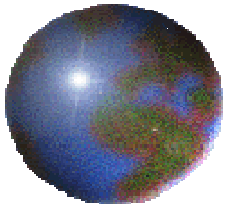
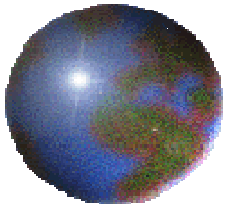


Scale-up and Process Robustness of Solid Dosage Forms

Prof. Dr. Hans Leuenberger

Pharmacenter of the University of Basel

E-mail:Hans.Leuenberger@unibas.ch
http:// www.pharma.unibas.ch/technology/index.html



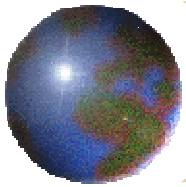
Classical Scale-up Operations

See literature:

New Trends in the Production of Pharmaceutical Granules:

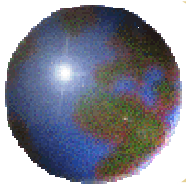
- The classical batch concept and the problem of scale-up
- Batch versus Continuous Processing

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



Solid Dosage Form Design

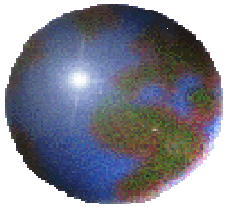
- Research in Powder Technology:
  - Formulation Research: Design of Robust Formulations
  - Use of Novel Approaches based on Percolation Theory



Solid Dosage Form Design

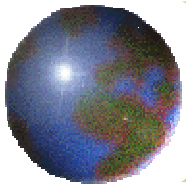
- $\Rightarrow$ Multicomponent Formulations need to take care of Percolation Theory

- Robustness and Percolation Thresholds $\Rightarrow$ Critical Concentrations of the components!



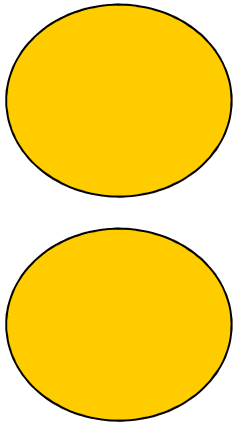
A Short Introduction to Percolation Theory

