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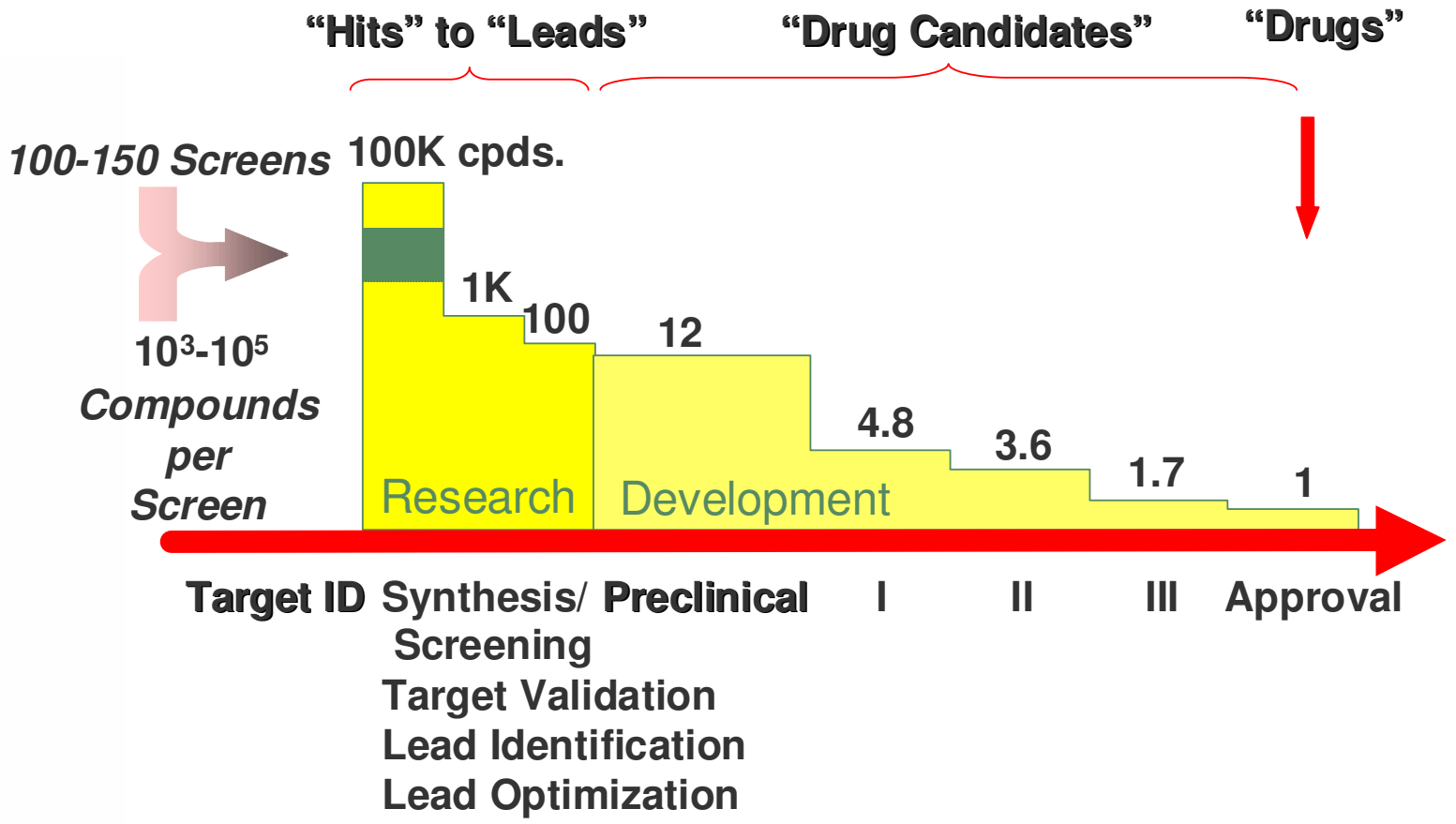
SWEDISH ACADEMY OF PHARMACEUTICAL SCIENCES

Continuous processes in manufacturing of solid oral dosage forms.

Hans Leuenberger
Maxim Puchkov
CINCAP LLC c/o Ifiip

Institute of Pharmaceutical Technology
Pharmacenter of the University
Klingelbergstrasse 50
CH-4056 Basel, Switzerland

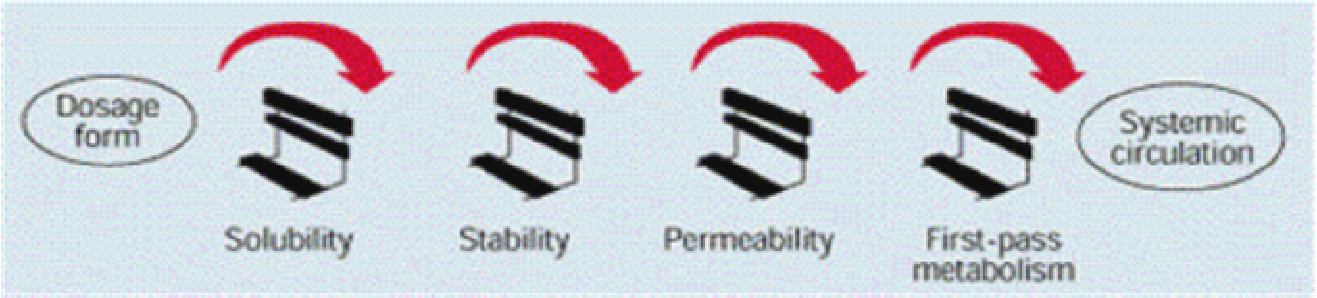
Traditional Pharmaceutical R&D Suffers High Attrition*

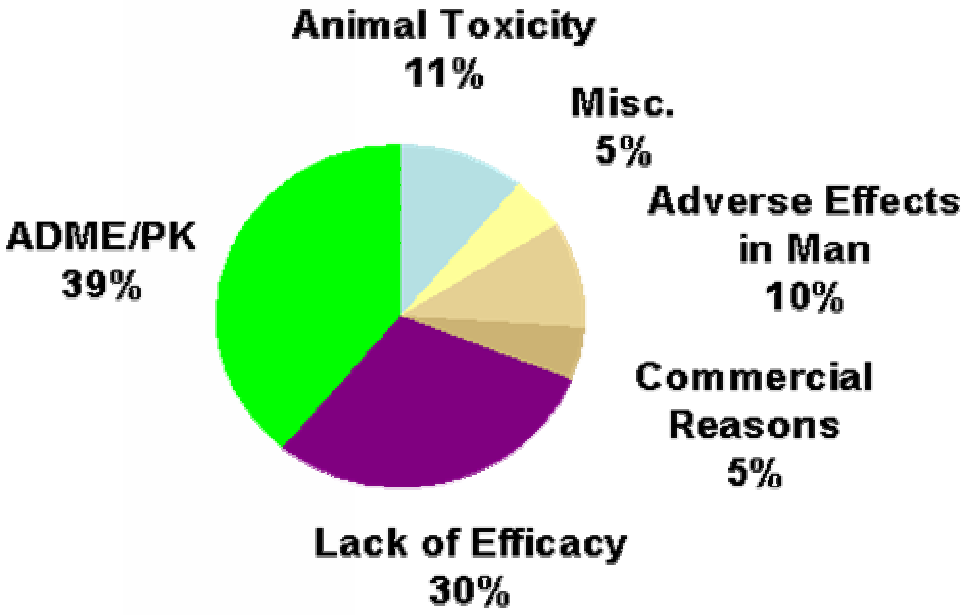


*Tufts CSDD, H&Q 1998, after Camitro

Slide: Courtesy Dr. A. Hussain, FDA

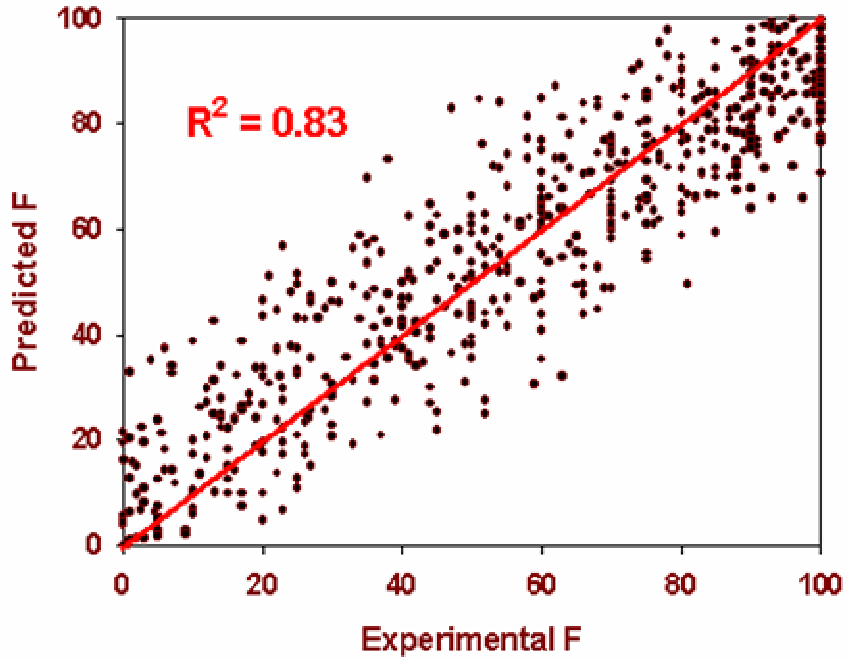
High Attrition due to? [1]





NMEs (n=198)

Kennedy, T. (1997) Drug Discovery Today, 2, 436-444.



Yu, et al. Quantitative Structure Bioavailability Relationship (QSBR): Pharm Res. 17:639-644 (2000)

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.

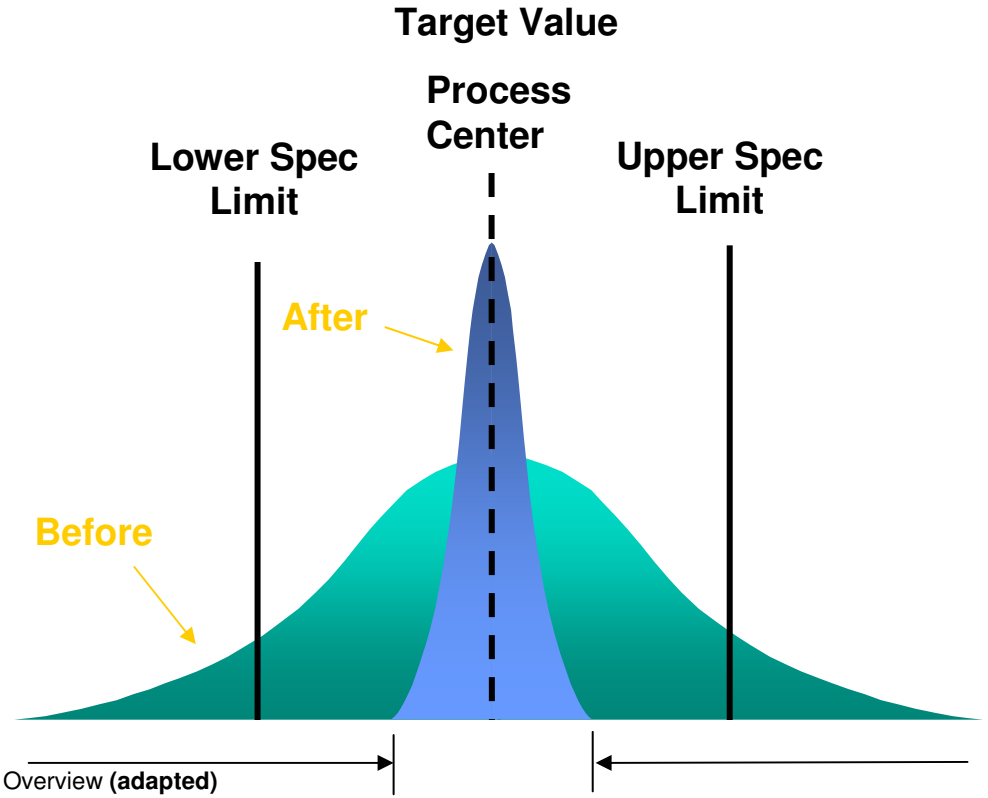
The SIGMA Concept II

- 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).

