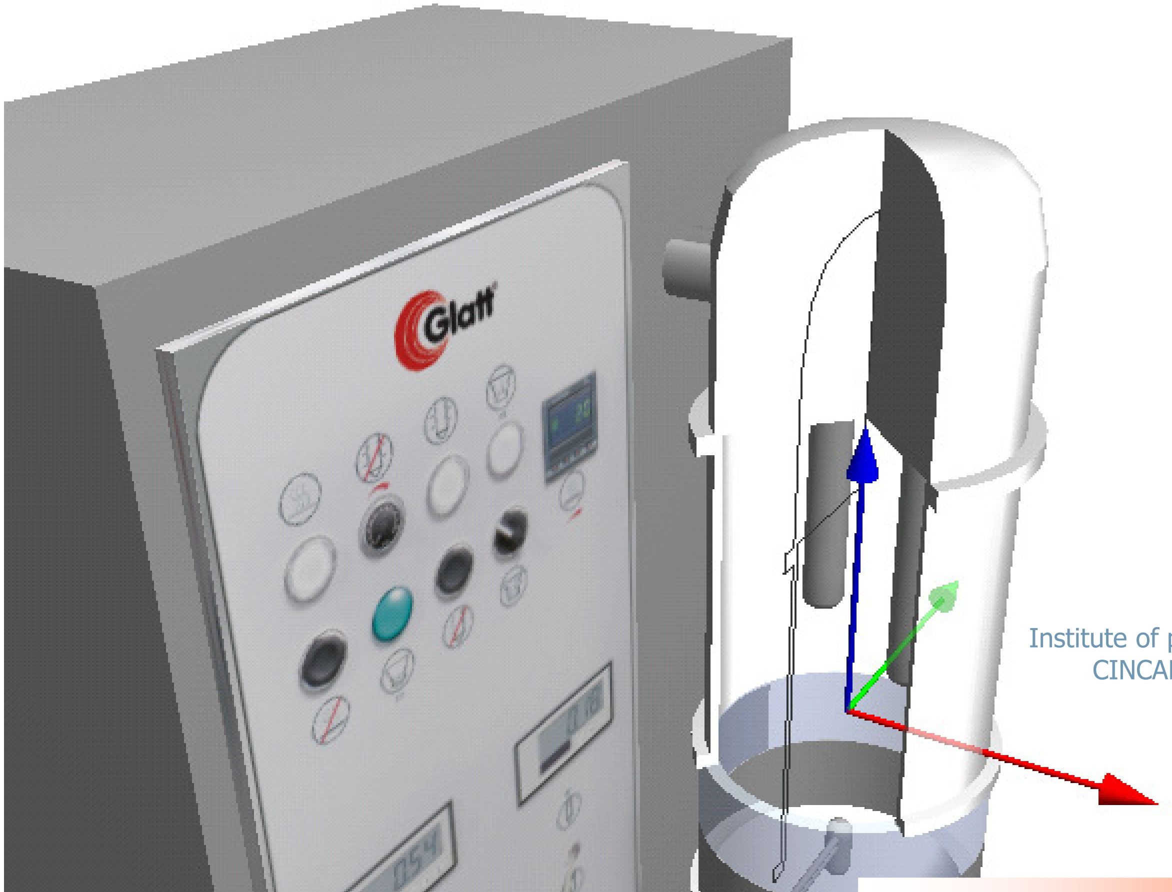

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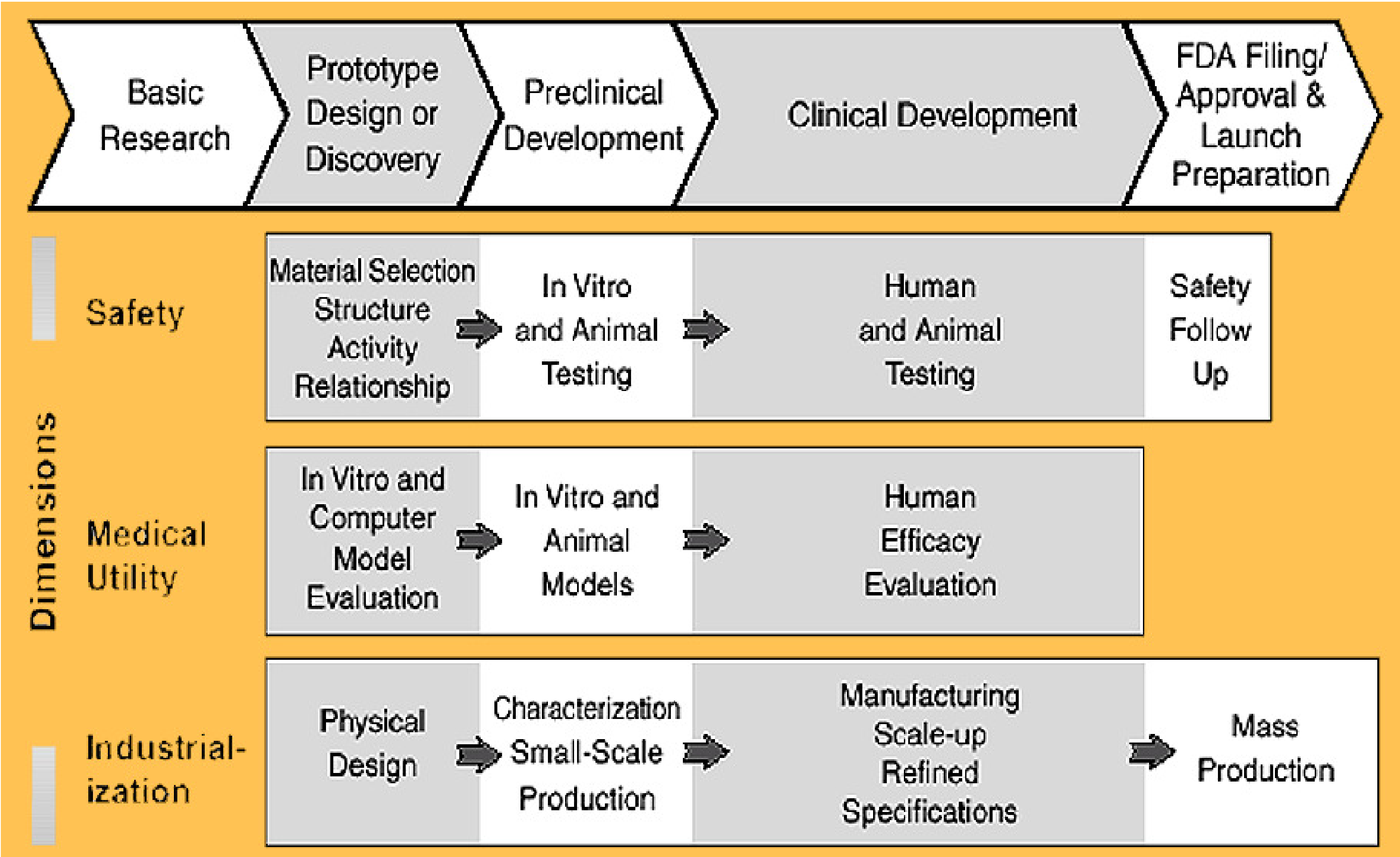
Virtual Equipment Simulators (VES) in pharmaceutical production – a novel tool for continuous education and personnel training