Application of Percolation Theory



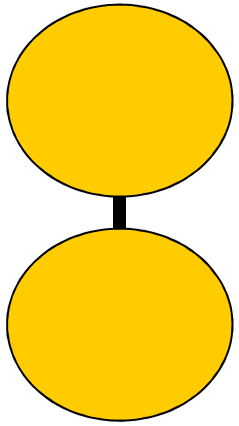
Percolation

Site

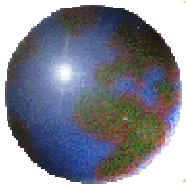


Cluster size = 2

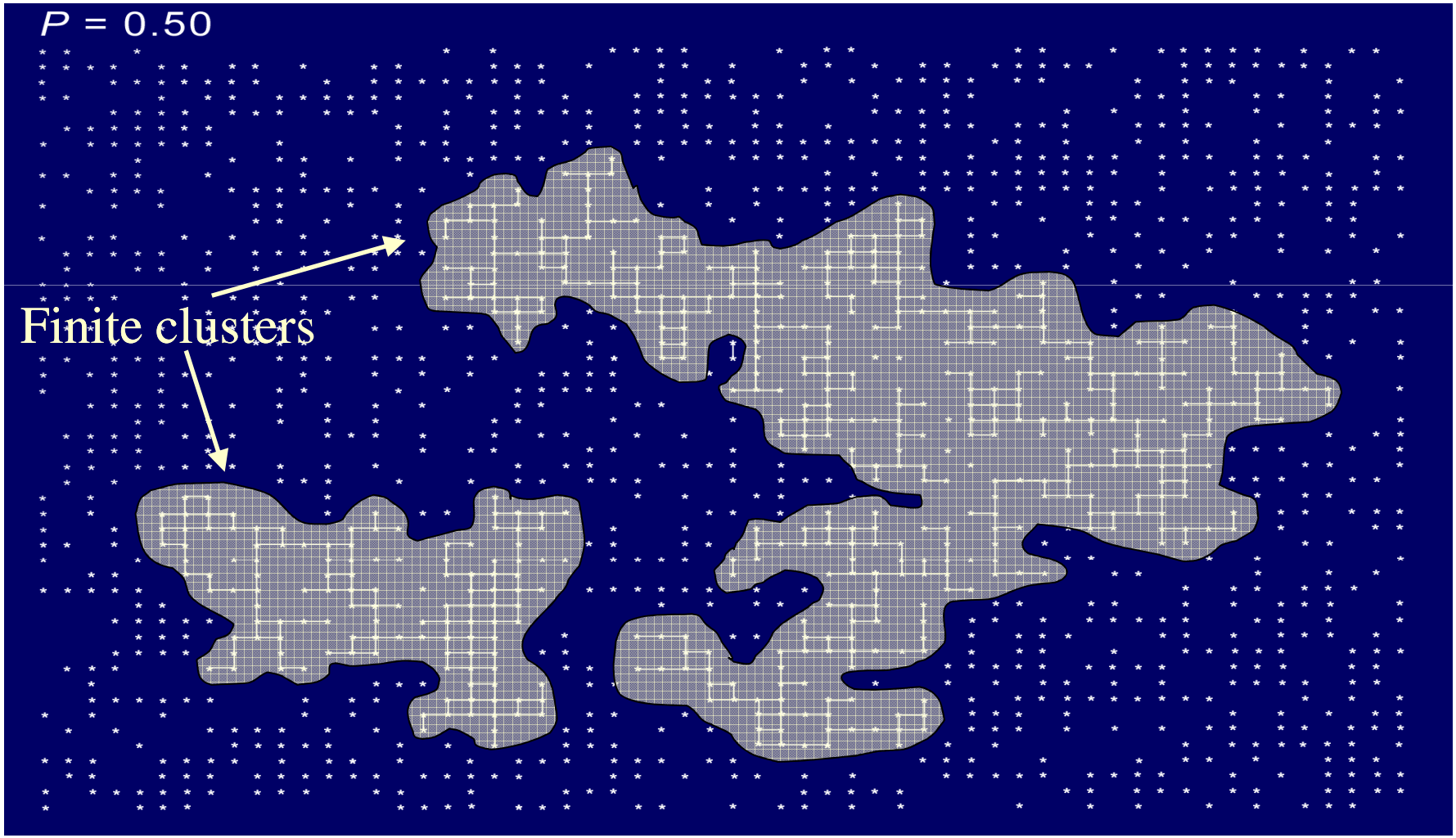
Bond

