of most pharmaceutical processes needs to be reduced.
- The performance of a process can be described by its Sigma value.

The SIGMA Concept II

- The champion is the chip industry with a six Sigma manufacturing performance (**static values**)
  - i.e. with an amount of defective samples ≤ 2 ppb.
- The performance of the pharmaceutical industry is around 2 Sigma
  (≤ 4.6 % defectives).

FDA Whitepaper March 2004
Three Dimensions of the Critical Path

Assessing Safety	**Show that product is adequately safe for each stage of development**	**• Preclinical: product safe enough for early human testing Eliminate products with safety problems early** **• Clinical: show that product is safe enough for commercial distribution**
Demonstrating Medical Utility	**Show that the product benefits people**	**• Preclinical: Select appropriate design (devices) or candidate (drugs) with high probability of effectiveness** **• Clinical: Show effectiveness in people**
Industrialization	**Go from lab concept or prototype to manufacturable product**	**• Design a high-quality product** - Physical design/Characterization/Specifications **• Develop mass production capacity** - Manufacturing scale-up/Quality control

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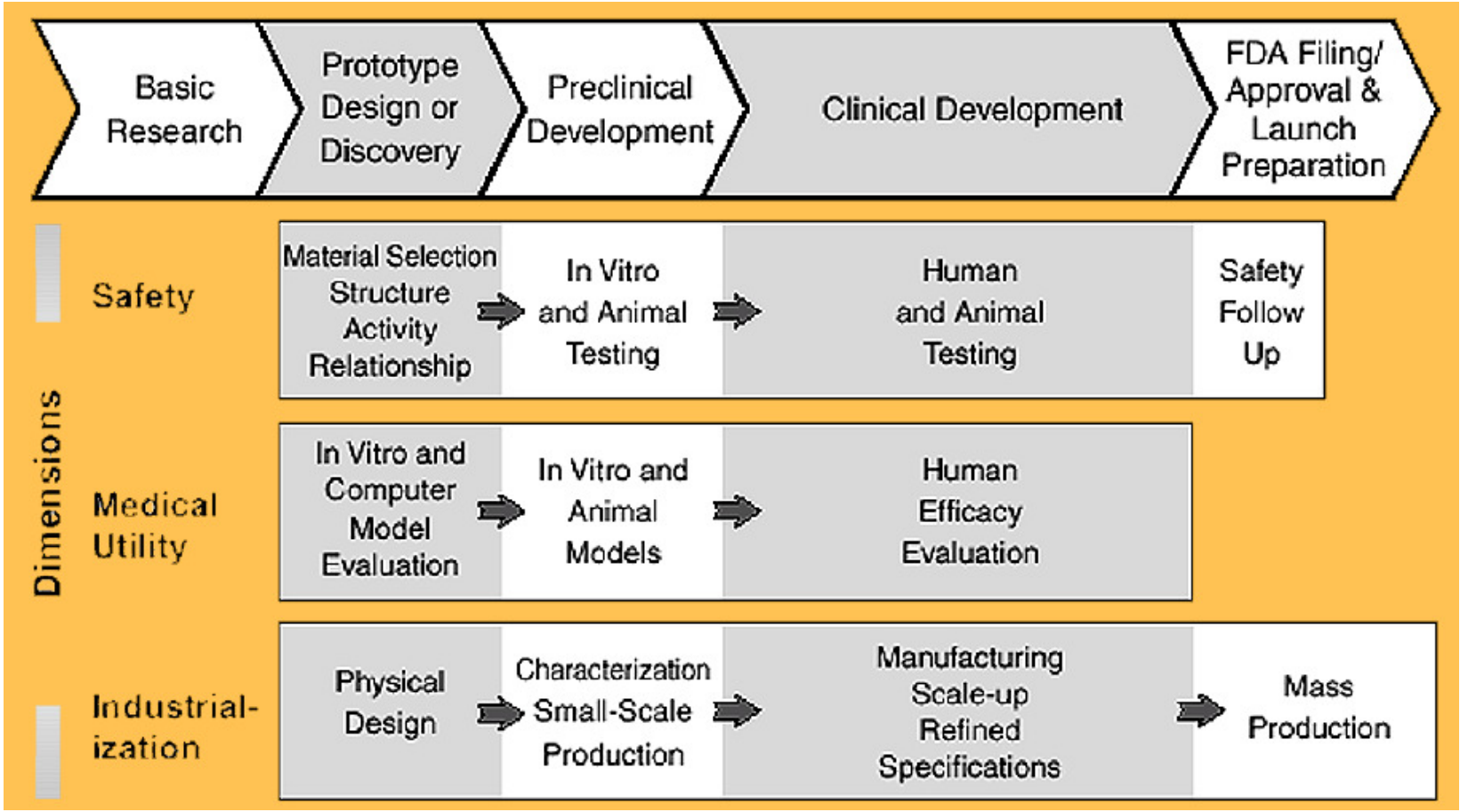
Three Dimensions of the Critical Path