Beyond PAT: FDA Whitepaper March 2004
Three Dimensions of the Critical Path



PAT: The SIGMA Concept

- The champion of the manufacturers is the semiconductor industry with a six Sigma performance
  - i.e. with an amount of defective samples ≤ 2 ppb.

- The performance of the pharmaceutical industry is around 2 Sigma (≤ 4.6 % defectives)! ("static" values), i.e. a possible change of the mean value of the tested property (variability in time) is not taken into account!
- Do it right the first time!! No rejection of batches!!

Faster Time to Market:
Dosage Form Development!

- The development of a dosage form from production of the first formulation in the preclinical research up to registration of the commercial form is very costly and lasts between 8 to 12 years.

- To reduce time to market it is important to think about an integrated approach and a better connectivity between pharma R&D and manufacturing.

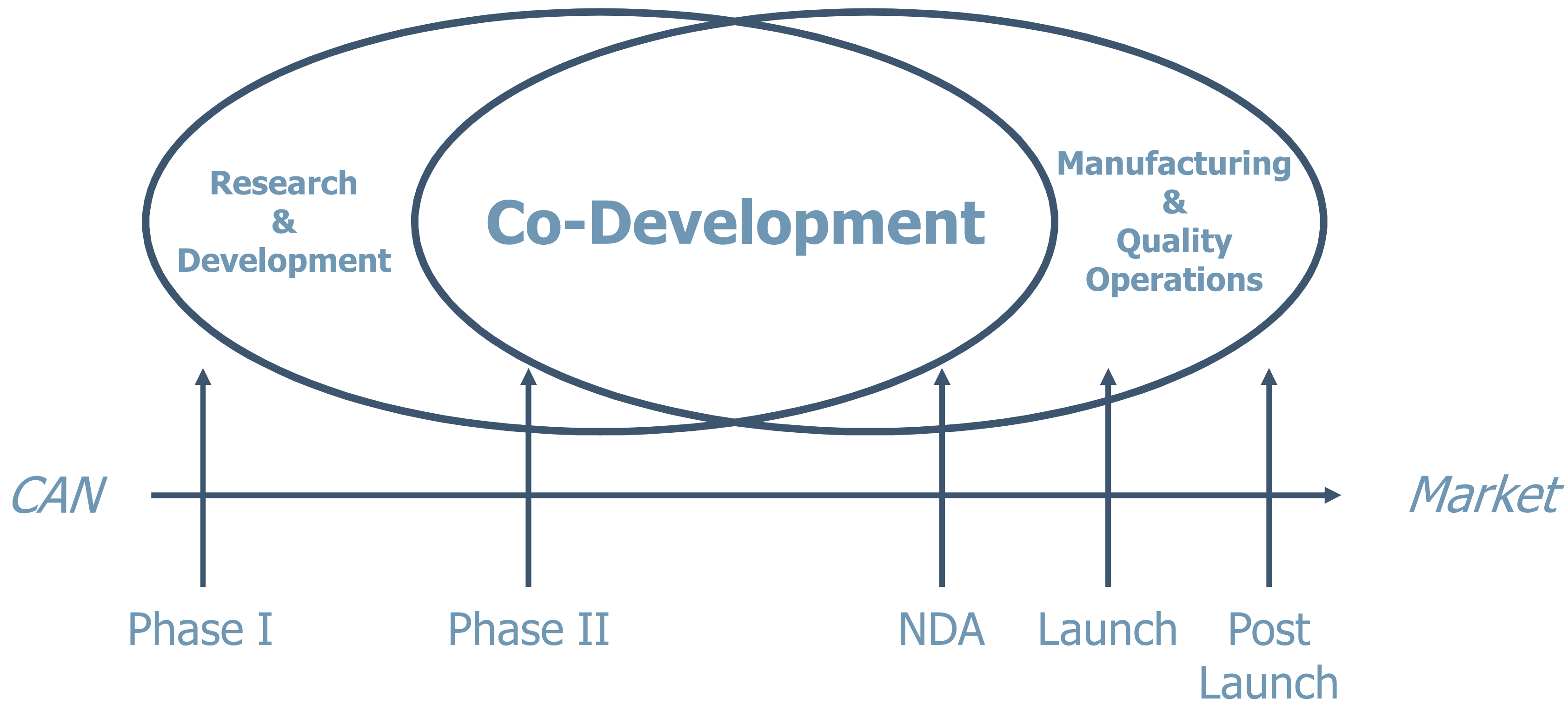
Poor Connectivity:

"… Companies tend to ***operate in silos*** *– R&D, manufacturing, marketing. This is a very proprietary culture. Knowledge and information sharing is the basis to overcome inefficiencies …"*

John Moore, Analyst

Source: Catching up with Reengineering June 2, 2003
Chemical & Engineering News, Vol. 81, N° 22