6 Sigma dynamic value in time !

- A customer-focused, data driven approach to understanding process variation (stability) and defect reduction (capability).
- A performance target of 3.4 defects per million opportunities.

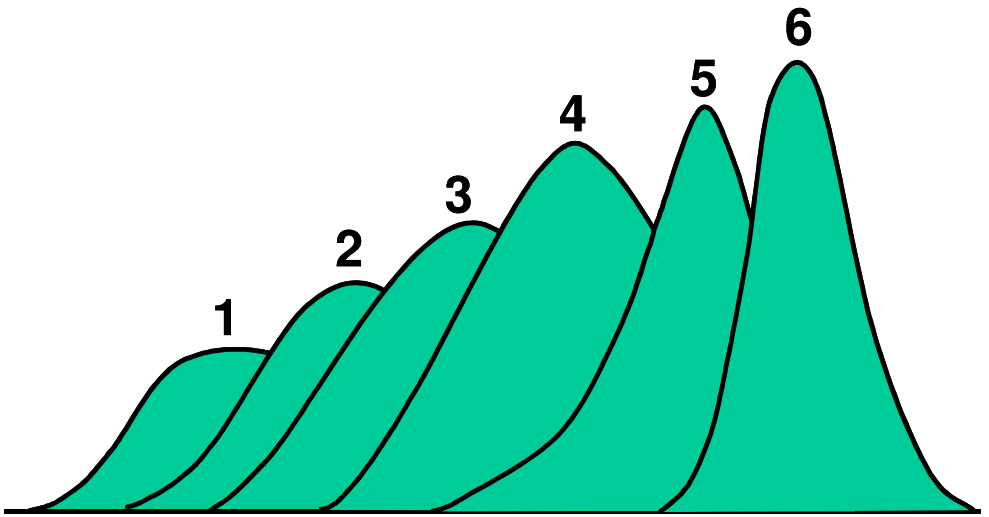


Source: Rath & Strong, Lean Sigma Overview **(adapted)**

Sigma: A Measure of Process Capability

- Sigma is a measure that focuses on the variation of the process output.

SIGMA	DPMO	YIELD
0.0	1,000,000	0.0000%
1.0	691,462	30.8538%
2.0	308,538	69.1462%
3.0	66,807	93.3193%
4.0	6,210	99.3790%
5.0	233	99.9767%
6.0	3.4	99.9997%

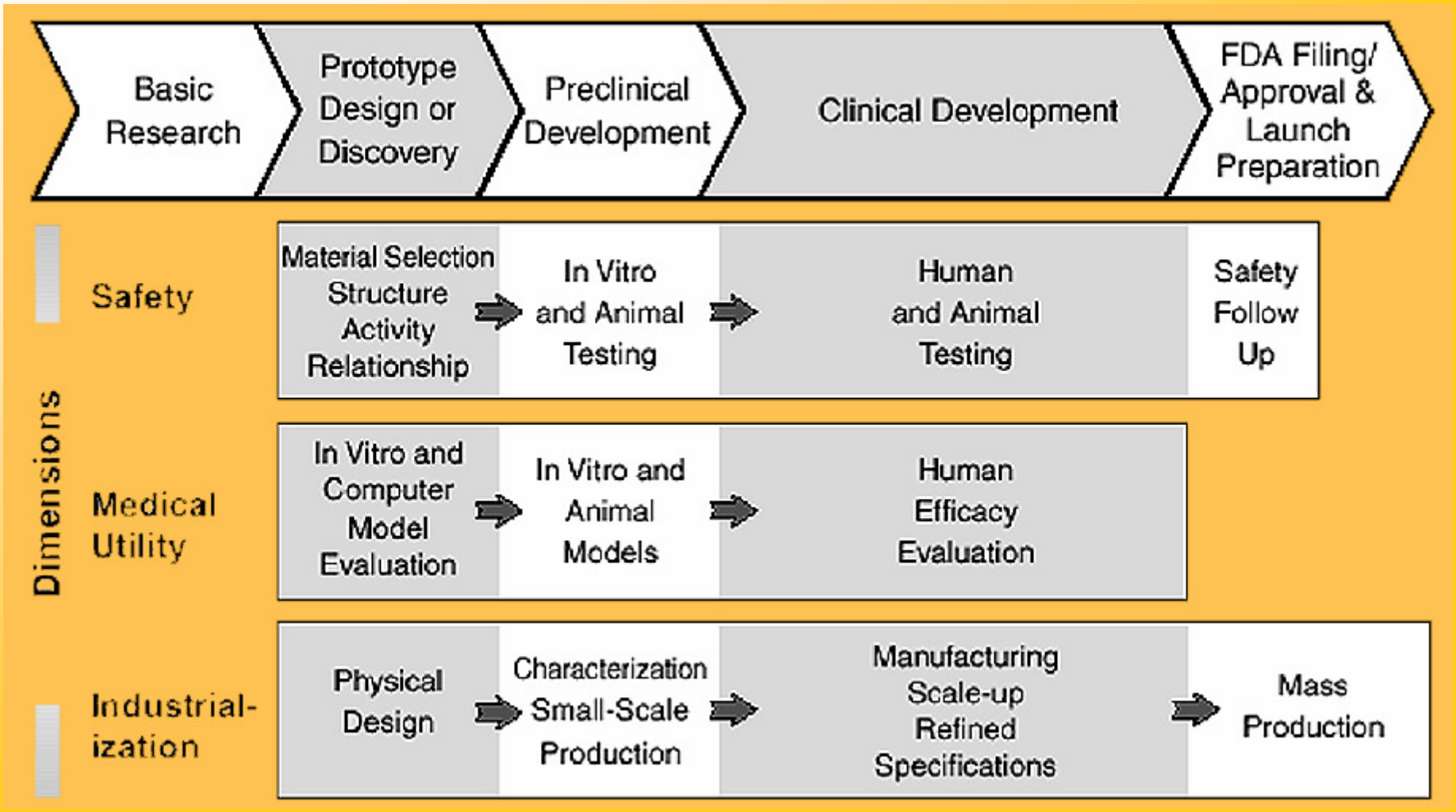


Source: Rath & Strong, Lean Sigma Overview

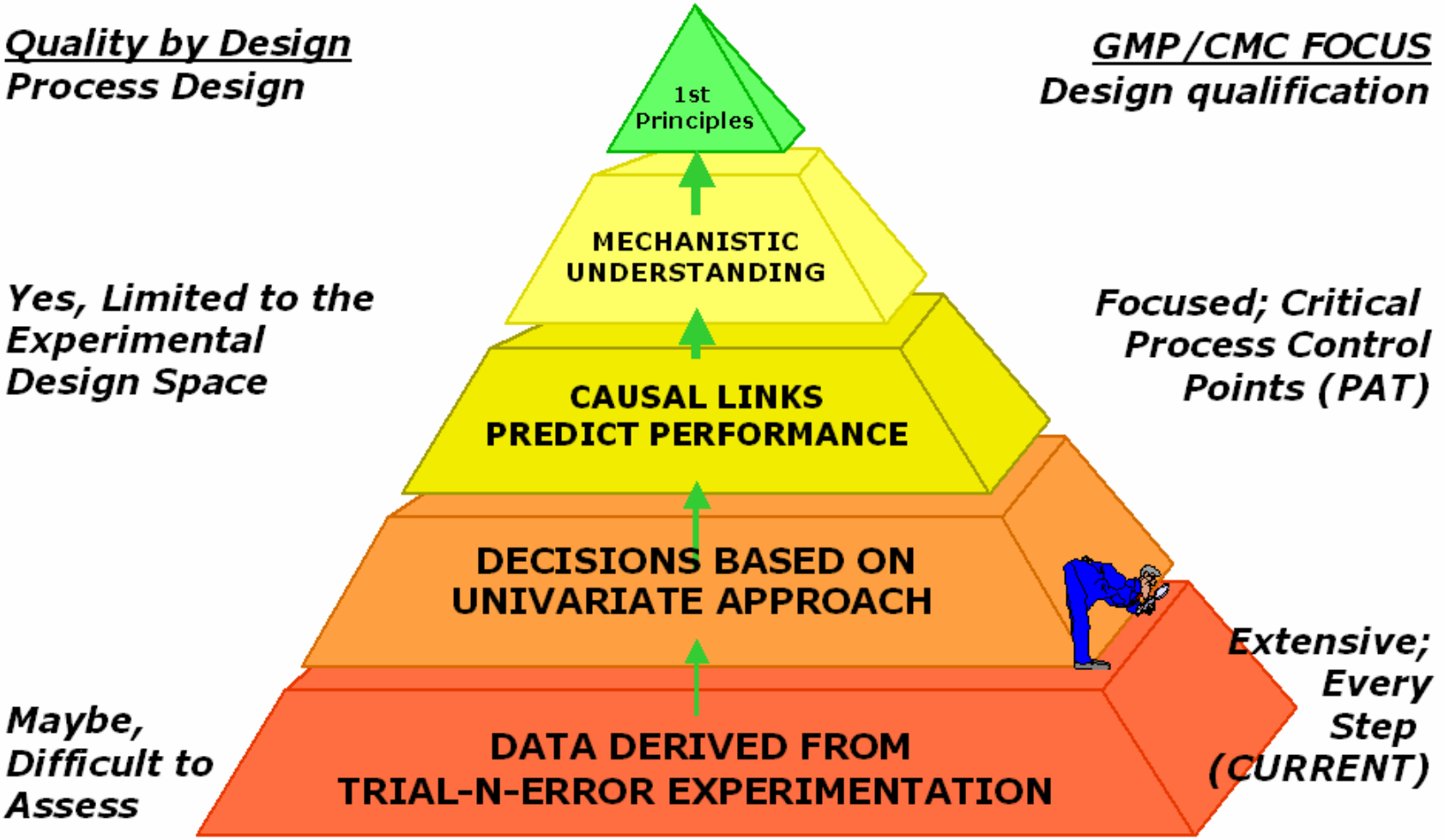
FDA Whitepaper March 2004
Three Dimensions of the Critical Path

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**
Demon-strating 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**
Industria-lization	**Go from lab concept or prototype to manufactura ble product**	• **Design a high-quality product** - Physical design/Characterization/Specifications • **Develop mass production capacity** - Manufacturing scale-up/Quality control