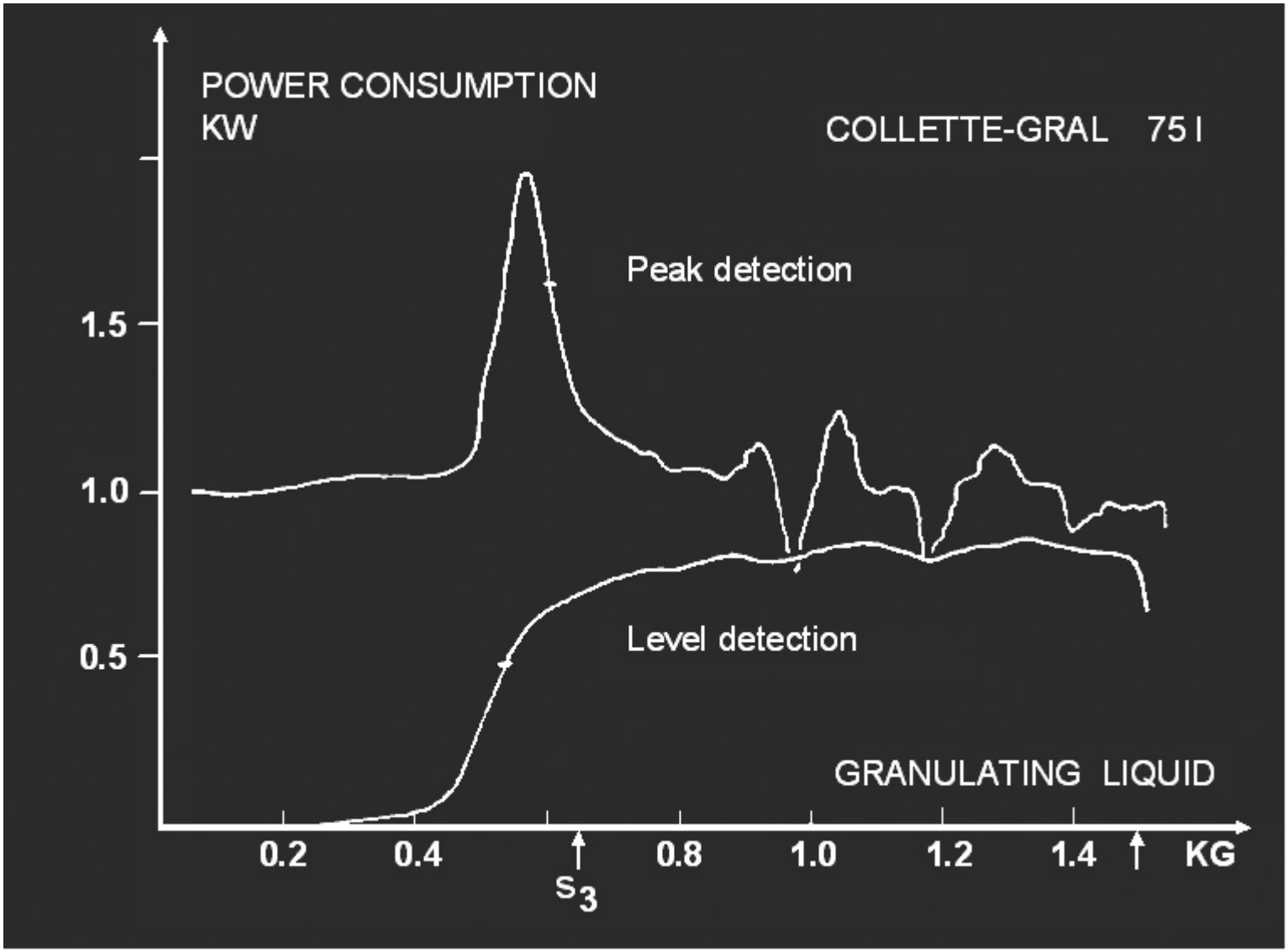
PAT: Identification of critical processes

1.The wet agglomeration process

- Critical parameters
  - The type of binder
  - The amount of granulation liquid
  - The massing time

Is the granulation "end-point" a myth?