Improved connectivity: Co-Development Strategy

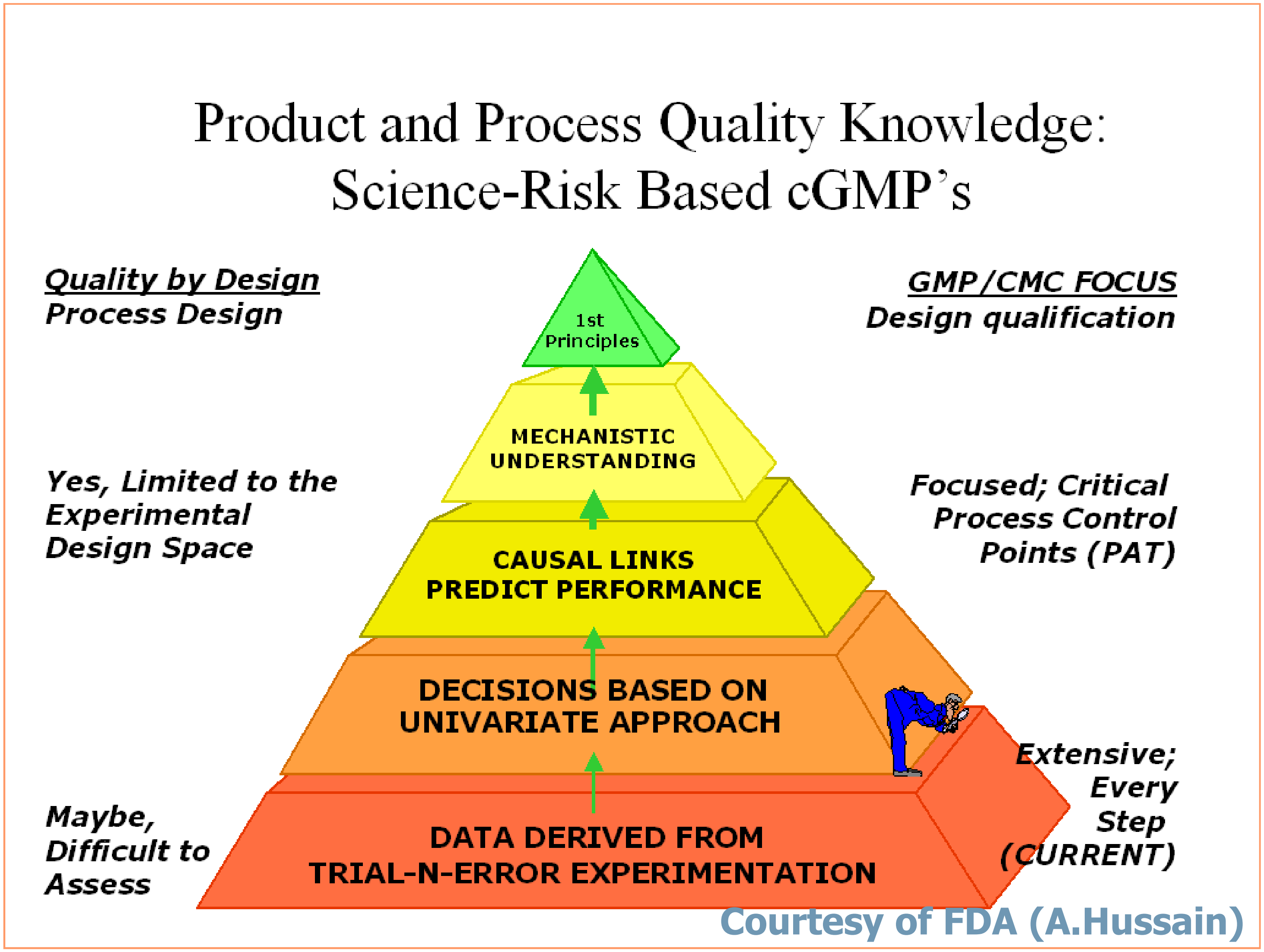


Courtesy of J.Werani (Pfizer)

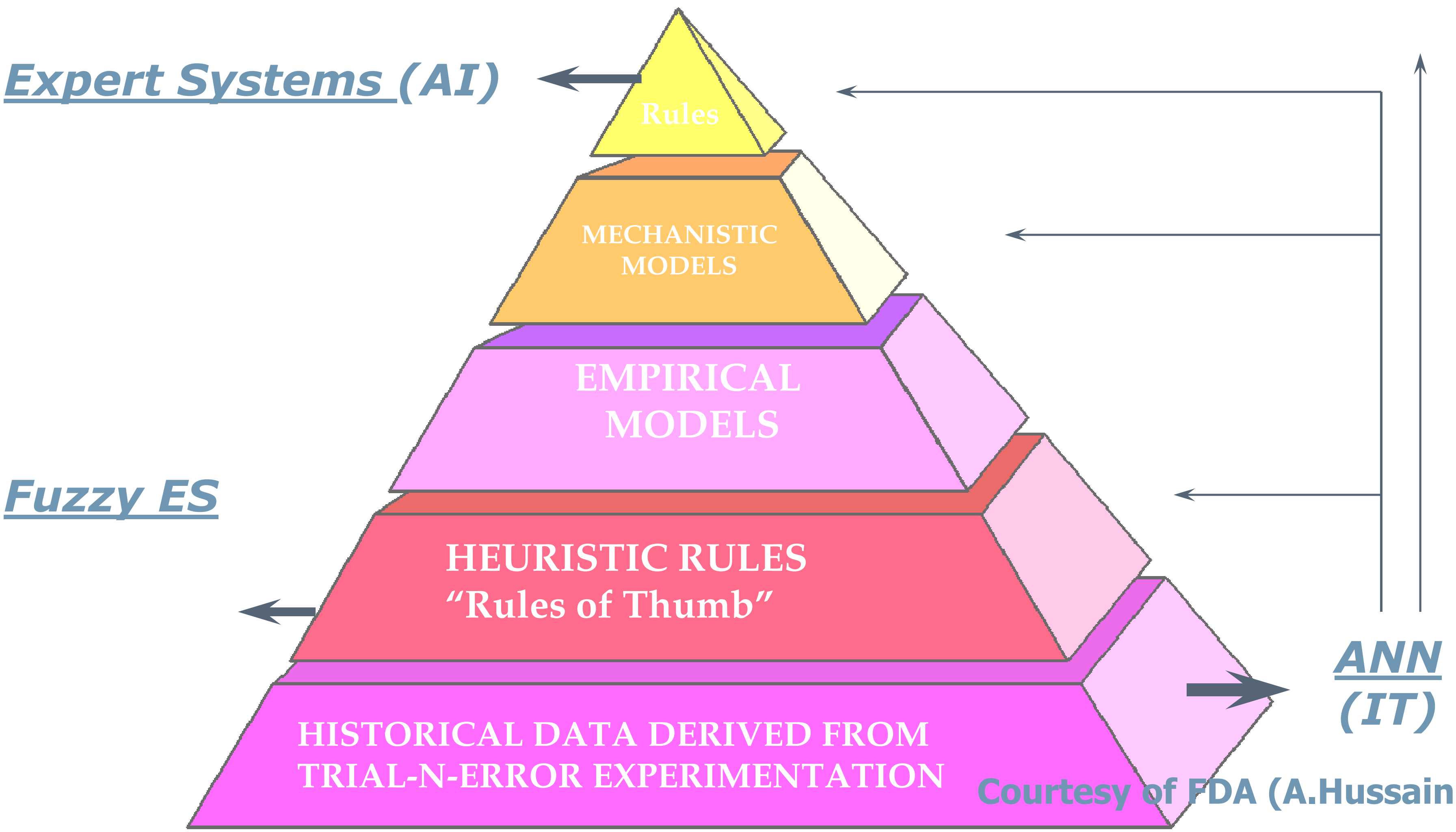
Rationale: design of quality + reduce human errors