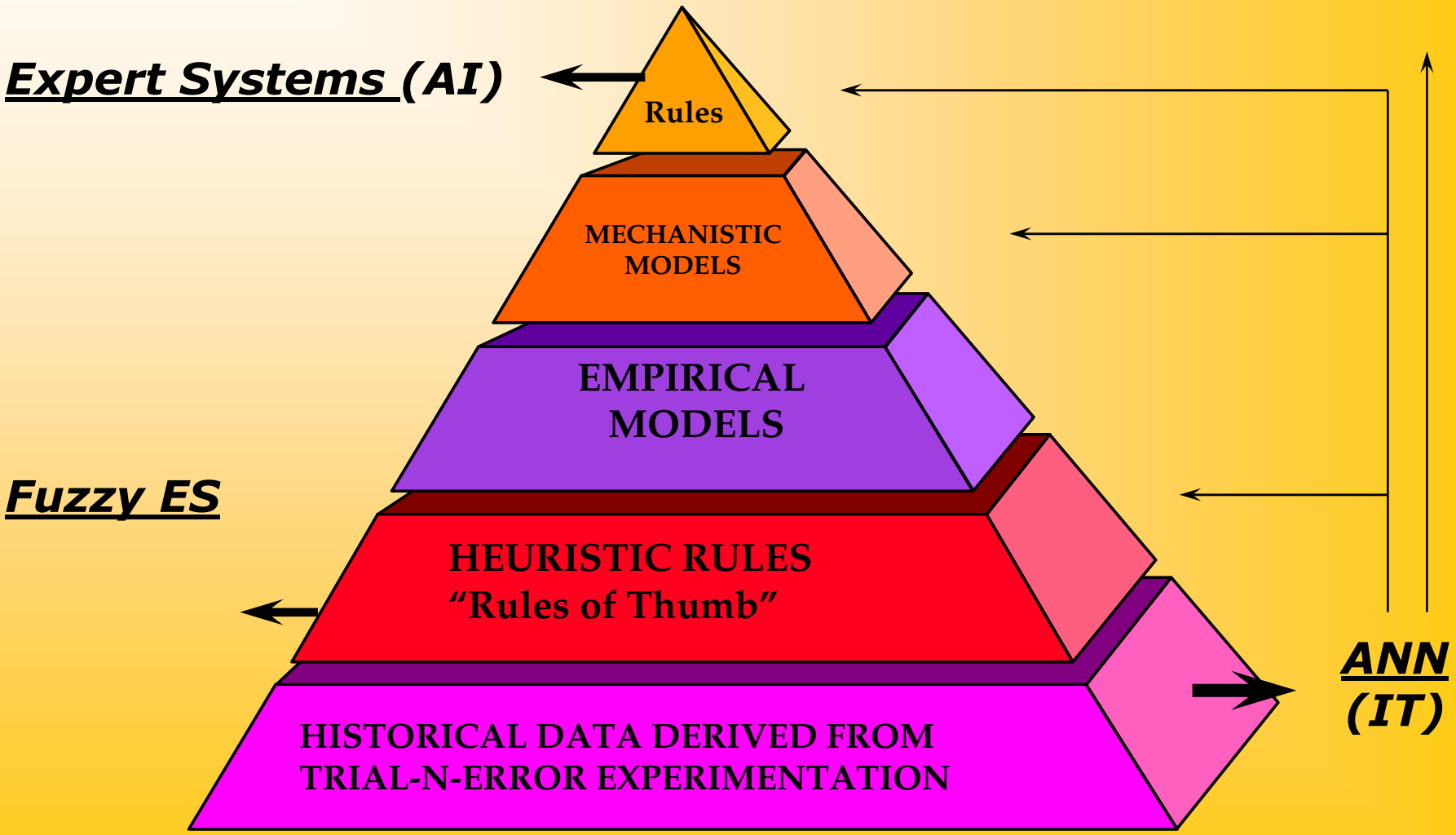
FDA Whitepaper March 2004
Three Dimensions of the Critical Path



Product and Process Quality Knowledge: Science-Risk Based cGMP's



Artificial Intelligence AI & Information Technology IT can Improve the Utility of Historical Data



Prediction of optimum amount of disintegrant . . .

. . . to minimize the disintegration time (use of expert system CINCAP):

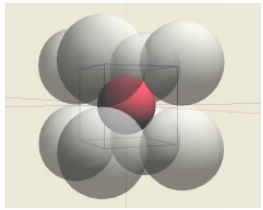
- based on percolation theory and cellular automata

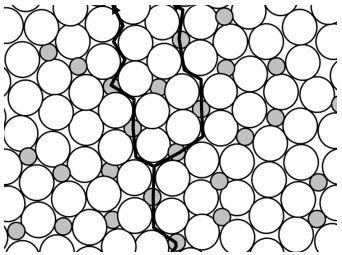
- mathematical description based only on geometrical and physical

dependent on chemical properties of compounds!

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

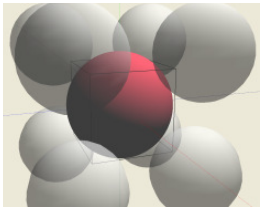
Case1: $r \le \left(\sqrt{3}-1\right)\times R$

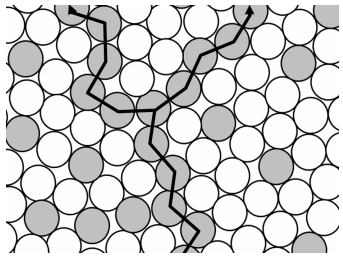




$$\chi_{dis} = \left(\frac{p_s^{rcp}}{1-\varepsilon} - \varepsilon \right) \times 100$$

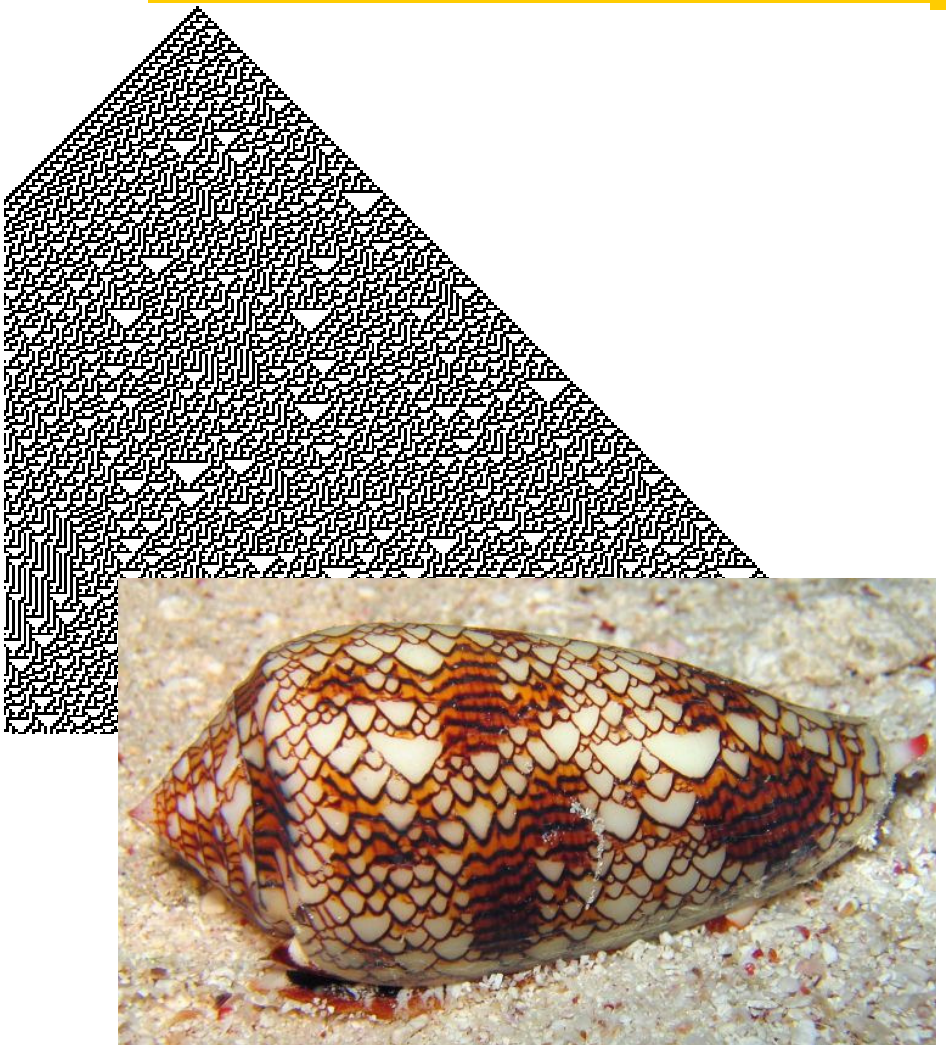
Case2: $r > \left(\sqrt{3}-1\right)\times R$

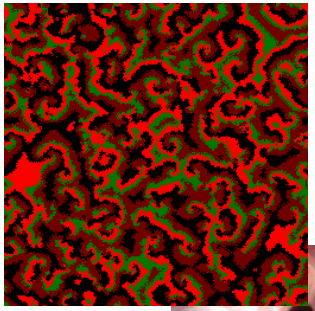




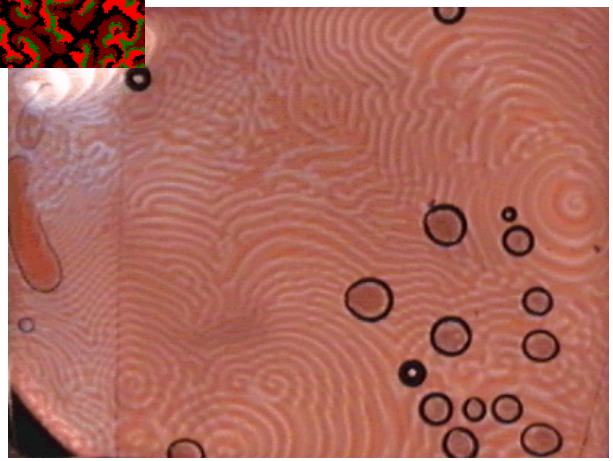
$$\chi_{dis} = \left(\frac{p_s^{rcp}}{1-\varepsilon} \right) \times 100$$