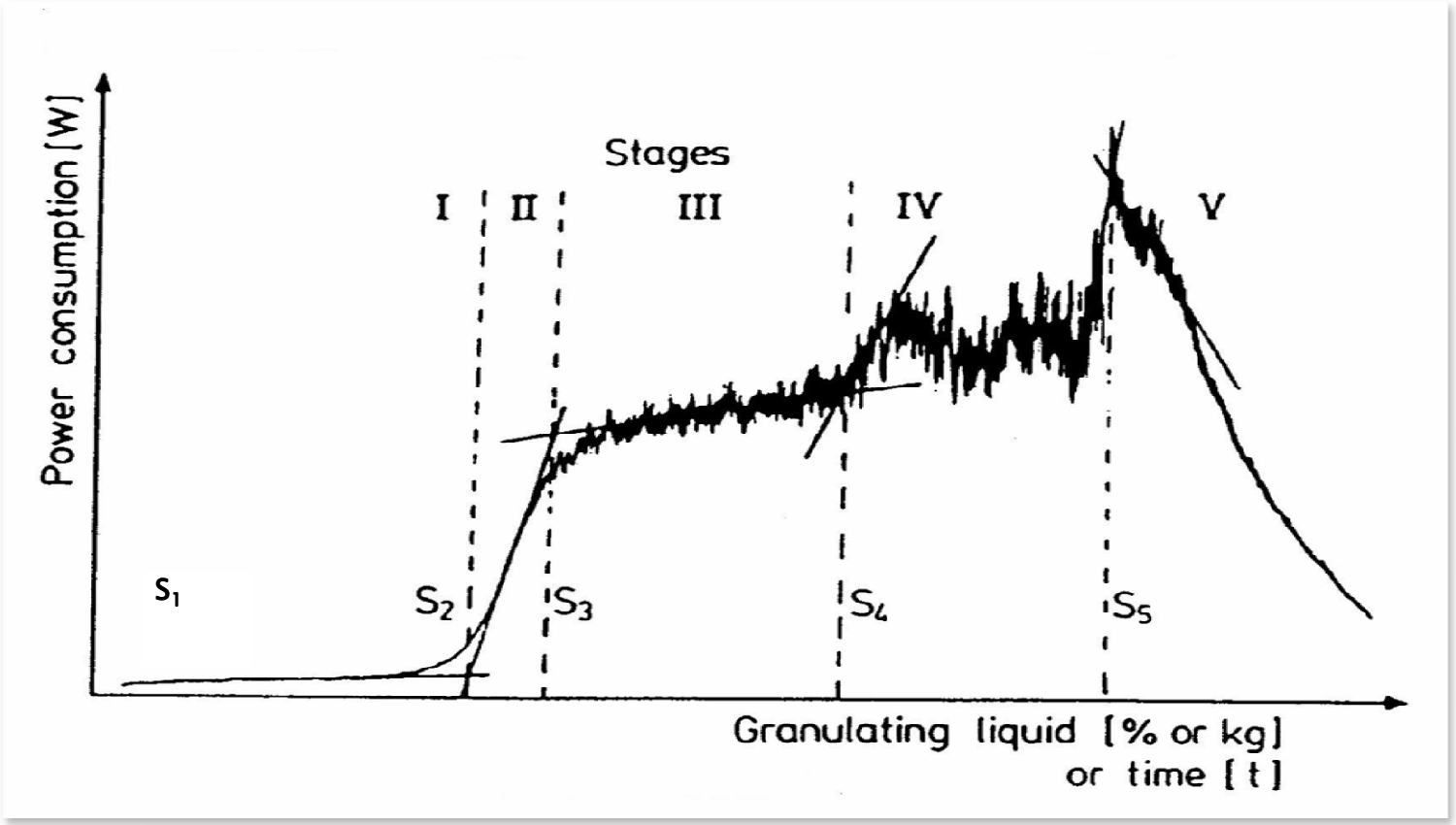
See next slide


POWER CONSUMPTION
KW
COLLETTE-GRAL 75 l
Peak detection
Level detection
GRANULATING LIQUID
1.5
1.0
0.5
0.2
0.4
0.8
1.0
1.2
1.4
KG
S3