- Need for robust formulation and process design
  - Formulation screening is costly and time consuming
  - Non-robust formulation will jeopardise full-scale production
- Need for mechanistic models and expert systems
- Need to reduce possibility of **human error**
  - Batch-wise production is an „agar plate“ for growth and flourish of manufacturing failures
  - Floor operators skill assessment and continuous education

Knowledge pyramid



Science based predictive models for a faster time to market: use of expert systems



Courtesy of FDA (A.Hussain)

Co-Development Toolbox

Co-Development

Research & Development

In silico Formulation design

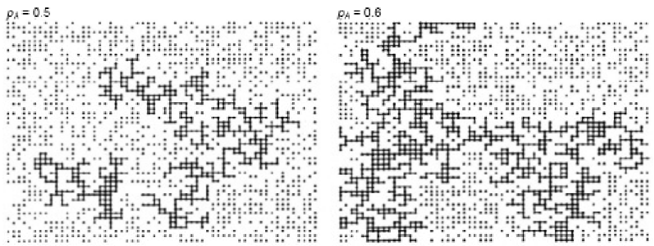
Virtual Training

Manufacturing & Quality Operations

Prediction of optimum amount of disintegrant by using expert system

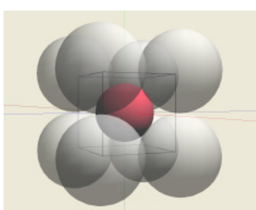
Prediction of the optimum amount of disintegrant to minimize the disintegration time (use of expert system CINCAP):

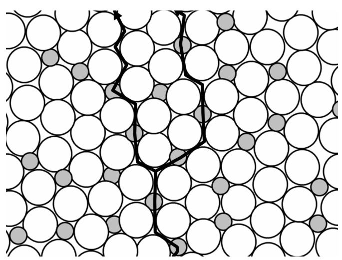
- based on percolation theory and cellular automata
- mathematical description based only on geometrical and physical considerations independent on chemical properties of compounds!



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

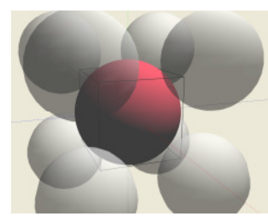
Case1: $r \leq \left(\sqrt{3}-1\right) \times R$

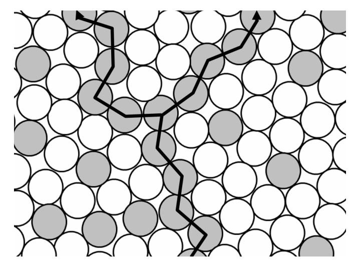




$$\chi_{dis} = \left(\frac{p_s^{rcp}}{1-\varepsilon} - \varepsilon\right) \times 100$$

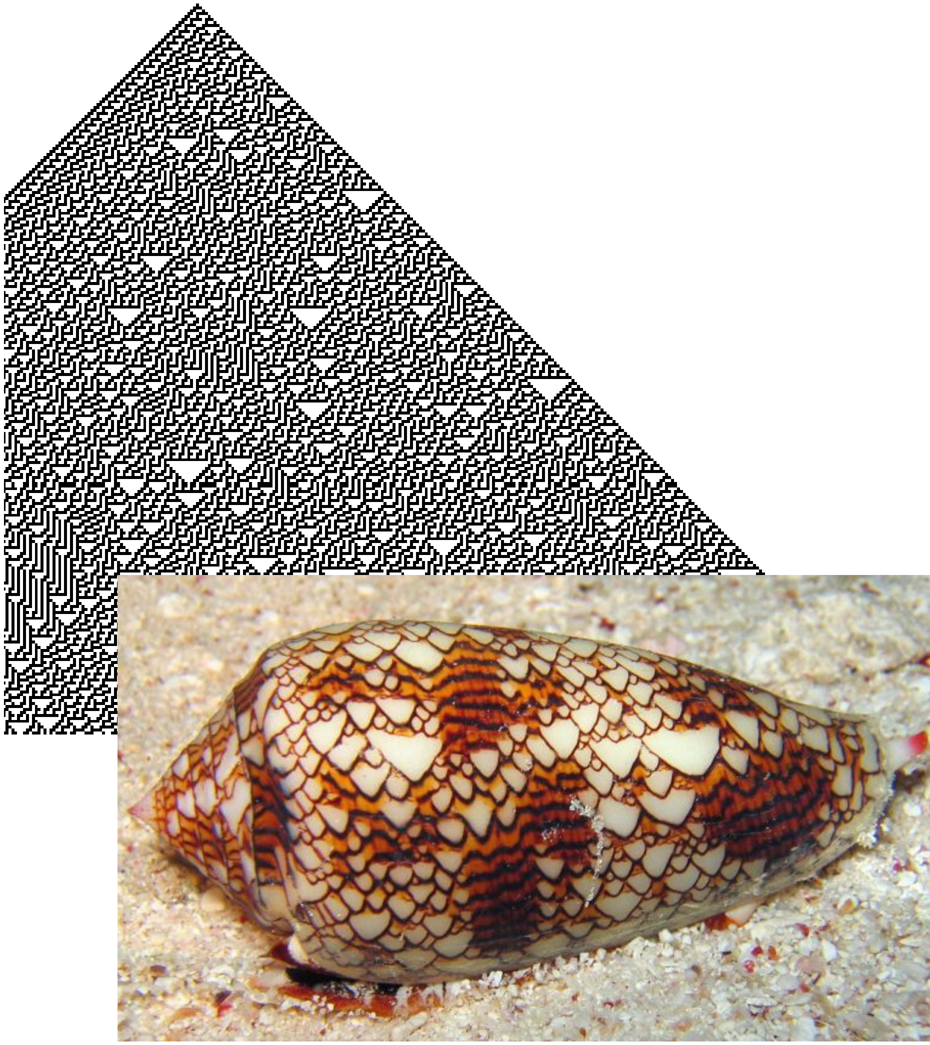
Case2: $r > \left(\sqrt{3}-1\right) \times R$