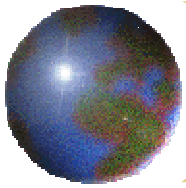


Cluster size = 1

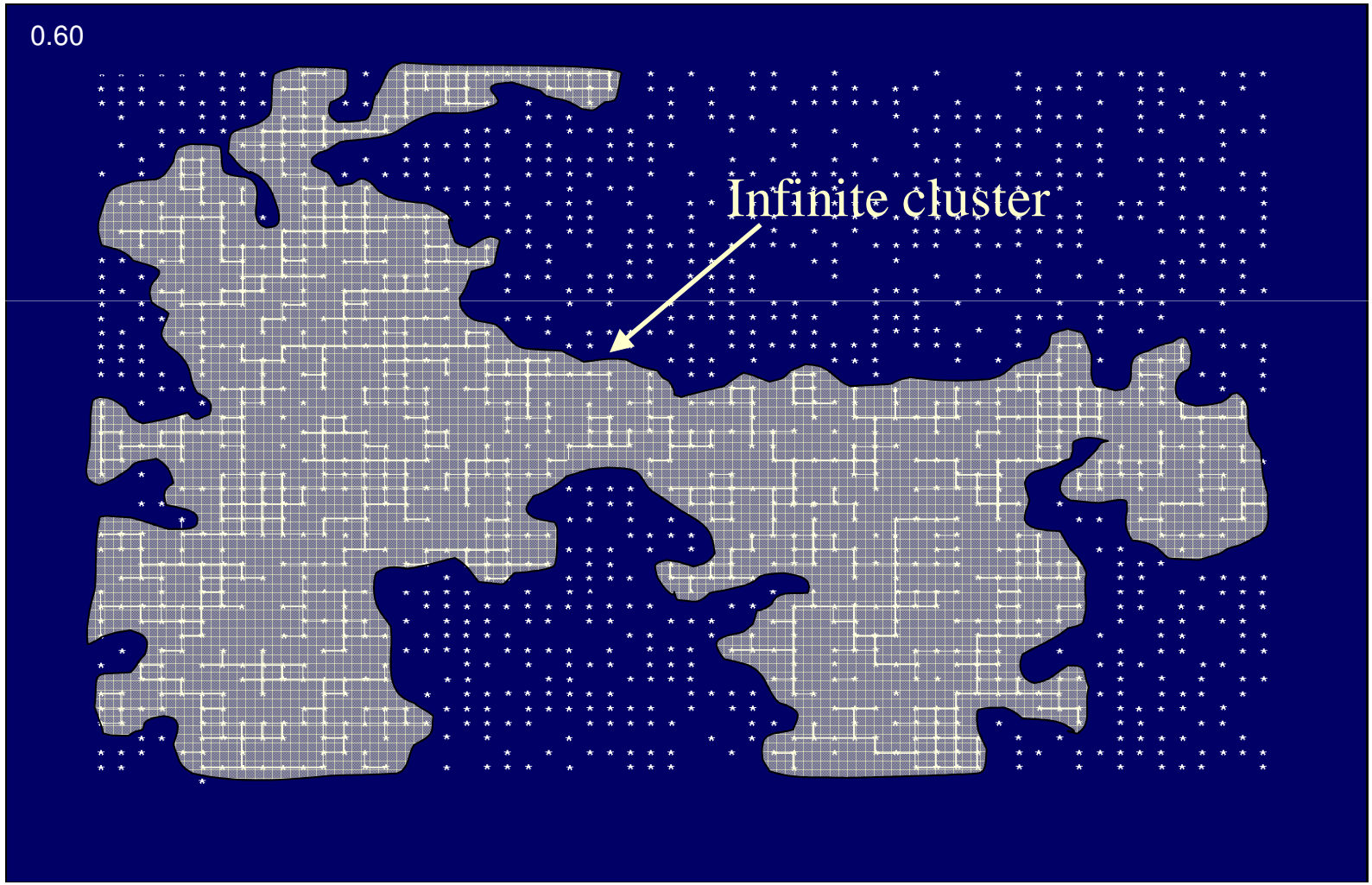


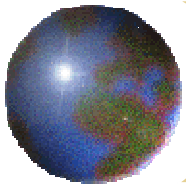
2-dim. square lattice
occupation probability p = 0.50 - no infinite cluster