Typical Materials (example)

- polyvinylpyrrolidone 4% (w/w)
- lactose (86% w/w)
- corn starch (10% w/w).
- demineralized water was pumped to the powder mix at constant rate of 15 g $min^{-1}kg^{-1}$

Division of a power consumption curve according to Leuenberger



The typical power profile consists of five different phases:

- **Phase I (S_1-S_2):** Up-take of the added amount of granulating liquid by the components to saturate the moisture content (equilibrium moisture content at 100% relative humidity of the air).
- **Phase II (S_2-S_3):** Start of the formation of liquid bridges (pendular state) between the primary particles
- **Phase III (S_3-S_4):** Plateau phase, i.e. filling up the inter-particulate void space with the granulating liquid (transition from the pendular to the funicular state). The liquid bridges are mobile.

The typical power profile consists of five different phases:

- **Phase IV (S_4-S_5):** Funicular state with isolated 3-dimensional clusters (snow balls) having already reached the capillary state.
- **Phase V(>S_5):** Transition from the capillary state (i.e. void space between the primary particles completely occupied by the granulating liquid) to a suspension.

Plateau region S_3 - S_4

- Usable granulates can be produced in a conventional way only within the plateau region S_3 - S_4.
- It is important to realize that the liquid bridges of Phase III are mobile and thus the granulation liquid needs to have a low viscosity.

Control device based on the power consumption method

- The formulation and the wet agglomeration process needs to show if possible an ideal power consumption profile
  - components (drug substance, excipients) are not too soluble in the granulating liquid.
  - increase before the end-point, i.e. before the point of no return is reached;
- constant amount of binder in the formulation (dry premix)
- low viscous a granulating liquid, preferably deionized water should be used
- absolute prerequisite to add the granulating liquid with a pump at a constant speed
- validation of the moist agglomeration process needs to include the subsequent screening and drying
- an excellent check is the higher homogeneity of the yield of the granule size distribution. Nevertheless other granule properties such as the compression profile and the properties of the final tablets should be tested, too.

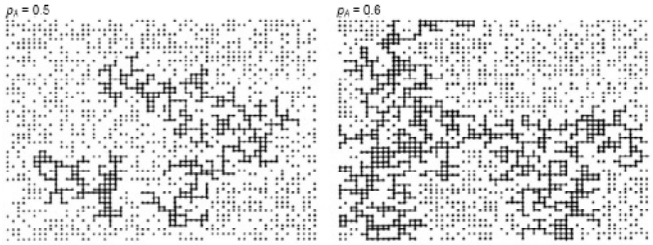
Wet agglomeration process - manual and automatic mode

Type of mode	yield (% w/w) 90 - 710 µm	% undersize < 710 µm	undersize < 90 µm
Manual mode n = 20 batches	81.03 ± 2.42	88.30 ± 2.05	6.80 ± 0.51
Automatic mode n = 18 batches	91.45 ± 0.36	96.80 ± 0.31	5.40 ± 0.35

Granule size distribution

- Robust formulations are today an absolute prerequisite.
- Concerning the production of granules, the granule size distribution should not vary from batch to batch.
- The key factors are the correct amount* and the type of granulating liquid.
- *) e.g. by monitoring the power consumption profile and fine-tuning the required amount

Example: granule size and tablet disintegration

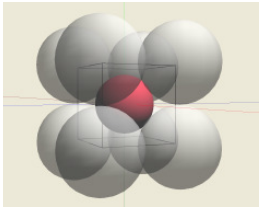


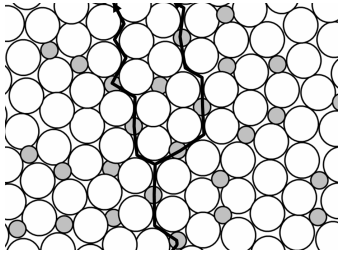
Prediction of the optimum amount of disintegrant to minimize the disintegration time (use of expert system CINCAP):

- based on percolation theory and cellular automata
- mathematical description based only on geometrical and physical considerations independent on chemical properties of compounds!