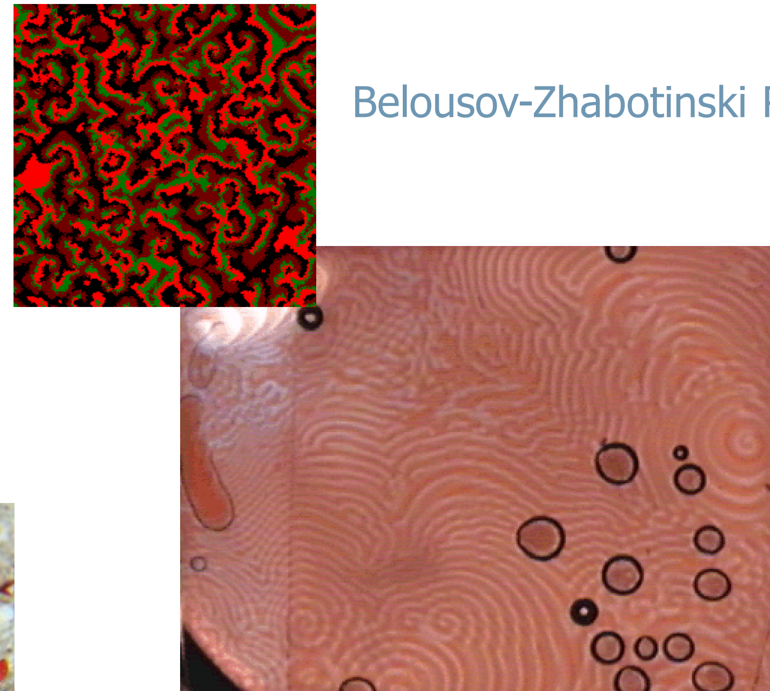


$$\chi_{dis} = \left(\frac{p_s^{rcp}}{1-\varepsilon}\right) \times 100$$

Cellular automata enable to model natural phenomena

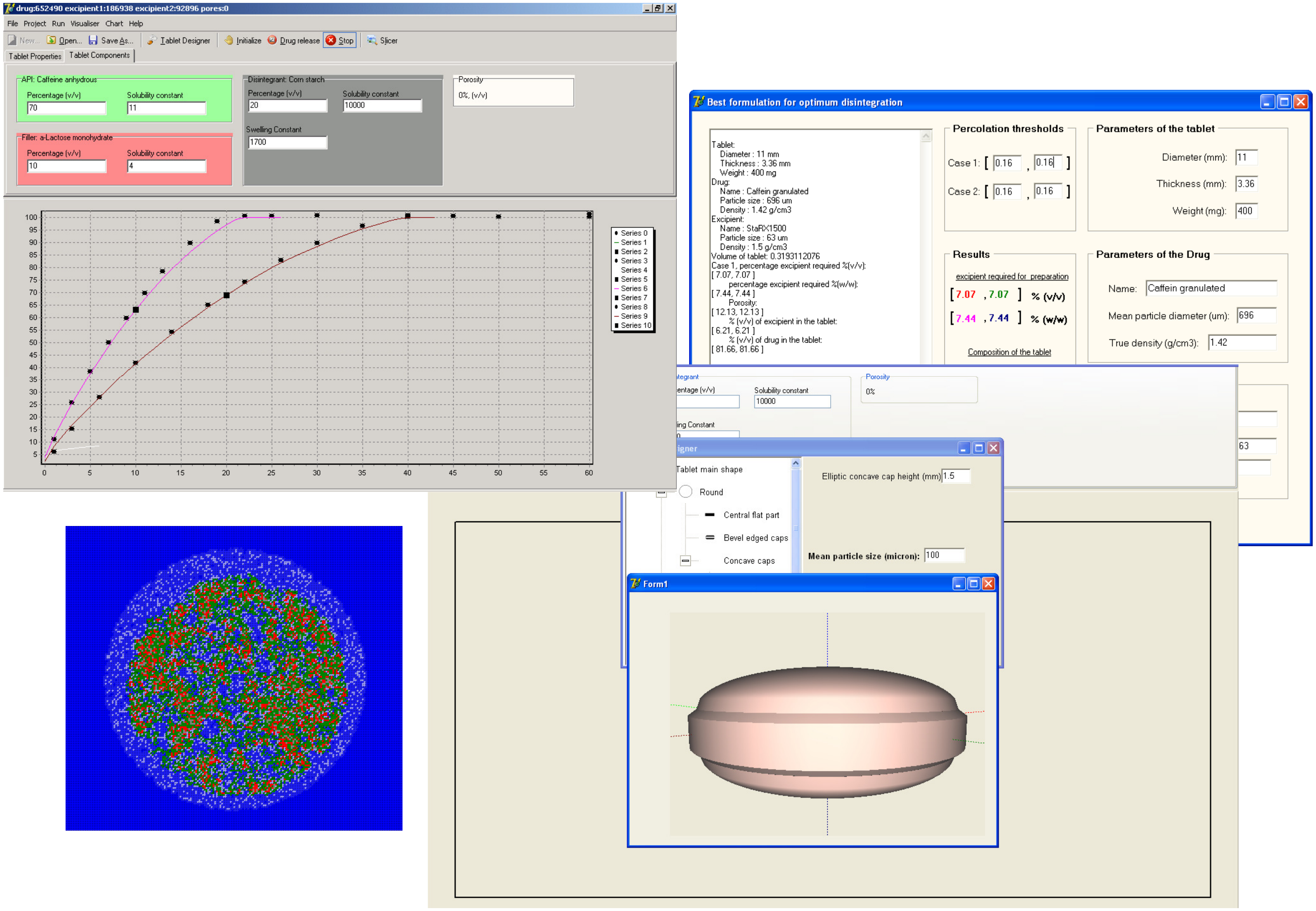


www.directopedia.org



Belousov-Zhabotinski Reaction

Formulation Design Studio: Expert System CINCAP



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

Case study: Look&Feel (example MiniGLATT)

Interactive controls

Video sensitive to control position