2- dim. Square Lattice
occupation probability p = 0.60 - infinite cluster

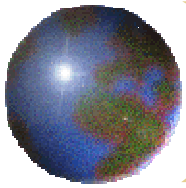




PERCOLATION THRESHOLDS

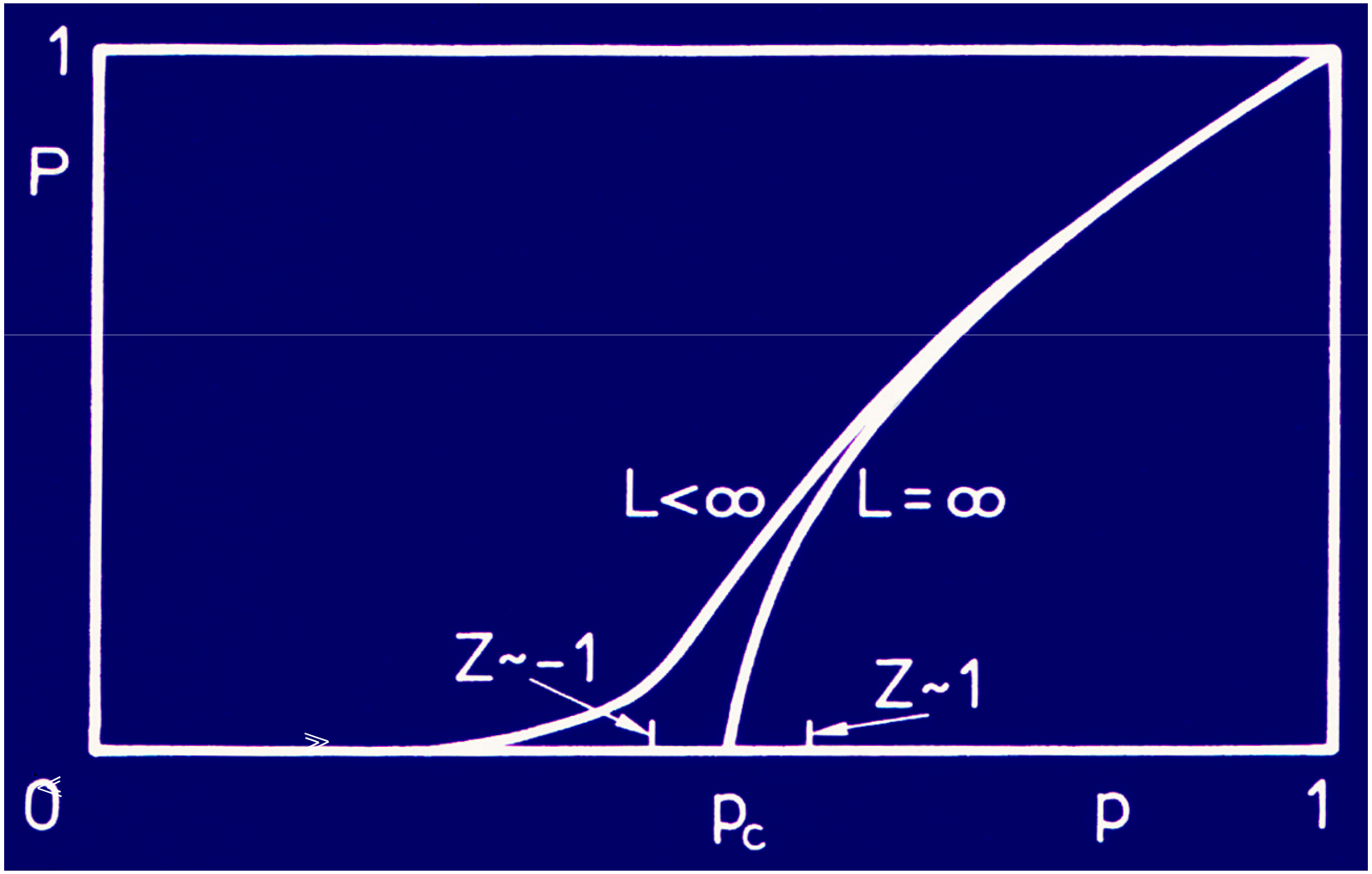
- For Site and Bond Percolation

Lattice	Site	Bond
Honeycomb	0.6962	0.65271
Square	0.59275	0.50000
Triangular	0.50000	0.34729
Diamond	0.428	0.388
Simple cubic	0.3117	0.2492
BCC	0.245	0.1785
FCC	0.198	0.119