Cellular automata enable to model natural phenomena



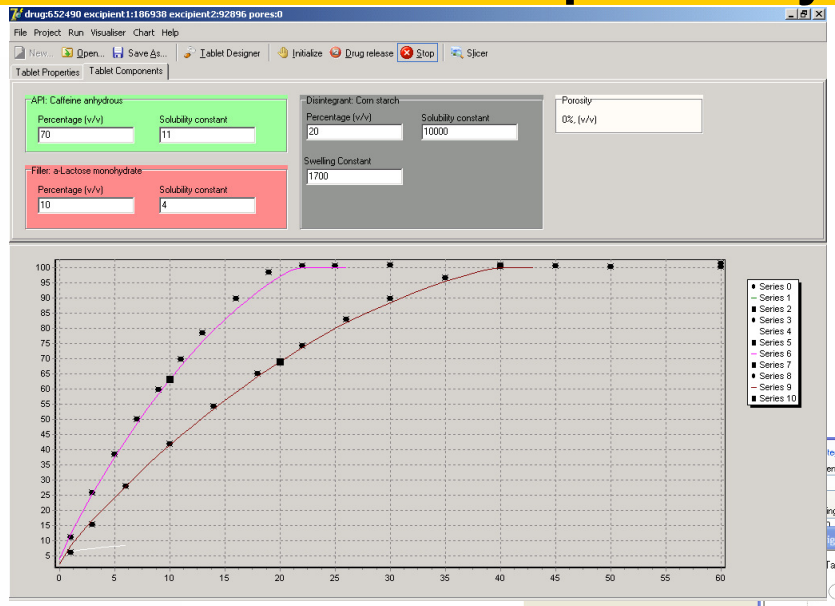


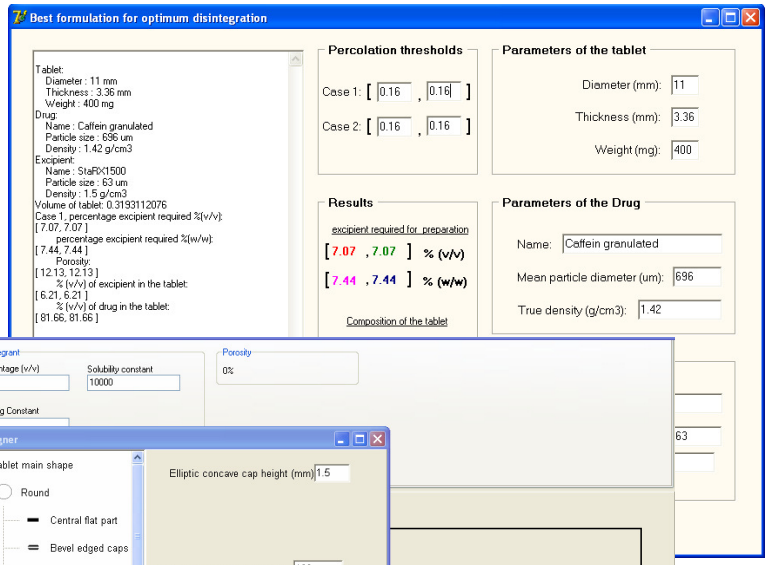
Belousov-Zhabotinski Reaction

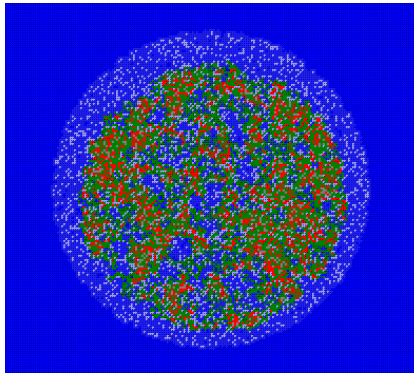


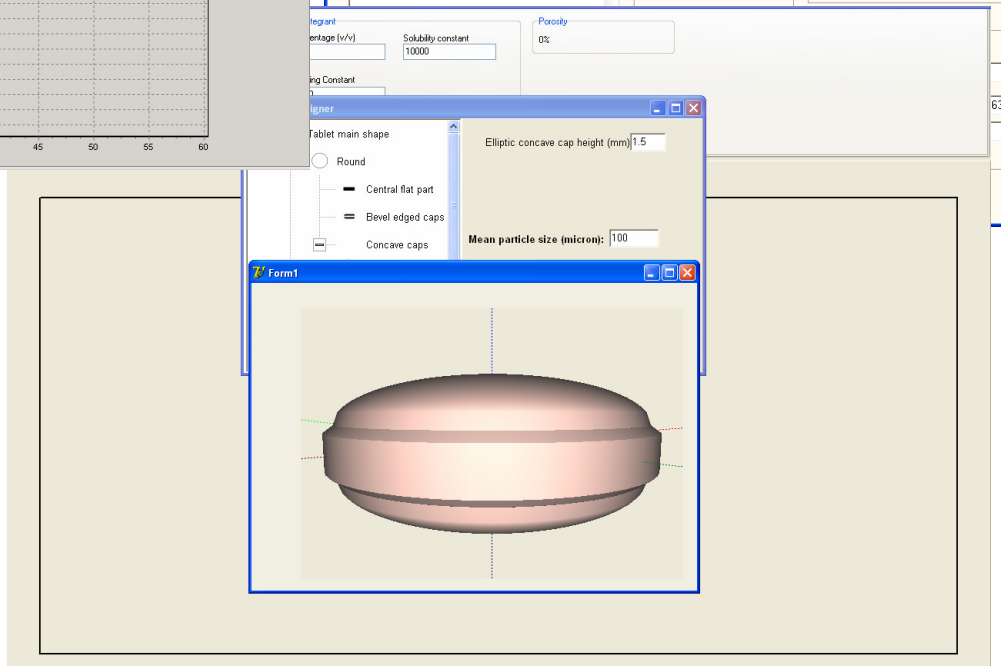
www.directopedia.org

Formulation Design Studio: Expert System CINCAP









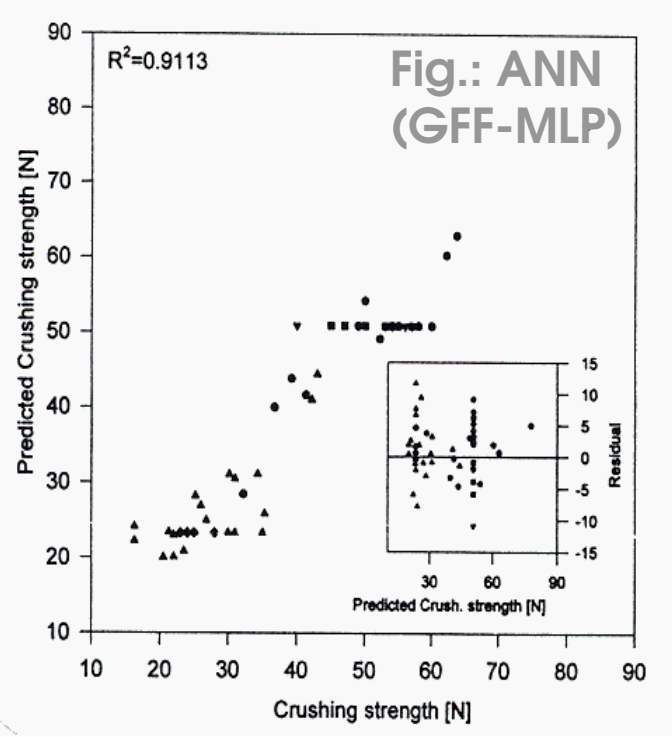
Identification of critical processes

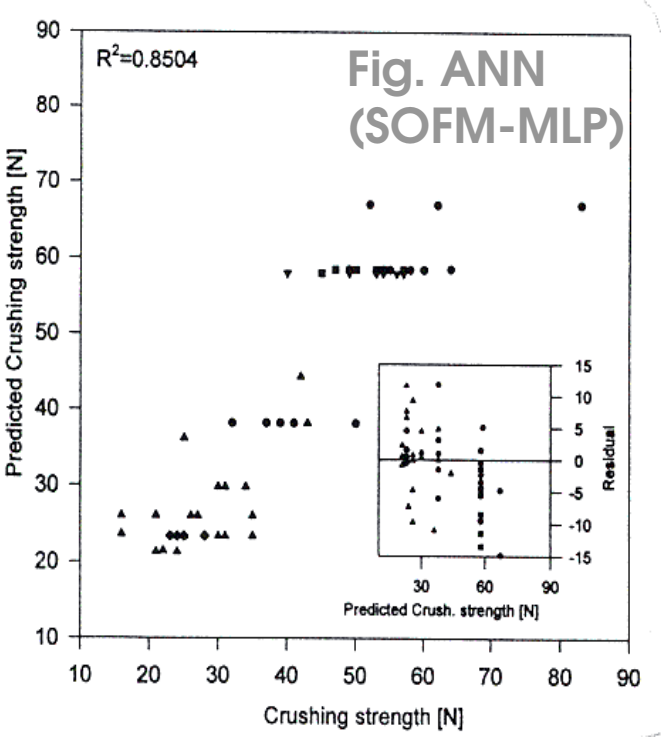
The wet agglomoration process

- Critical parameters
  - The amount of granulationg liqid
  - The massing time
  - The drying process
- Next slide: results of a experiments analysed with two ANN (Artifical neural networks)

Results$_1$ of the 2 networks

and of the RSM – technique





Hardness (Crushing strength) values and dissolution rate data

Results$_2$ of the 2 networks

and of the RSM - technique

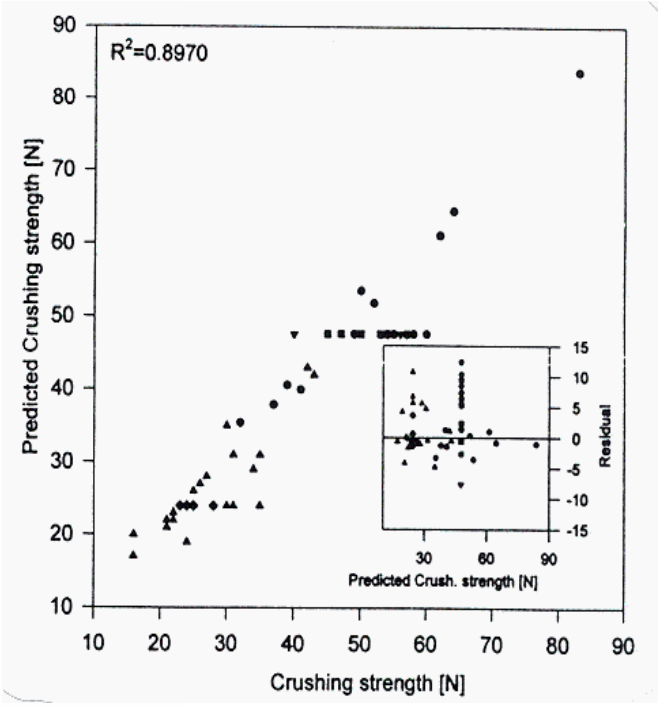


Fig.: RSM - technique

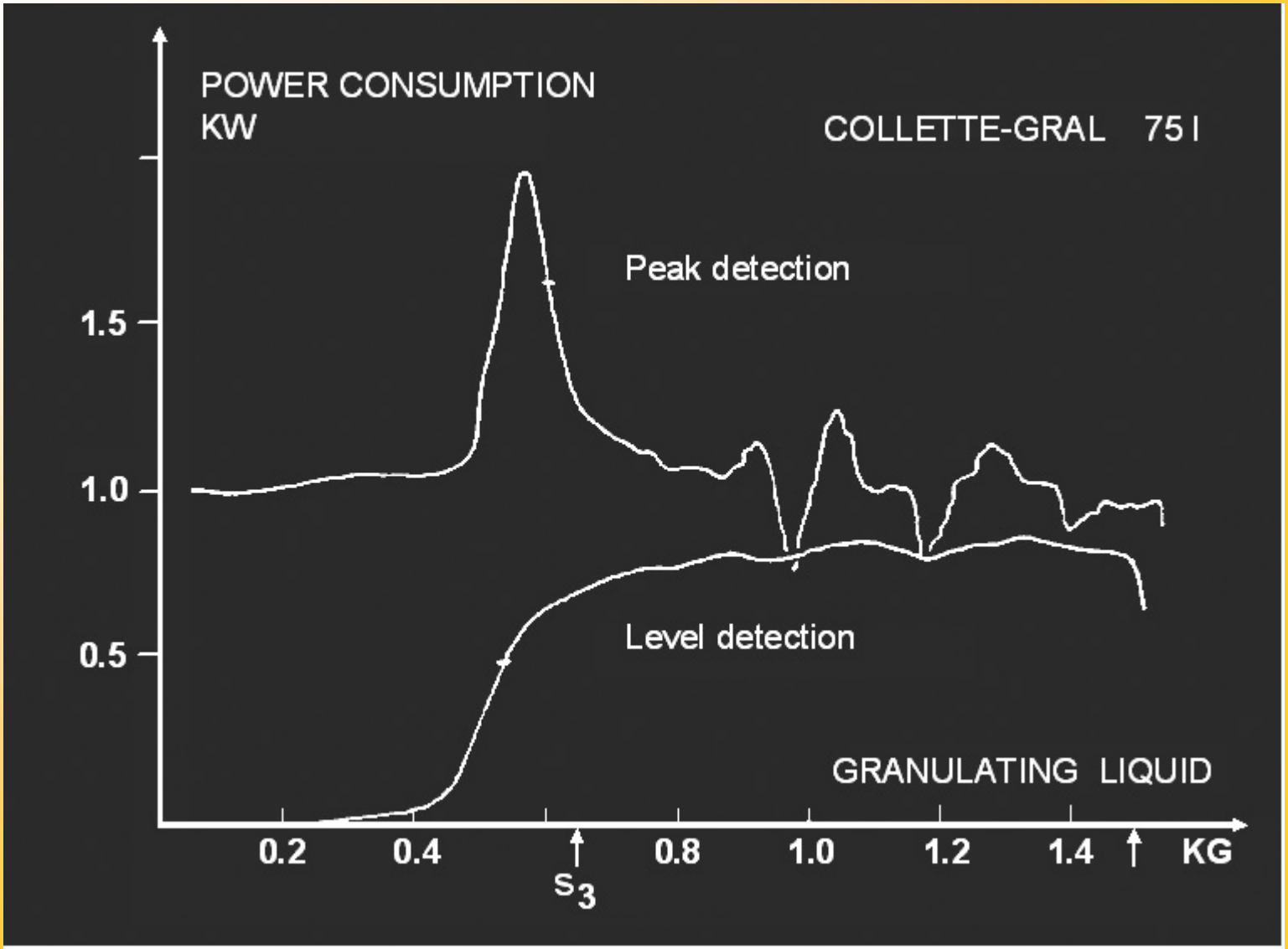
Percentage of Drug Dissolved After 15 min (%)
R-Square Results for the Tablet Compression Study