Two cases of water penetration into a tablet as a factor of particles size:

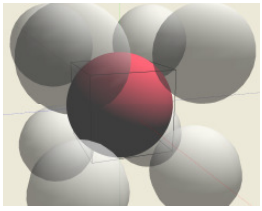
Case1: $r \le \left(\sqrt{3}-1\right)\times R$

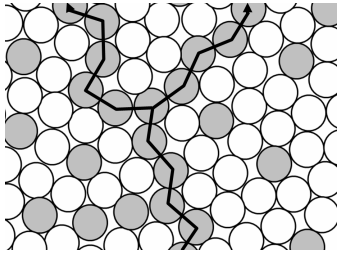




$$\chi_{dis} = \left(\frac{p_s^{rcp}}{1-\varepsilon} - \varepsilon\right)\times 100$$

Case2: $r > \left(\sqrt{3}-1\right)\times R$





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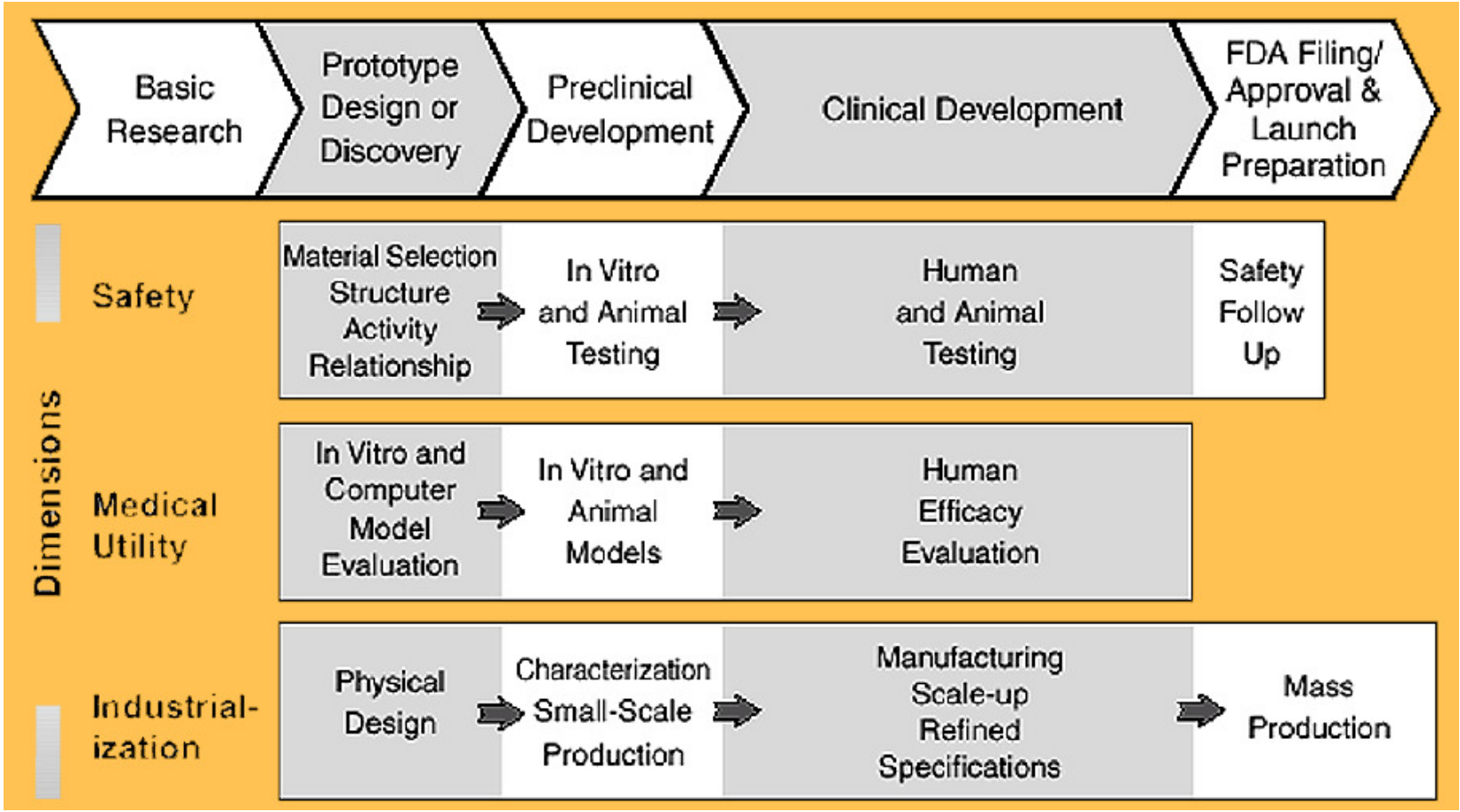
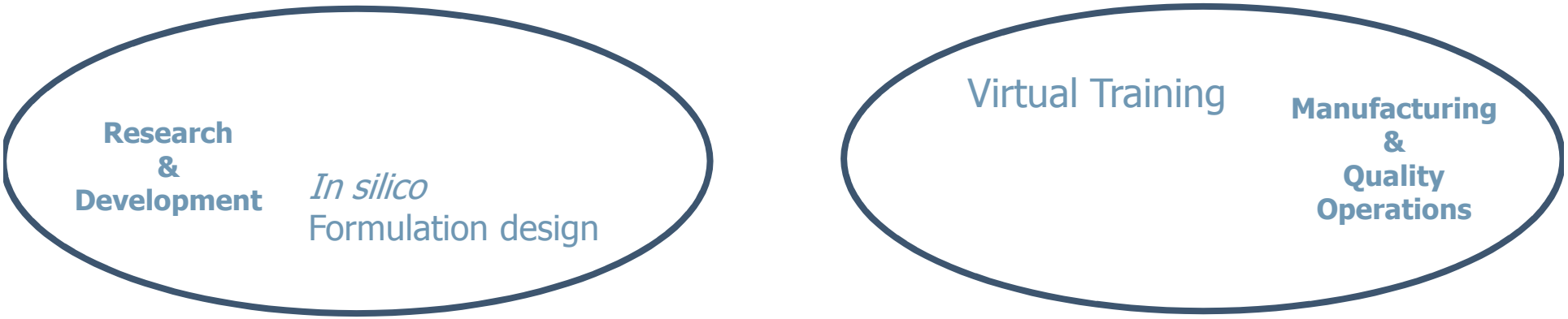