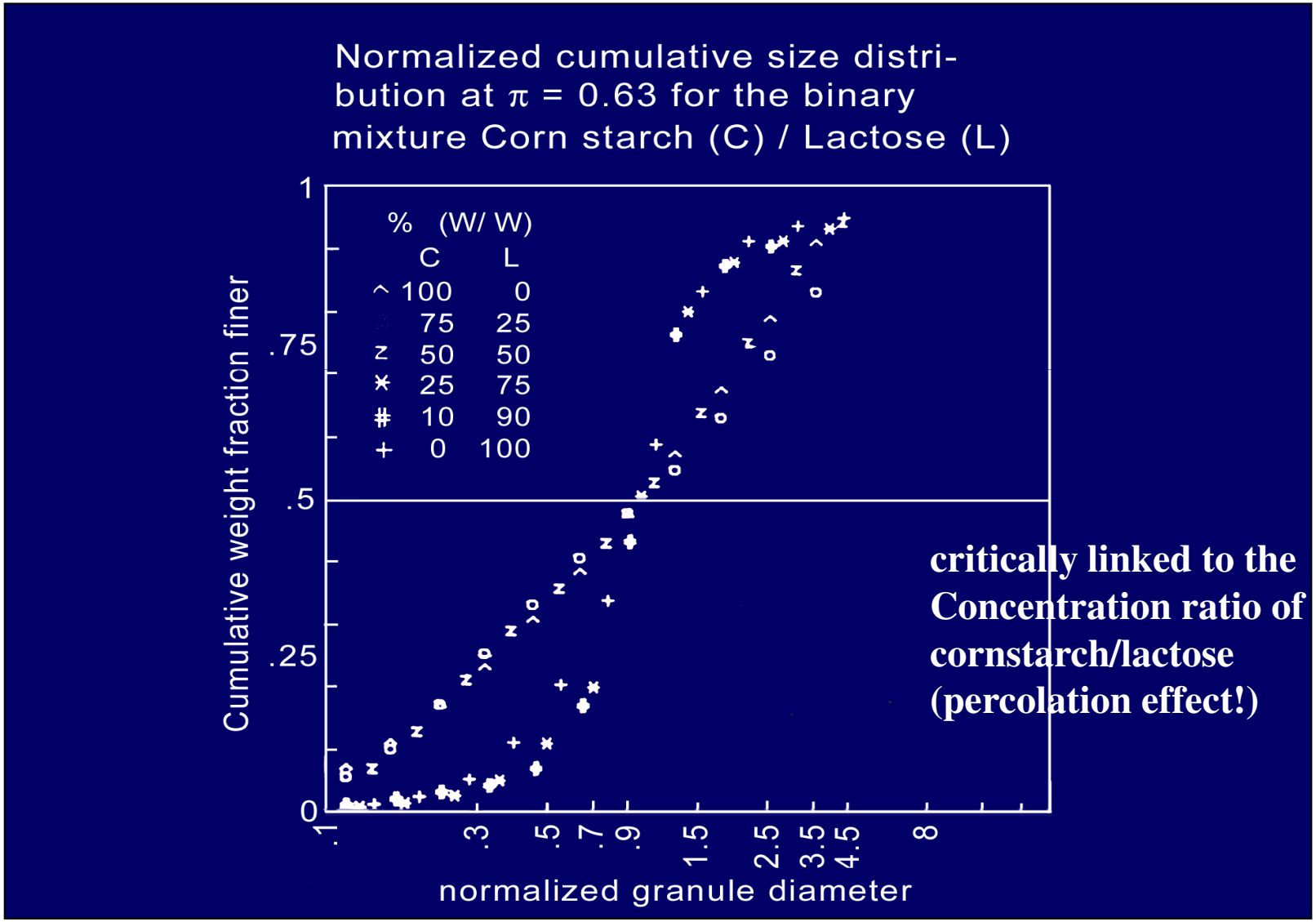


Percolation threshold

is not always a sharp transition



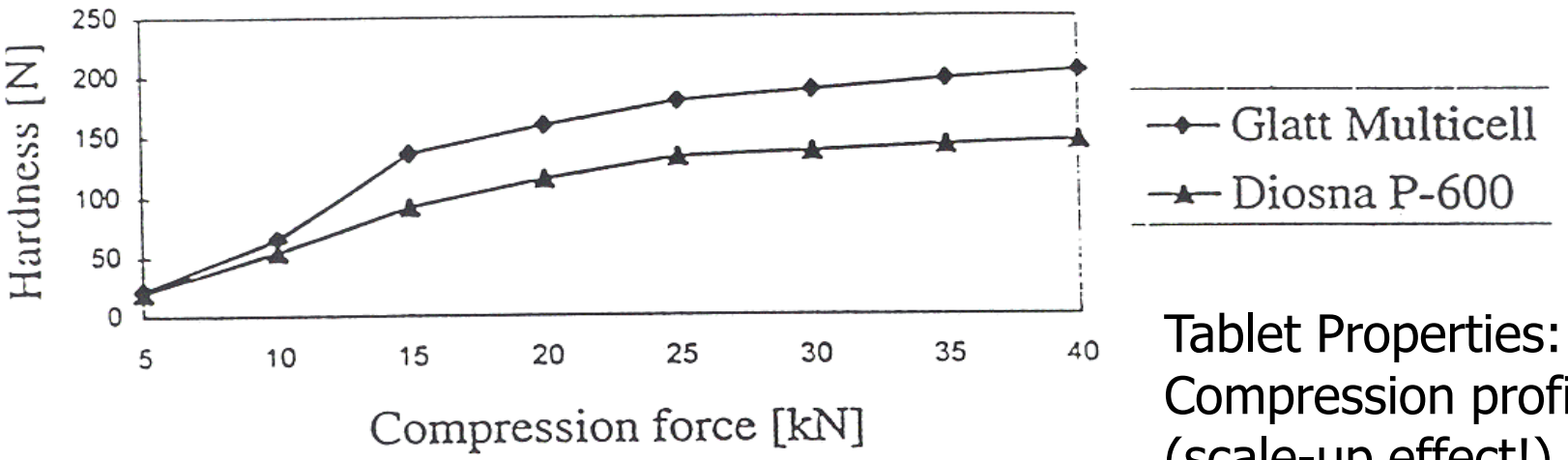
Linear and S-shaped granule size distribution