	GFF-MLP	SOFM-MLP	RSM
R^2 without factor "Batch"	0.2589	0.1040	0.1366
R^2 with factor "Batch"	0.8809	0.8775	0.8679

Time to 50% Drug Dissolution (min)
R-Square Results for the Tablet Compression Study

	GFF-MLP	SOFM-MLP	RSM
R^2 without factor "Batch"	0.3411	0.2942	0.2739
R^2 with factor "Batch"	0.8709	0.8536	0.8449

Fig. R_2 - Results „Dissolution Rate“


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

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

Identification of critical processes

2. Scale-up exercise

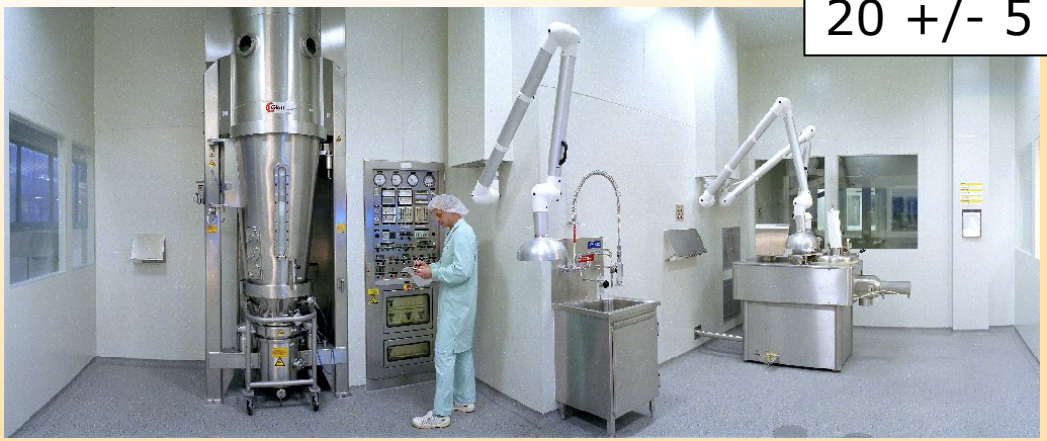
- the major problem consists in the fact, that the formulation is optimised on a small scale equipment, but is no longer optimal on a large scale equipment.

  →Leuenberger H., New Trends in the Production of Pharm. Granules: The classical batch concept and the problem of scale-up / Batch versus continuous processing.

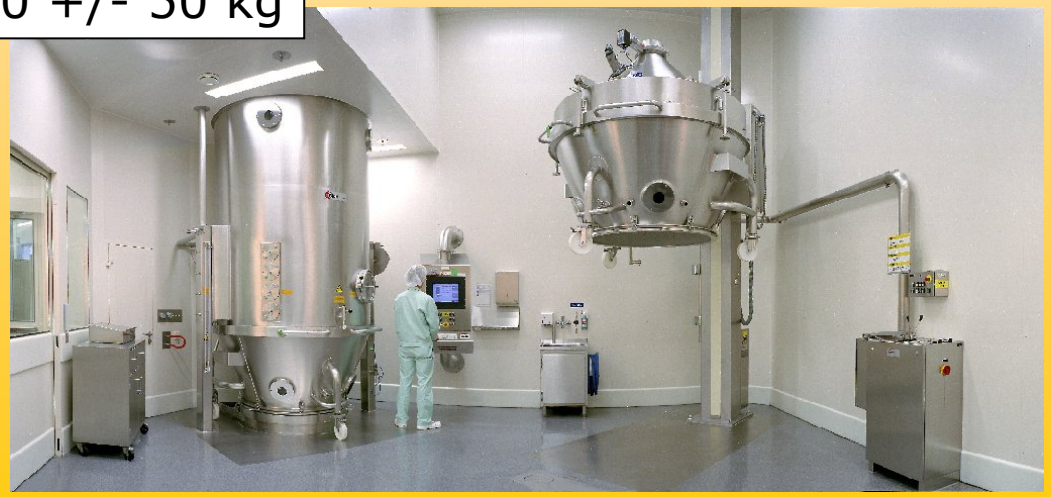
  Eur. J. Pharm. Biopharm. 52(3), 2001, 279-296.

Classical scale-up:
Pfizer Technology Service Center Freiburg

20 +/- 5 kg



250 +/- 50 kg



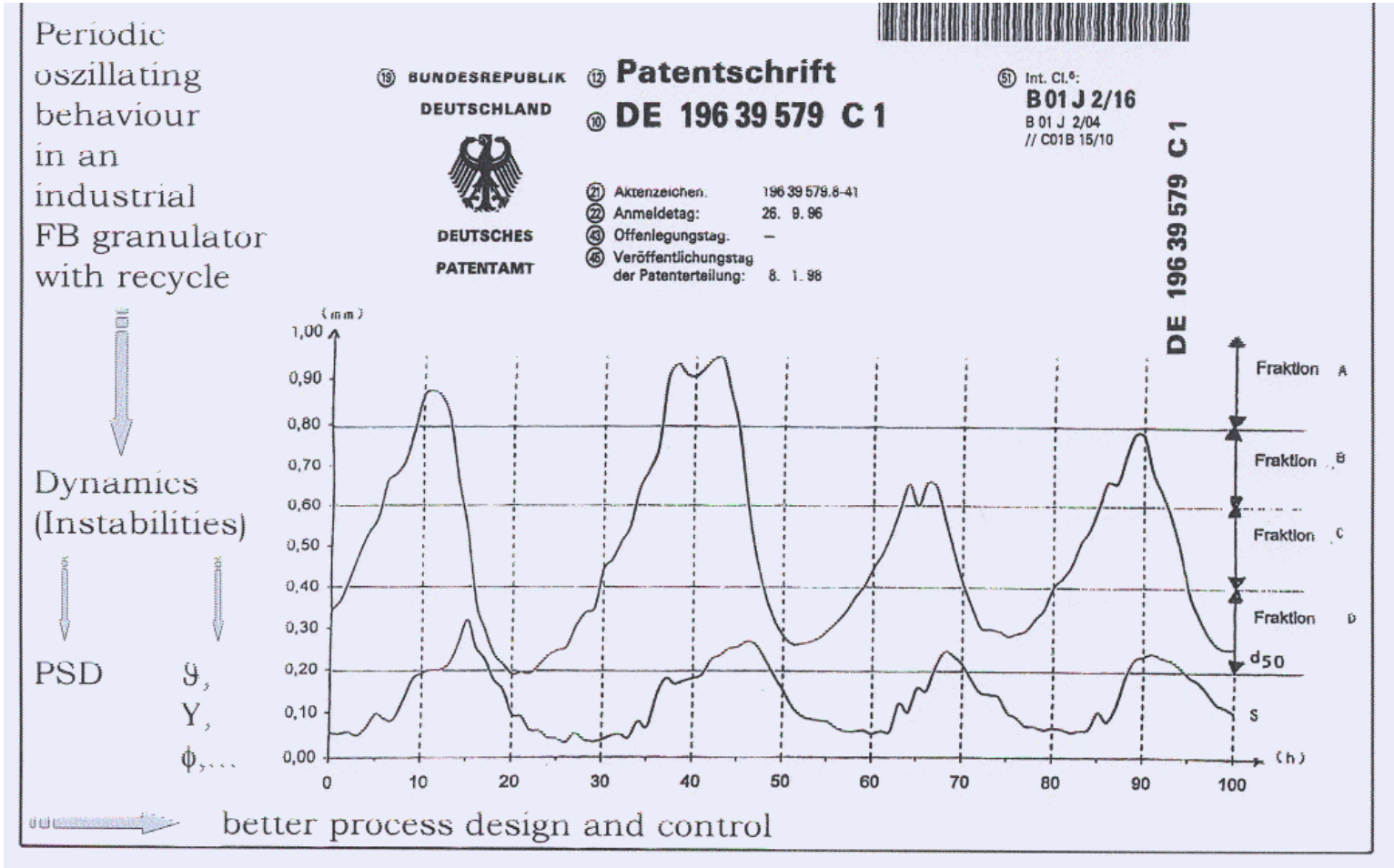
80 +/- 20 kg

Total area:
4,240 m²
2,450 m² GMP related
1,790 m² Tech. Infrastructure

Capacity:
250 Mio. - 1,500 Mio.
SKUs/Year

Real continuous or preferably a quasi-continuous process?

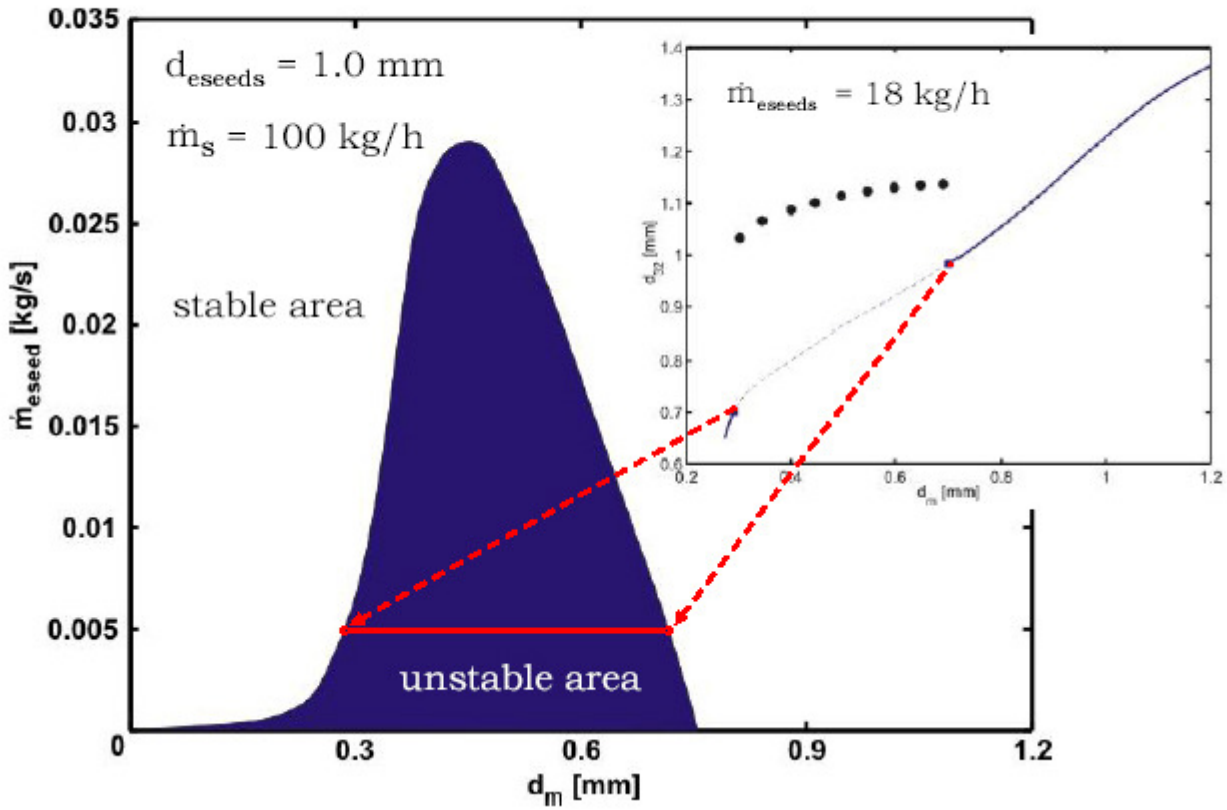
Problem of a dynamic instability in the real continuous granulation process



Real continuous: instability (Numerical Bifurcation Analysis)

2 Parameter Continuation

Influence of milling and external seeds



Literature

Heinrich, S., Peglow, M., Mörl, L.:
Unsteady and steady state particle size distributions in batch and continuous fluidized bed granulation systems,
Chemical Engineering Journal, 6 (2002) 1-2, 223-231.