Co-Development Toolbox

Co-Development



Co-Development Toolbox

Virtual Equipment Simulators (VES) in order to reduce human failures

- What do you do for a continuous training and education of your production floor operators in order to improve process quality?
- What happens when you start to use new equipment?
- What do you do if your collaborators feel bored and /or frustrated using the operation manual?
- How to train your personnel to correctly respond to critical situations without putting at risk the quality of your product?
- How to fulfill the requirements of continuous education as requested by authorities such as FDA, etc?

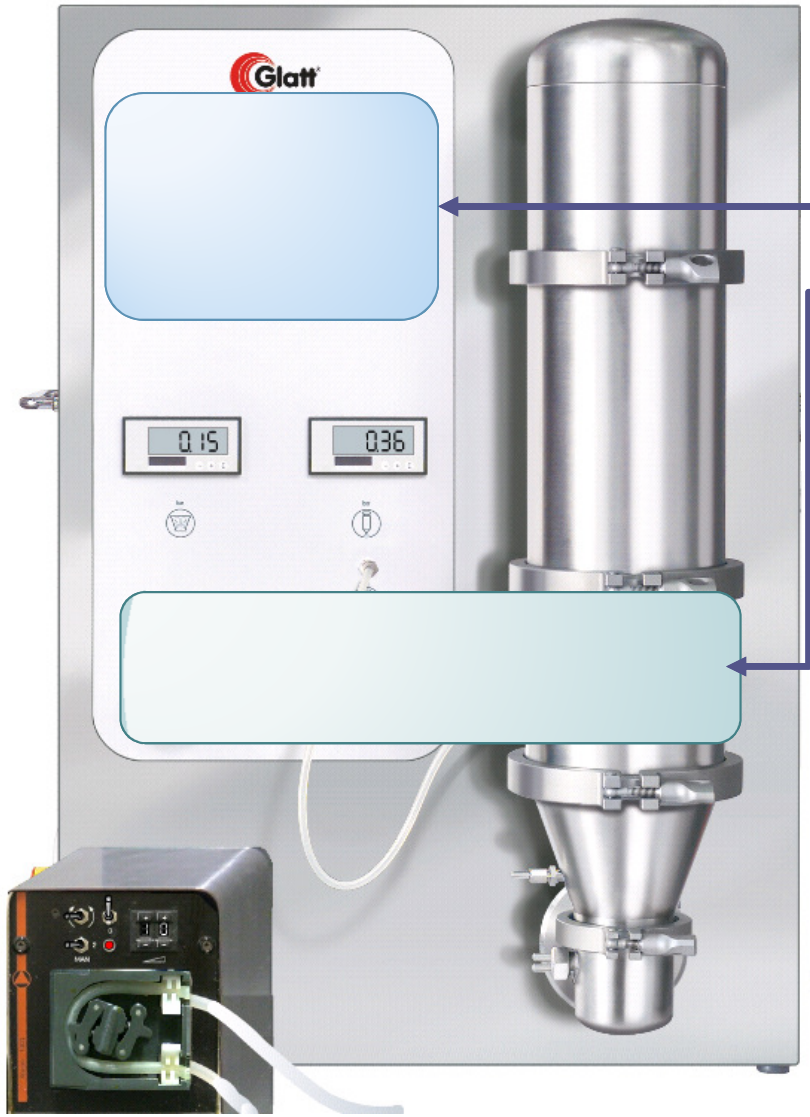
What are VES?