critically linked to the Concentration ratio of cornstarch/lactose (percolation effect!)

Scale – up Surprises

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



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

Classical scale-up: Pfizer Technology Service Center Freiburg

20 +/- 5 kg

80 +/- 20 kg

250 +/- 50 kg

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

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

Case Study for Innovation

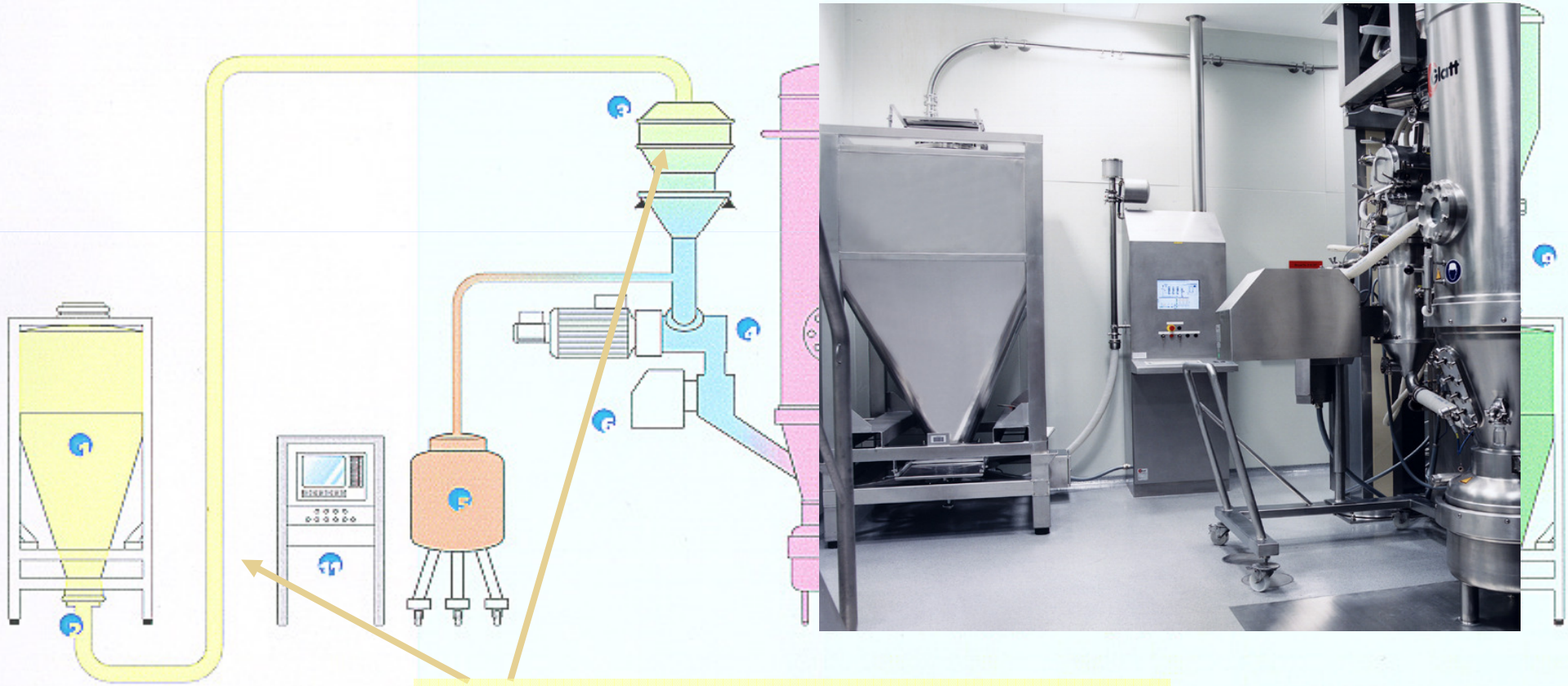
- Development of new solid oral dosage technologies should focus on four targets