Auxiliary tools

REAL TIME!

Virtual Equipment Simulators (VES)

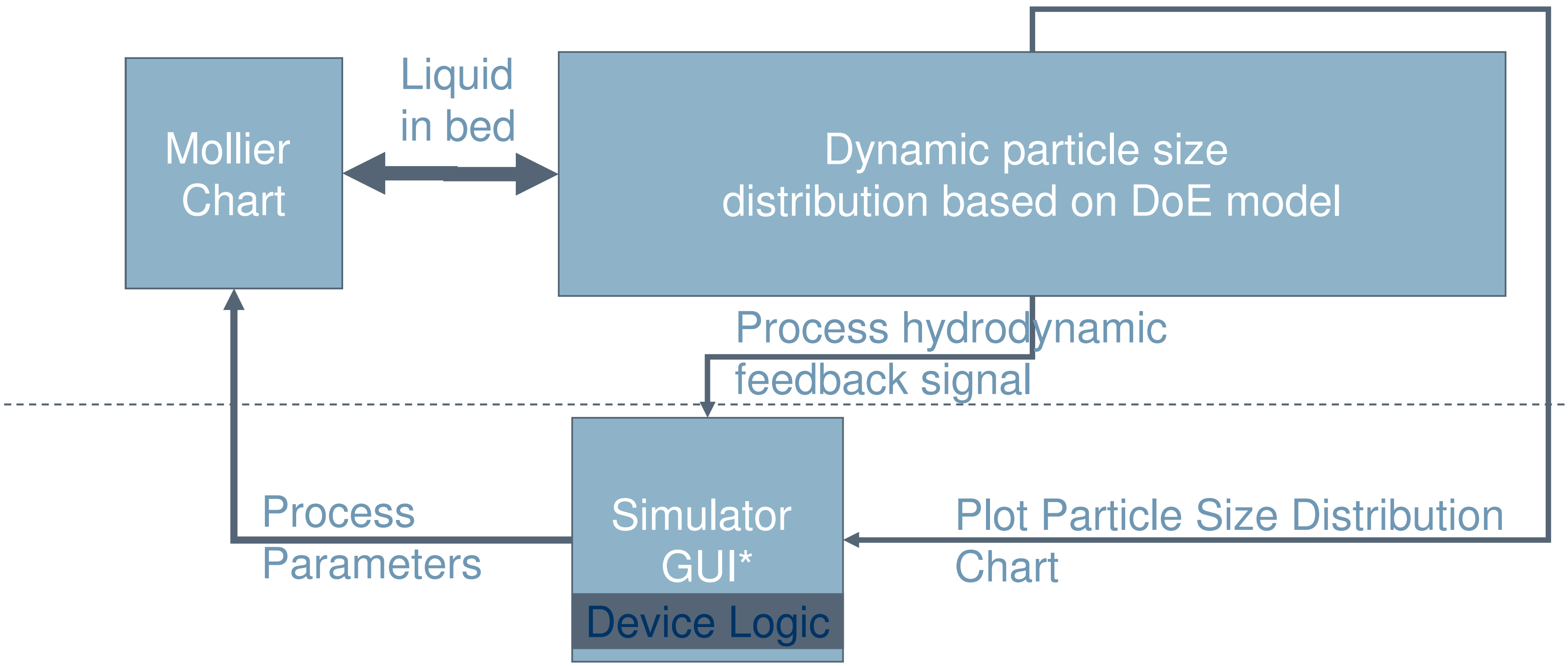
- VES is an ideal tool to get a better process understanding (Process Analytical Technology);
- VES is an ideal tool to explore the limits of the process without putting to danger operators and product;
- VES is an ideal tool for training especially to reduce human errors during real operation;

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.