- Technically speaking, simulation is modeling process's behavior, form and visual appearance.
- "… like a flight simulator?"
- **Comparable to the effectiveness of flight simulator to pilot training!**

Simulator vs. interactive animation

- Interactive animation → just reproducing visual appearance.
- Simulation → wider range of possible situations, allowing prediction and exploratory learning.
- Need: strong mechanistic model model for an optimal VES
- CINCAP VES → Beyond interactive animation

Look&Feel (example MiniGLATT)



Interactive controls

Video sensitive
to control position

Auxiliary tools

REAL TIME!

Virtual Equipment Simulators (VES)

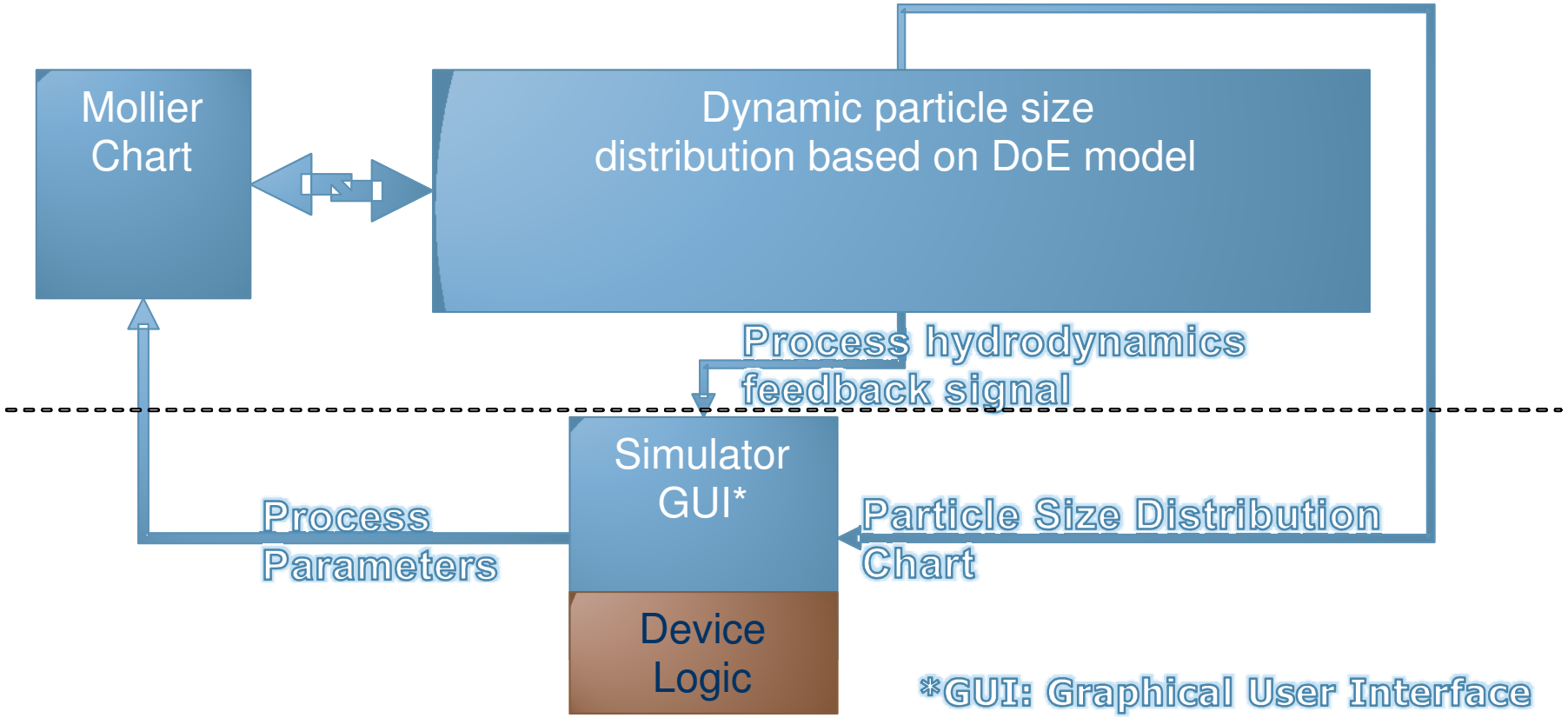
- VES is an ideal tool to get a better process understanding (Process Analytical Technology);
- VES is an ideal tool to explore the limits of the process without putting to danger operators and product;
- VES is an ideal tool for training especially to reduce human errors during real operation;