  - **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

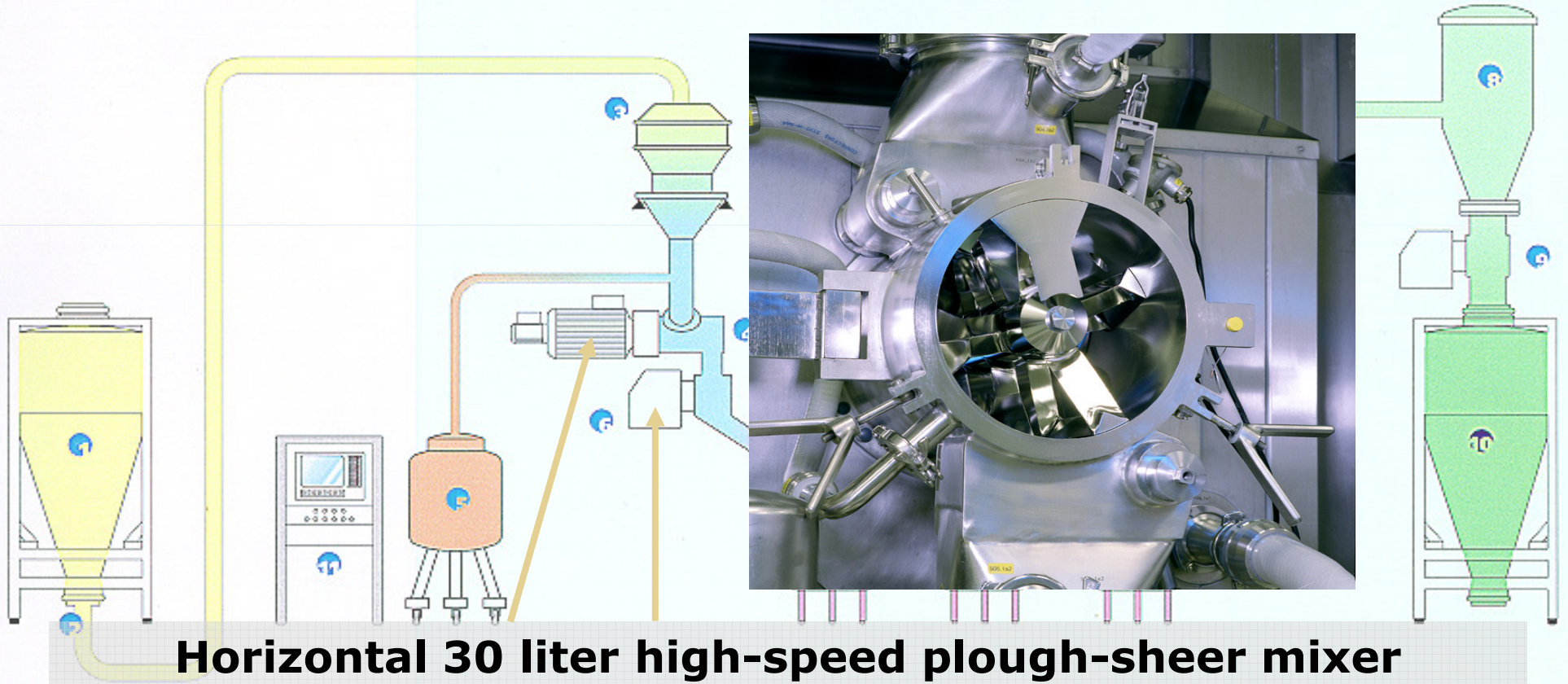


Feeding and dosing system

Case Study for Innovation

Glatt Multicell GMC 30

Semi continuous granulation and drying process