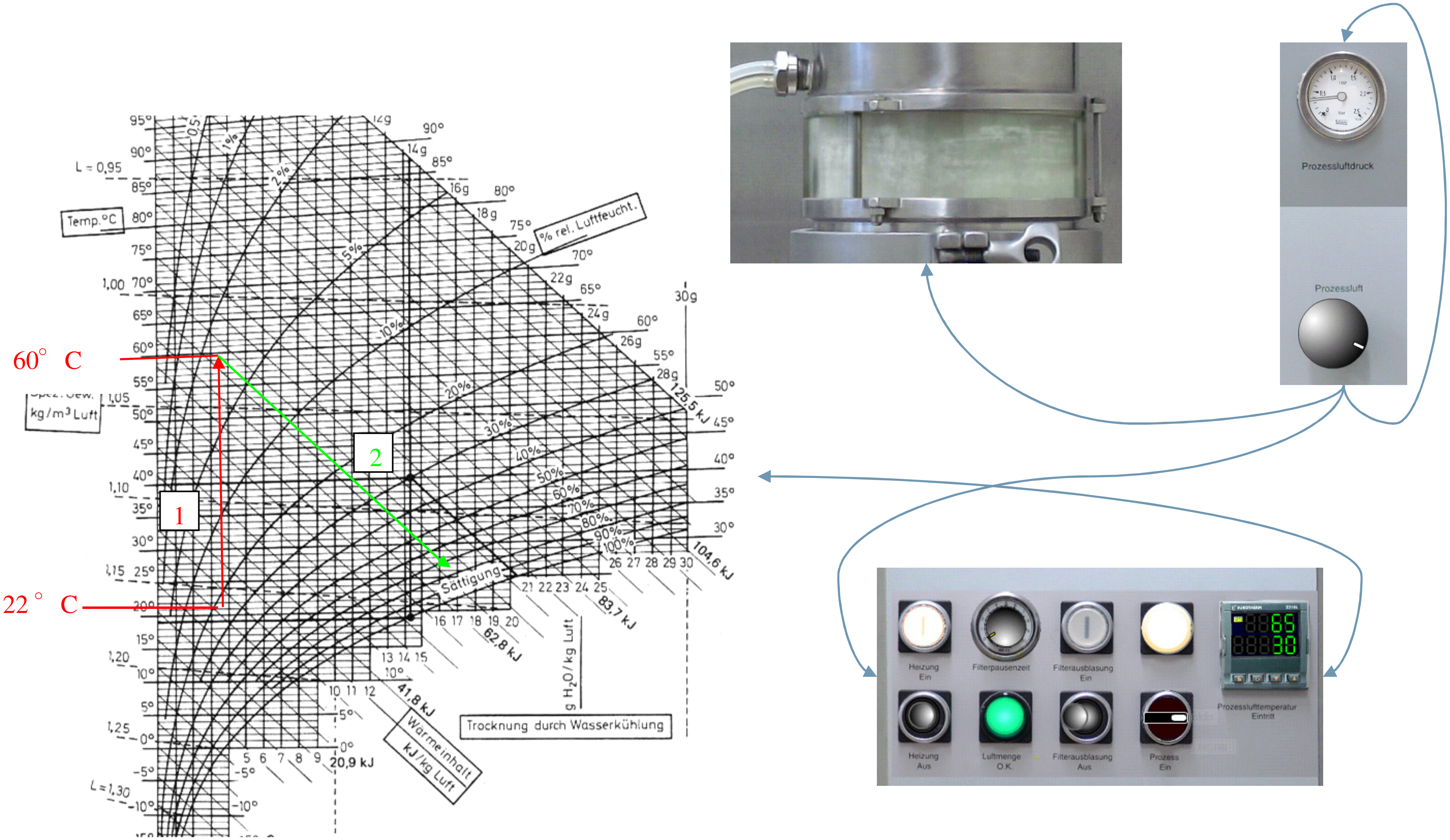
Science-based VES (e.g. fluid-bed granulator)