VES and PAT

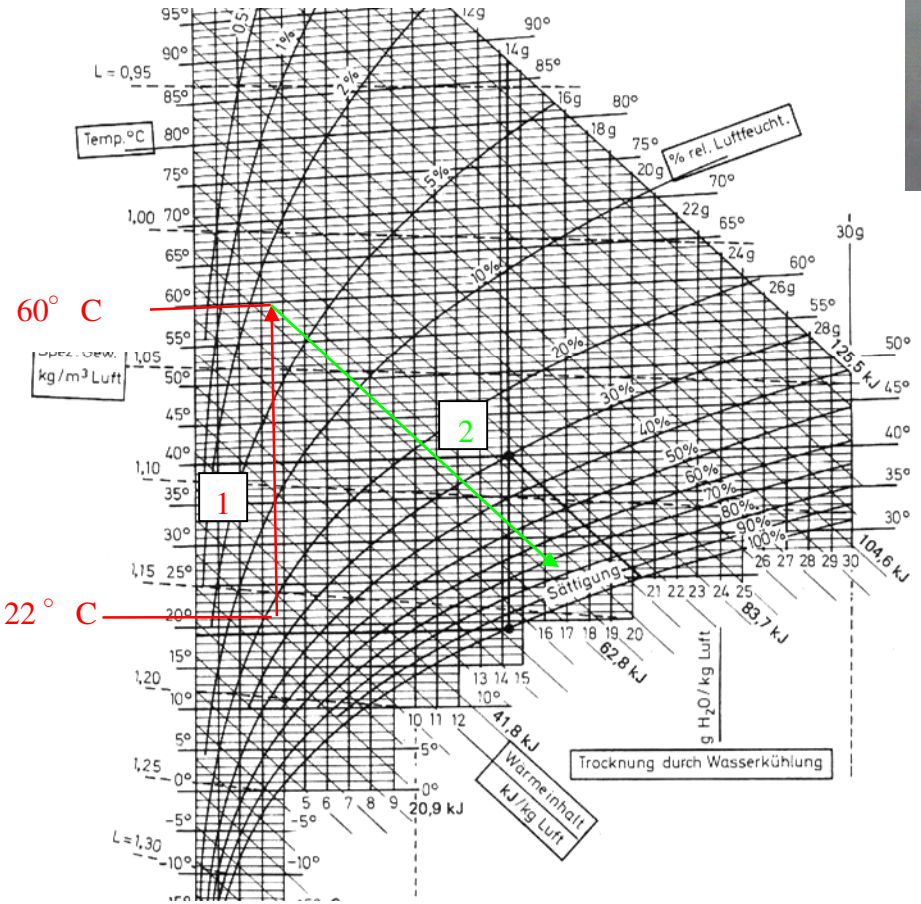
- Need: High-quality equipment simulator which is BASED on process understanding → PAT.
- Need: incorporating mechanistic models which describe correctly the process itself.
- This type of VES is directly linked to a science-based expert system.

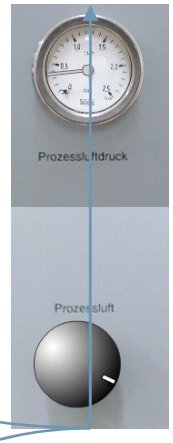
Science-based VES (e.g. fluid-bed granulator)

- Simple but effective



Mollier chart/ backbone of VES





Real-time simulations: modelling possibilities

- Balances → yes
- Response Surface Methodology: → yes
- Micro level modelling: → difficult, almost no.

Conclusion

- there is no evidence that there is a clear “end-point” for the wet agglomeration process neither in case of the high–shear granulation nor in case of the fluidized bed agglomeration and drying process.

Thank you for your attention!

Audience Q&A