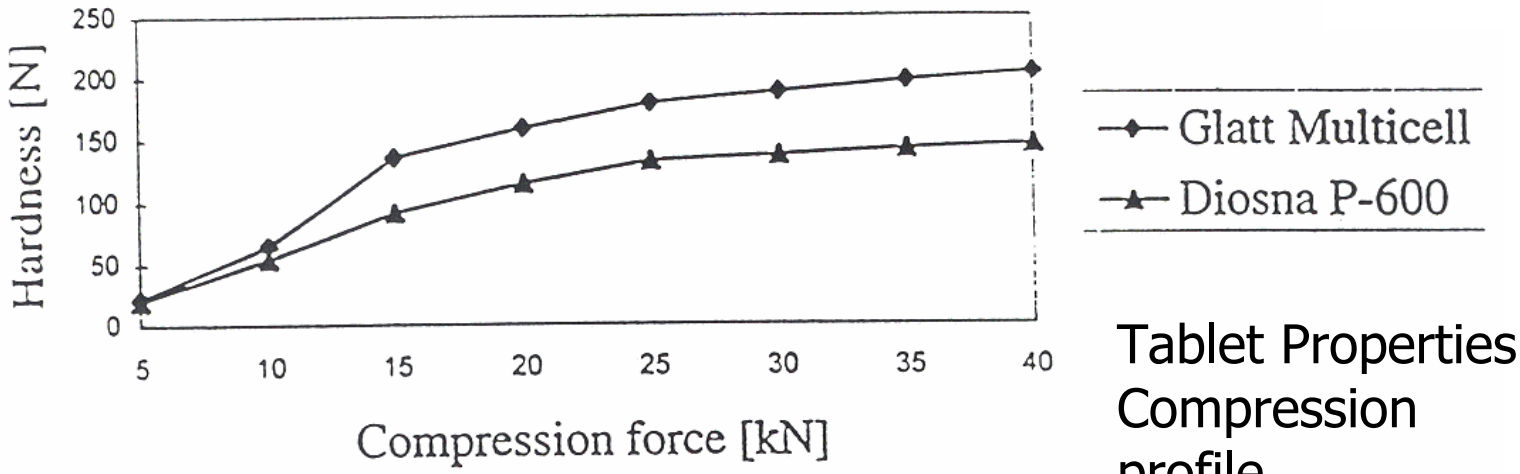
Heinrich, S., Peglow, M., Ihlow, M., Henneberg, M., Mörl, L.:
Analysis of the start-up process in continuous fluidized bed spray granulation by population balance modelling,
Chemical Engineering Science, 57 (2002), 4369-4390.

Heinrich, S., Peglow, M., Ihlow, M., Mörl, L.:
Particle population modeling in fluidized bed-spray granulation - Analysis of the steady-state and unsteady behavior,
Powder Technology, 130 (2003) 1-3, 154-161.

Radichkov, R., Kienle, A., Heinrich, S., Müller, T., Peglow, M., Mörl, L.:
A numerical bifurcation analysis of continuous fluidized bed spray granulation with external classification,
Chemical Engineering and Processing (submitted).

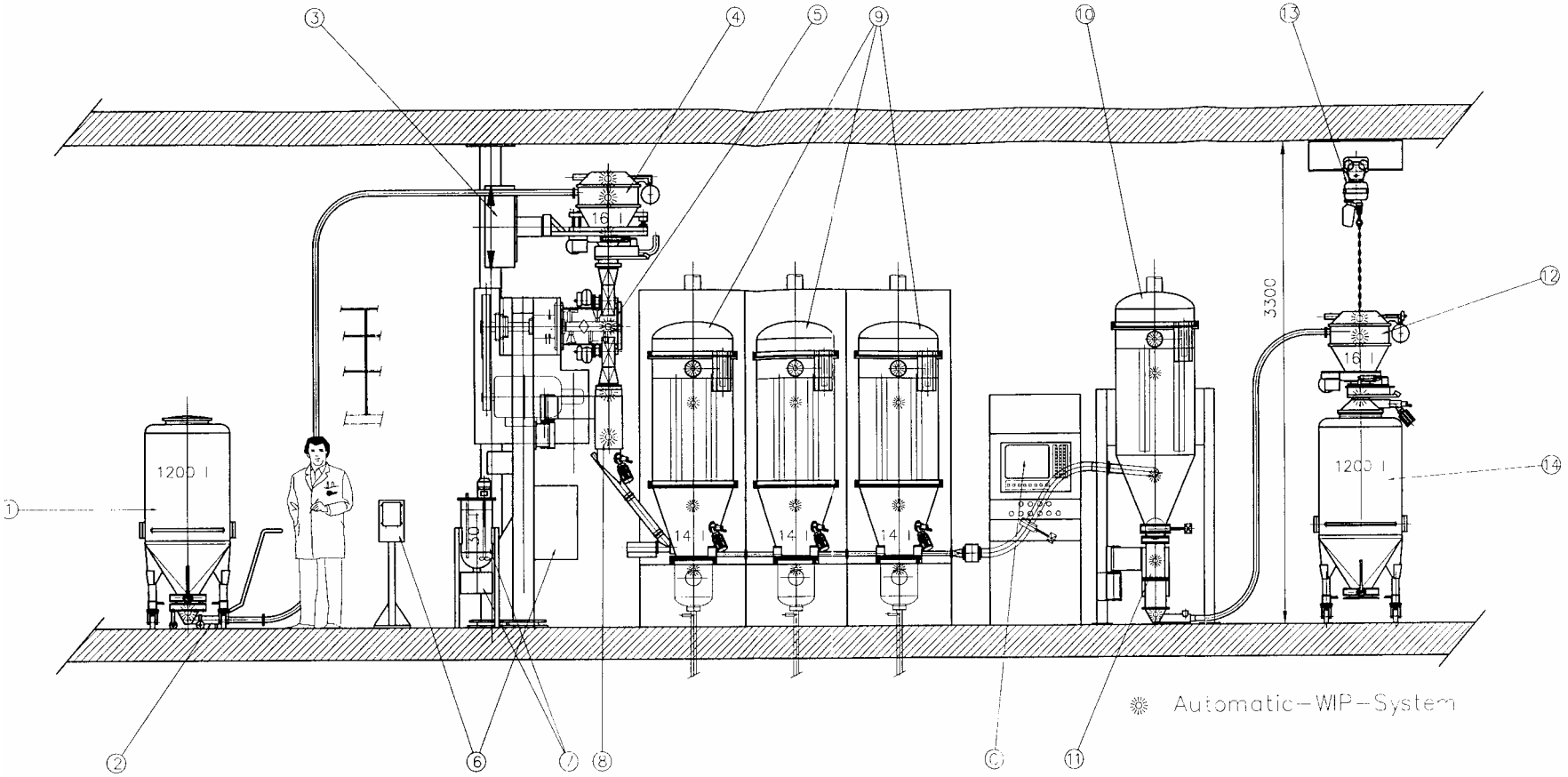
Scale – up Surprises

- Granule properties manufactured at a small scale (e.g.7kg subunit Glatt Multicell) may differ from a large scale operation (Diosna P-600, 600 Liters)
- Comparison Glatt Multicell™ and Conventional



Tablet Properties: Compression profile (scale-up effect!)

How to avoid conventional scale-up



The Glatt® Multicell ™ equipment
for small and large batches

Glatt®
MULTICELL™

Pfizer - Goedecke
Technology Center
Freiburg, Germany

Case Study for Innovation

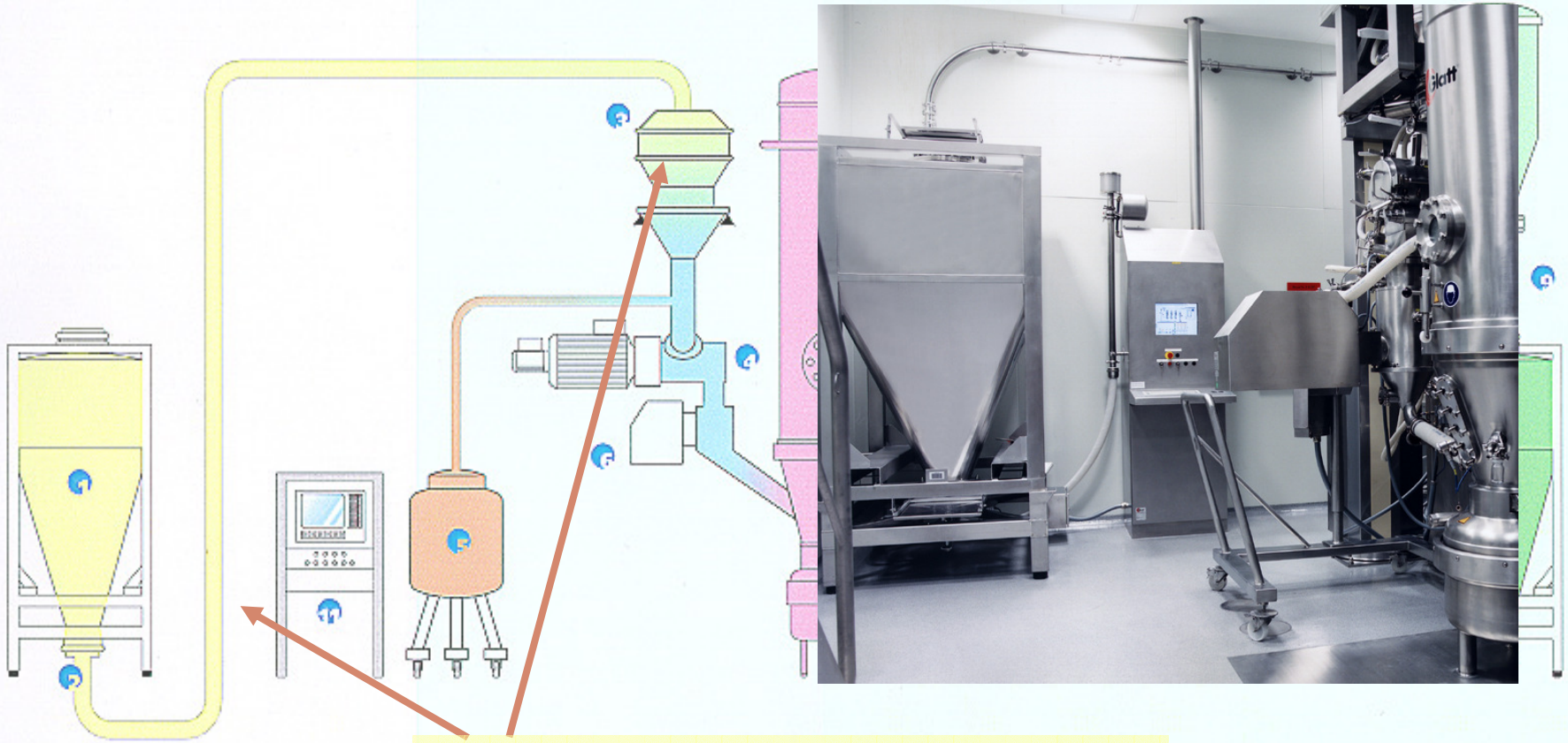
- Development of new solid oral dosage technologies should focus on four targets

  - **Move away** from batch concepts to full continuous processes for manufacturing.
  - **Optimize** manufacturing processes with regard to floor space and cycle times.
  - **Support** parametric release through in-line testing.
  - **Minimize** scale-up requirements during drug product development.