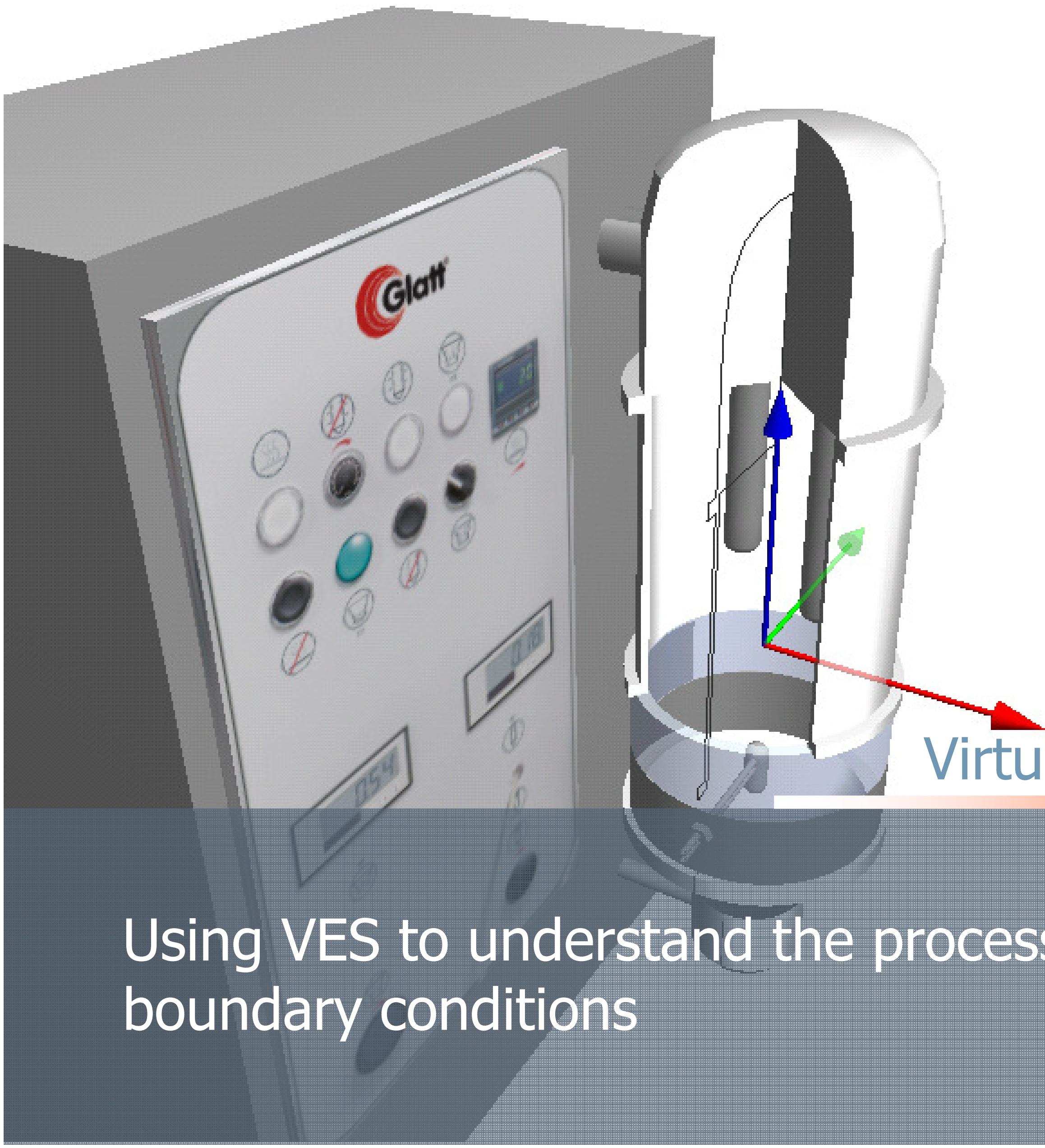
- Simple but effective



*GUI: Graphical User Interface

Mollier chart/ backbone of VES





Virtual Case-study: Granulation

Using VES to understand the process and its boundary conditions

Case Study: example task definition for a trainee

- Trainee must granulate starting powder mix (140 um.) to obtain mean granule size of ca. 300µm. This mean granule size distribution is achieved if binder concentration (PVP) has reached ca. 4% (w/w) in the formulation. Binder solution concentration: 5% (w/w)
- Task for the trainee: pump calibration; estimation of residence time; calculating amount of binder required; study the fluidization regimes; calculate required drying time; proper response to a given critical situation (e.g. air conditioning failure)
- Given process constants etc:
  - Air source: 20%RH, 25°C
  - Assumed exhaust air saturation is constant: 85% (can be changed)
  - Establish pressure (bar) to air throughput (m^3/h) calibration curve

Task: pump calibration

Tasks contd.

- Process parameters calculation
  - Mollier chart → water removal capacity of process air, product temperature
  - heat and mass balance → pumping rate, residence time, drying time
  - Select spray pressure from support resources
- Start experiment
  - Be aware to set 0.5bar spray pressure prior to start fluidization (prevents clogging of a nozzle)
  - Check the dynamics of particles growth

Task: critical situation

- It is possible to switch on the in-built generator of a critical situation
- Typical critical situations:
  - Air conditioning failure
  - Pump failure
  - Sudden clogging of filters
  - Temperature sensor failure
- Trainee must properly react to a failure and try to continue operation if possible.

Task: Drying and Reporting

- When product has reached required particle size distribution → switch to drying (stop pumping)
- Continue drying until required product residual moisture content.
- Stop the process by turning the process knob to "off" position.
- Report will be printed
  - Report includes a complete record of all events and user interactions during process
  - There is a possibility to "play back" the recorded process

Task: use VES to optimize process

- Using acquired knowledge trainee can repeat experiment with optimized conditions
  - Shorter residence time
  - Lowering energy consumption
  - Optimized conditions for thermo-labile products

"Simulation is a learning experience in which a learner performs a meaningful task in a specific context, receives consequential feedback, and has access to support resources"

Daniel Bielenberg (Accenture),
TechLearn, 2001

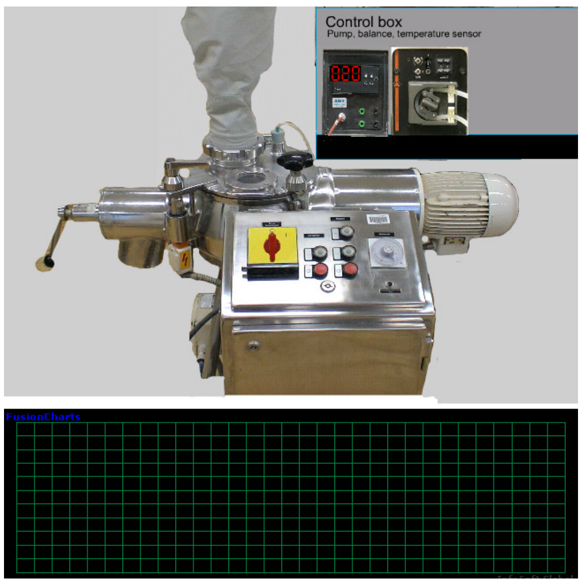
Building simulations without careful consideration of the learning experience is folly.

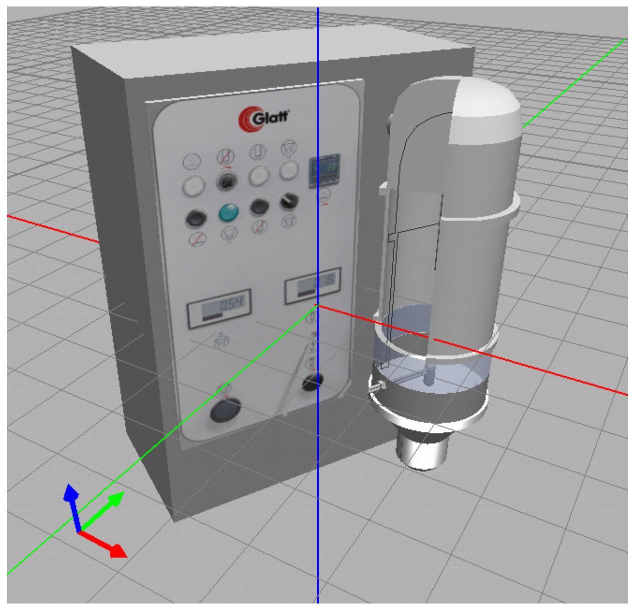
VES advantages

- Personnel training
  - Possibility of real personalized individual training
  - Identifying weaknesses and improving operator's skills
  - Testing existing SOPs and developing new SOPs
  - Testing formulation robustness **on large equipment!**
- Business perspective
  - Reducing human errors
  - Better process understanding leading to a higher quality
  - Facilitated troubleshooting with equipment vendor
- Business perspective (equipment manufacturers)
  - Try it virtually but buy it in a reality (formulation suitability check)
  - Reduce travel and logistical expenses
  - Improved customer satisfaction and better overall experience with the device

Under construction

- Virtual reality
  - Clean rooms
  - 3D versions of machinery (tablet presses, etc.)





Audience Q&A

Thank you for your attention!