Case Study for Innovation

Glatt Multicell GMC 30

Semi continuous granulation and drying process

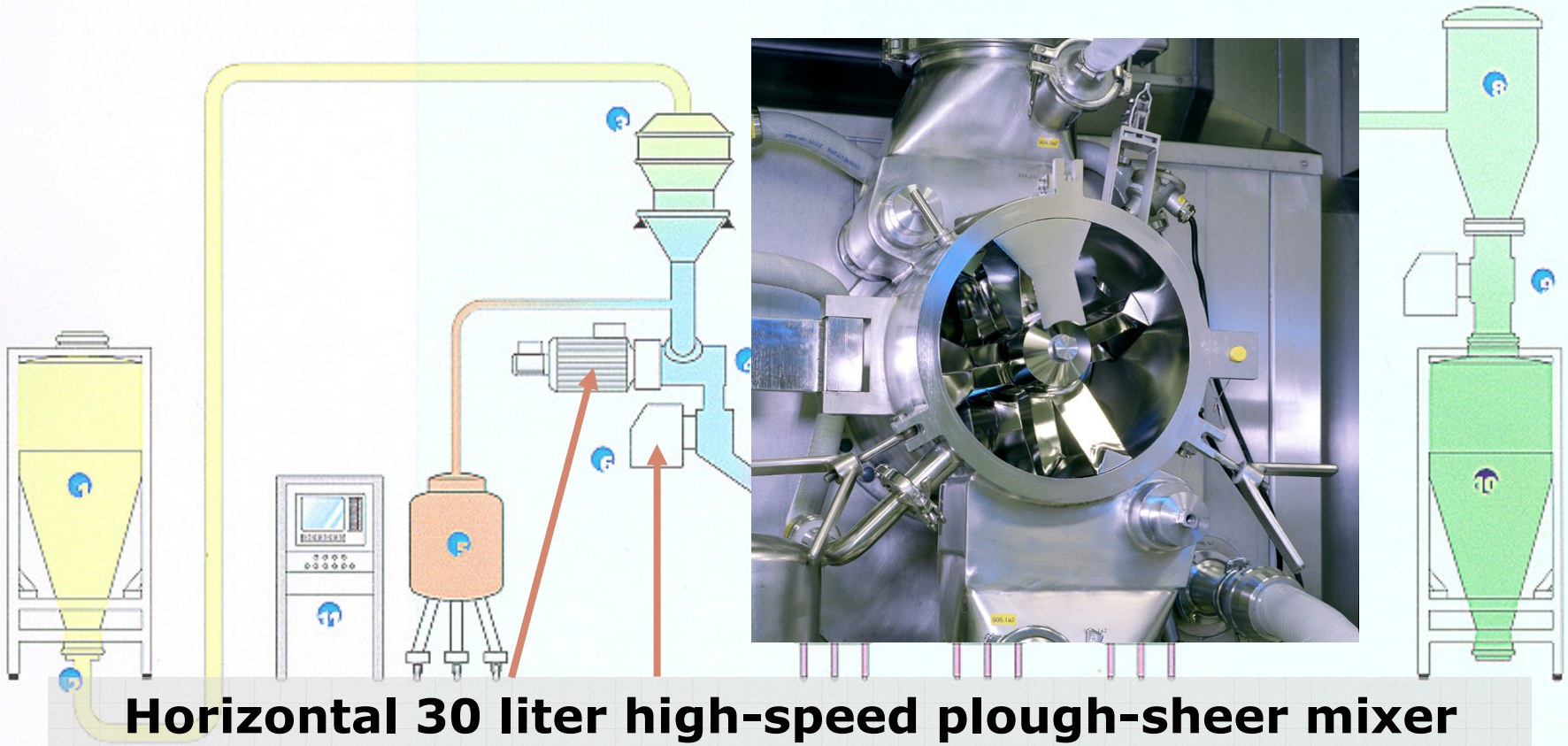


Feeding and dosing system

Case Study for Innovation

Glatt Multicell GMC 30

Semi continuous granulation and drying process

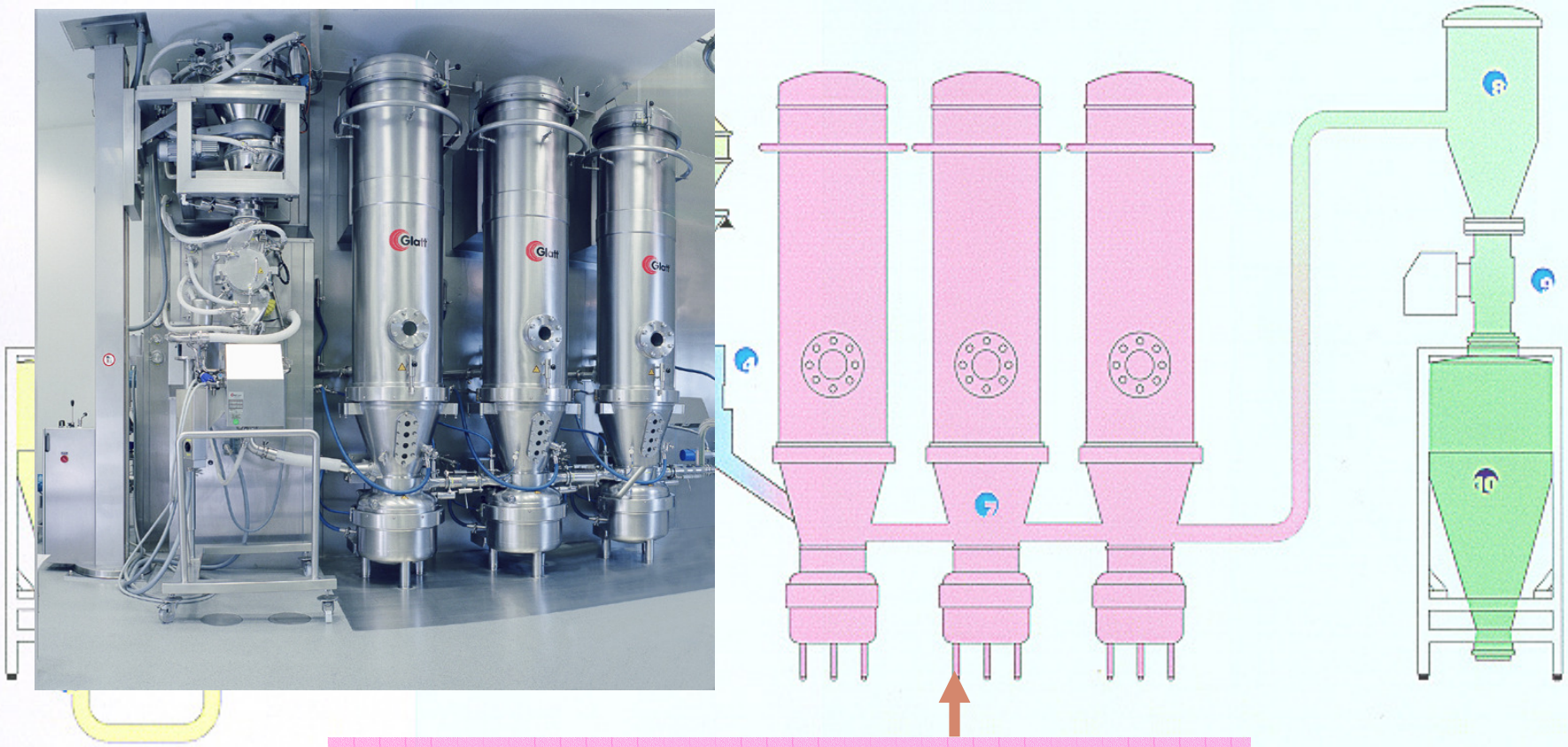


Horizontal 30 liter high-speed plough-sheer mixer and rotary high-speed sieving machine for wet sieving

Case Study for Innovation

Glatt Multicell GMC 30

Semi continuous granulation and drying process

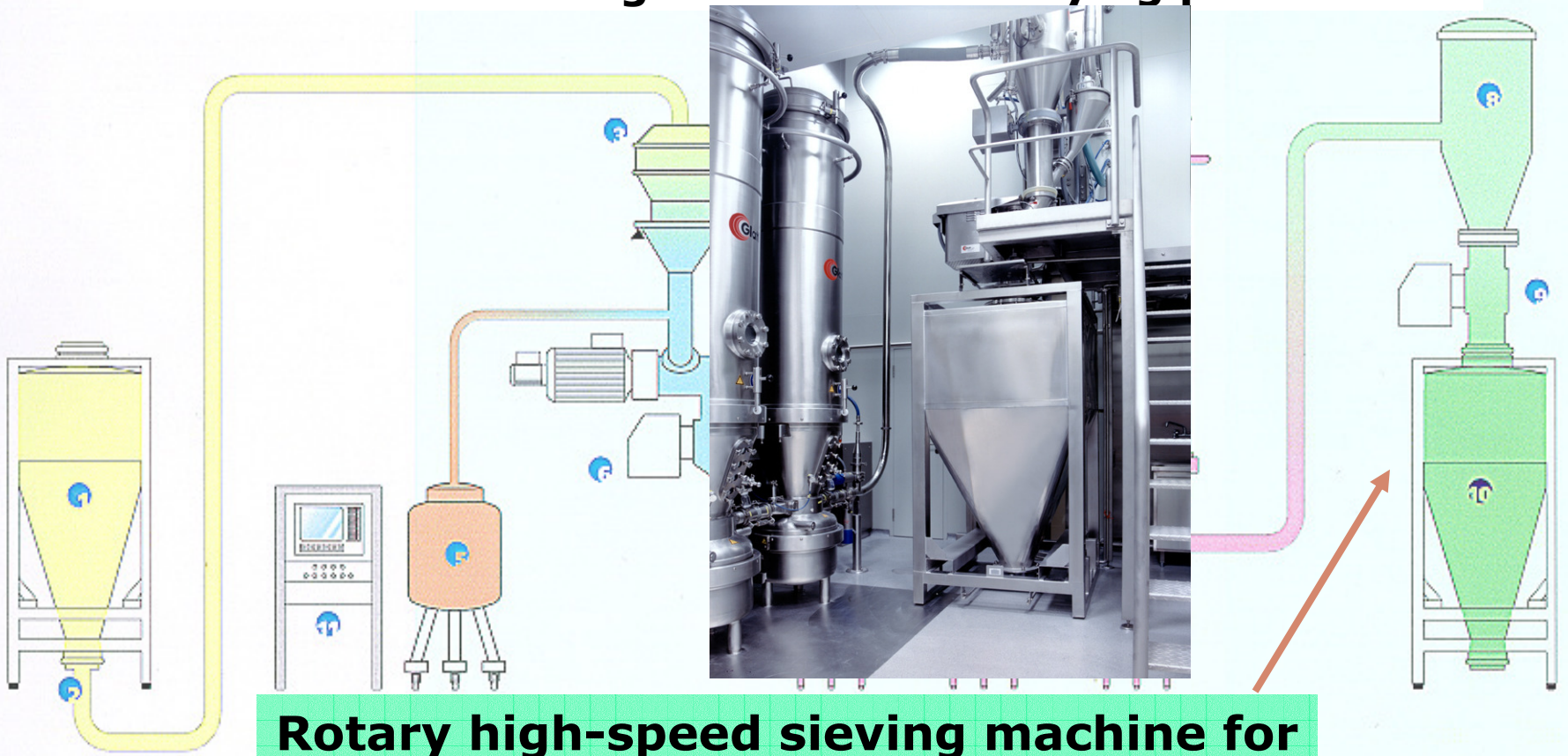


Three sequential fluid-bed dryers

Case Study for Innovation

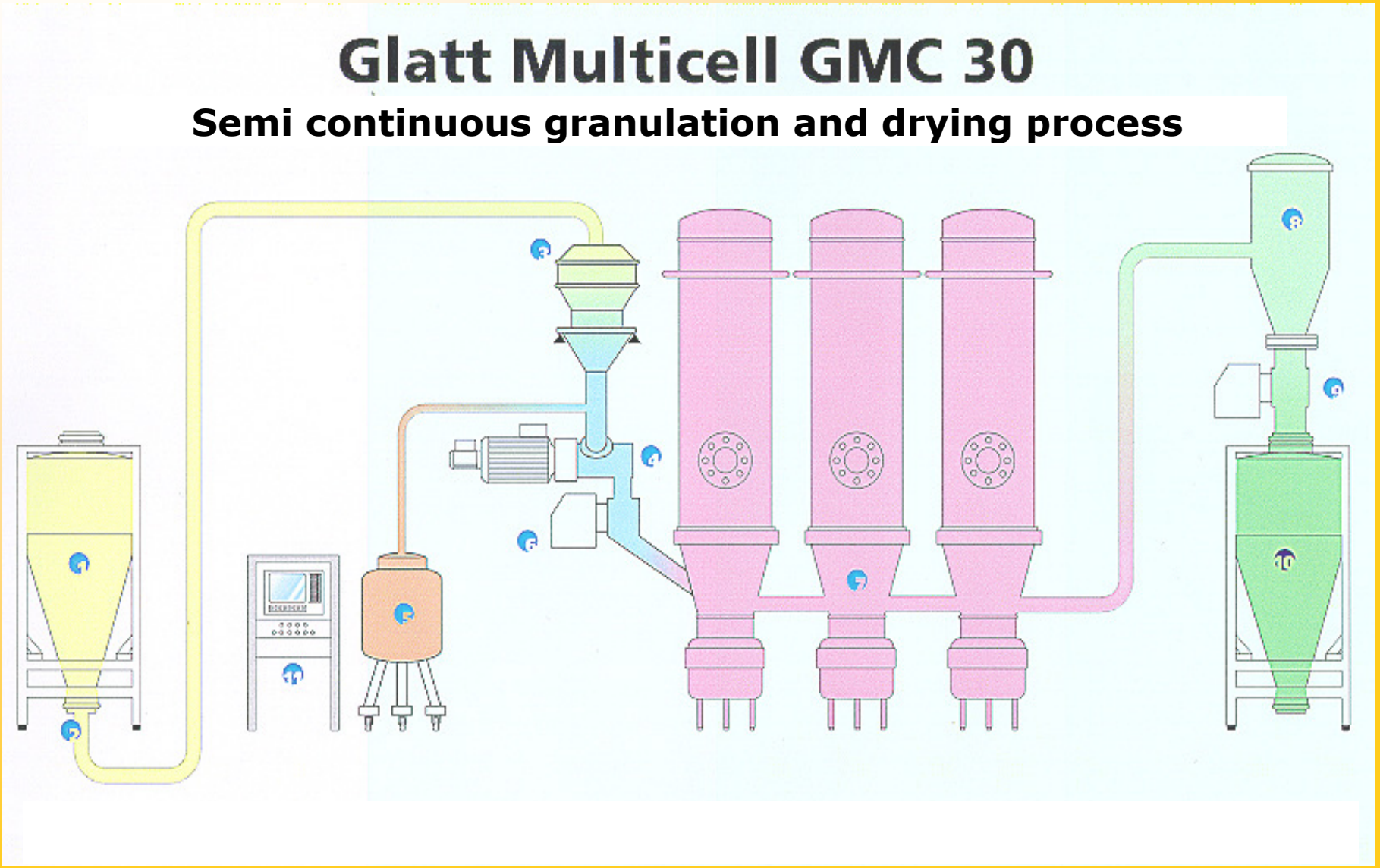
Glatt Multicell GMC 30

Semi continuous granulation and drying process



Rotary high-speed sieving machine for dry sieving and final product container

Case Study for Innovation



Highlights of the Glatt MULTICELL™ CONCEPT

- Reduction of Time to Market
  - can be best achieved if the R+D Department and the Production Department has the identical equipment to avoid any scale-up exercise, which means in practice:
- Optimize and validate
  - only once your formulation and process!
- A top quality and robust formulation
  - can be developed, which is not only optimal for small but also for large scale production.
- There is no need
  - for a “Bioequivalence” test between small and large scale batches due to a difference in the equipment/performance.

Highlights of the Glatt MULTICELL™ CONCEPT

- Early small scale batches
  - have the same quality as large scale production batches and can be used for long term stability trials etc.
- An Increase in the Productivity
  - as a result of Unattended Production, Lights-out operation
- Goal:
  - Significant Reduction of Cycle Time and Better Use of the capacity of the equipment

Case Study for Innovation

Summary of the Glatt Multicell Technology

- Process optimization of a small scale.
- No scale-up as pilot scale is identical with commercial scale.
- Stability results are available at an early development stage.
- No need for multiple bio-studies.

Case Study for Innovation

Technology	Lödige 900/WSG 300	Multicell	
Process	Batch process	Continuous process	
Batch size	Fixed to equipment capacity	Flexible depending on process time	
Mode of operation	Manual-driven and monitored	Almost lights-out-operated	
Floor space	130 m²	100 m²	-23%
Investment	1,6 Mio. US$	2 Mio. US$	+25%
Volume of equipment	900 l (270 +/- 50 kg)	30 l (8 +/- 2 kg)	
Output	55 kg/h	96 kg/h	+75%
Overall output	10 kg/24 h/m²	20 kg/24 h/m²	+100%

Glatt®
MULTICELL™

Pfizer - Goedecke
Technology Center
Freiburg, Germany

Continuous Dry Agglomeration

Roll compaction

Advantages

- Fully continuous
- Ideal for water sensitive drugs
- Addition of water and removal of water by drying not necessary

Continuous Dry Agglomeration

Continuous Dry Agglomeration

Continuous Dry Agglomeration

Roll compaction

Disadvantages

- Not all drugs/excipients are suitable for roller compaction
- Amount of fines produced can be too high
- Recycling of fines is not well received by regulatory agencies

Continuous Dry Agglomeration

Roll compaction

Disadvantages

- Produced quality depends on the compressibility/compactibility properties of the primary material
  - i.e. on the amount of crystalline defects, which can considerably change the properties
    soft iron versus hardened iron
  - and on the purity!

Continuous processes

Possible future developments

- Should we use Micro-Reactors?
  - For small specific “batches” (personalized medicine)
  - For nano-particulate medicine
  - For use in the early development stage, where only a small amount of drug is available

Continuous processes

Example: Research Project

- Production of nanoparticulate aerosols

PARTEC 2007

Aerosol Particle Processing in Micromixers

M. Heim[1)], R. Wengeler[1)], S. Dreher[2)], N. Kockmann[2)], P. Woias[2)], S. Mall-Gleissle[1)], K-H. Schaber[1)], H. Nirschl[1)] and G. Kasper[1)]

Institut für Mechanische Verfahrenstechnik und Mechanik, Universität Karlsruhe (TH), 76128 Karlsruhe, Germany

Institut für Mikrosystemtechnik, Universität Freiburg, Georges-Köhler-Allee 103, 79119 Freiburg, Germany

Production of nanoparticulate aerosols

Designing particle-based materials with complex product properties is

- often more easily achieved
  - through continuous, multistage processes,
  - rather than using classical unit operations.

Production of nanoparticulate aerosols

Micro-reactor technology has already demonstrated its

- suitability for many liquid phase applications and
- shows considerable potential to improve certain tasks in aerosol processing,
  - e.g. by promoting rapid mixing of aerosol streams to produce more uniform dispersions and coatings.

Production of nanoparticulate aerosols

The large surface-to-volume ratio of the micro-reactor

- which is advantageous in many applications

- requires special attention

  to be given to unwanted particle deposition on the micro-channel walls.

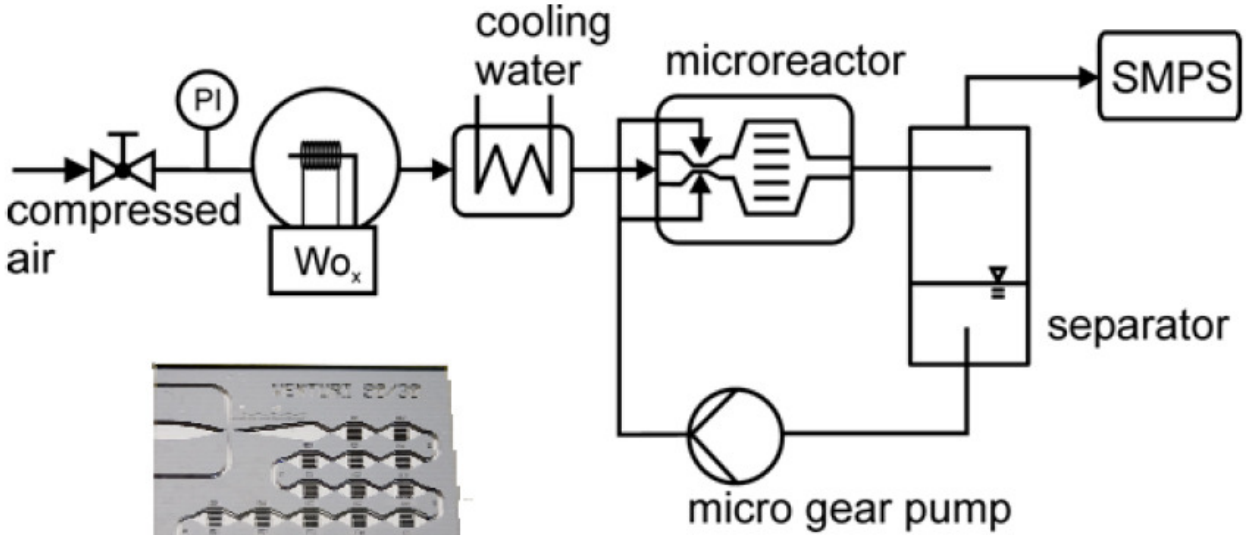
Production of nanoparticulate aerosols

The large surface-to-volume ratio

- is important for temperature driven processes, as it increases the heat transfer greatly.

Experimental setup for the deposition into a liquid media

The produced particle size distributions were measured by a standard SMPS System* with optional dilution.



* M.Heim, G.P.Reischl, C.Gerhard and G.Kasper: Performance of a new commercial Electrical Mobility Spectrometer; Aerosol Sci.Tech. 38 (S2), 2004, 3-14

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Thank you for your attention

Hans Leuenberger
Maxim Puchkov
CINCAP LLC c/o Ifiip

Institute of Pharmaceutical Technology
Pharmacenter of the University
Klingelbergstrasse 50
CH-4056 Basel, Switzerland