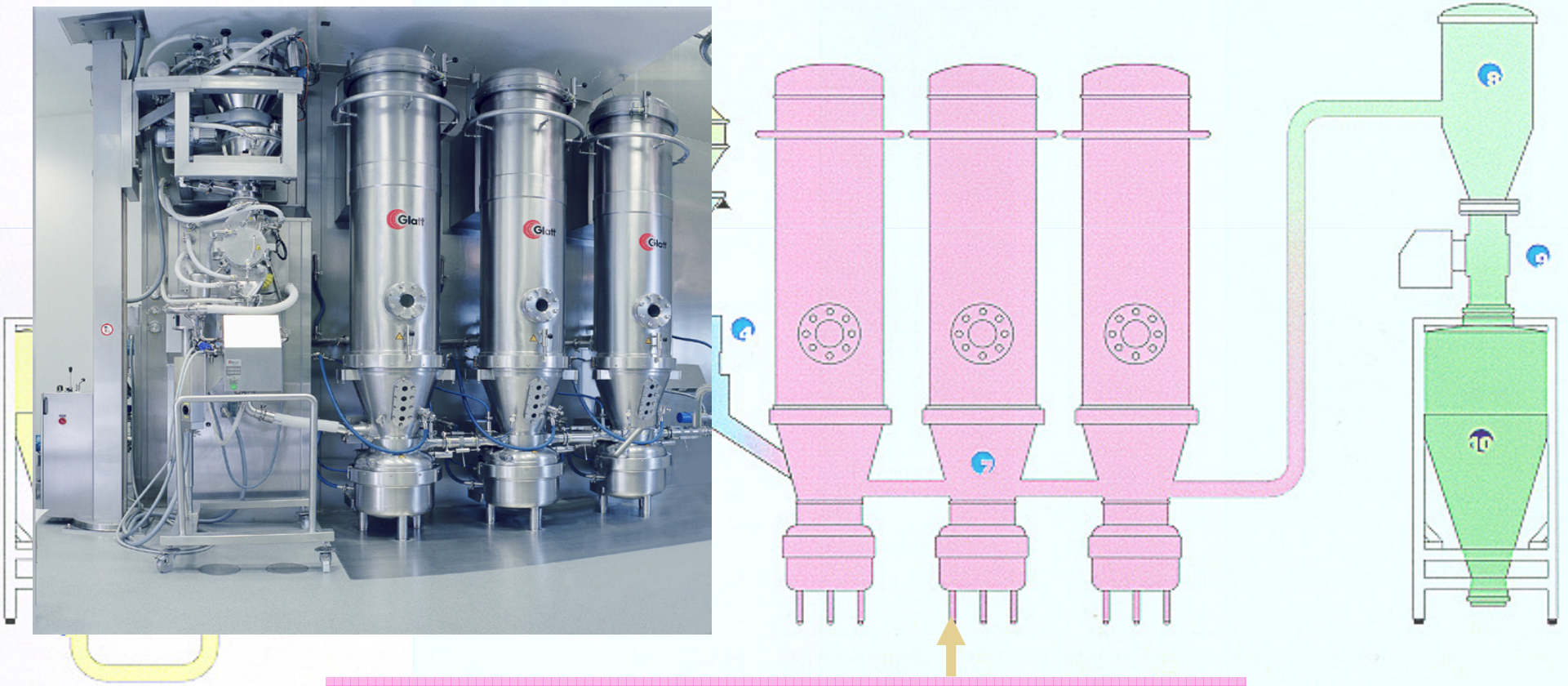


Horizontal 30 liter high-speed plough-sheer mixer and rotary high-speed sieving machine for wet sieving

Case Study for Innovation

Glatt Multicell GMC 30

Semi continuous granulation and drying process

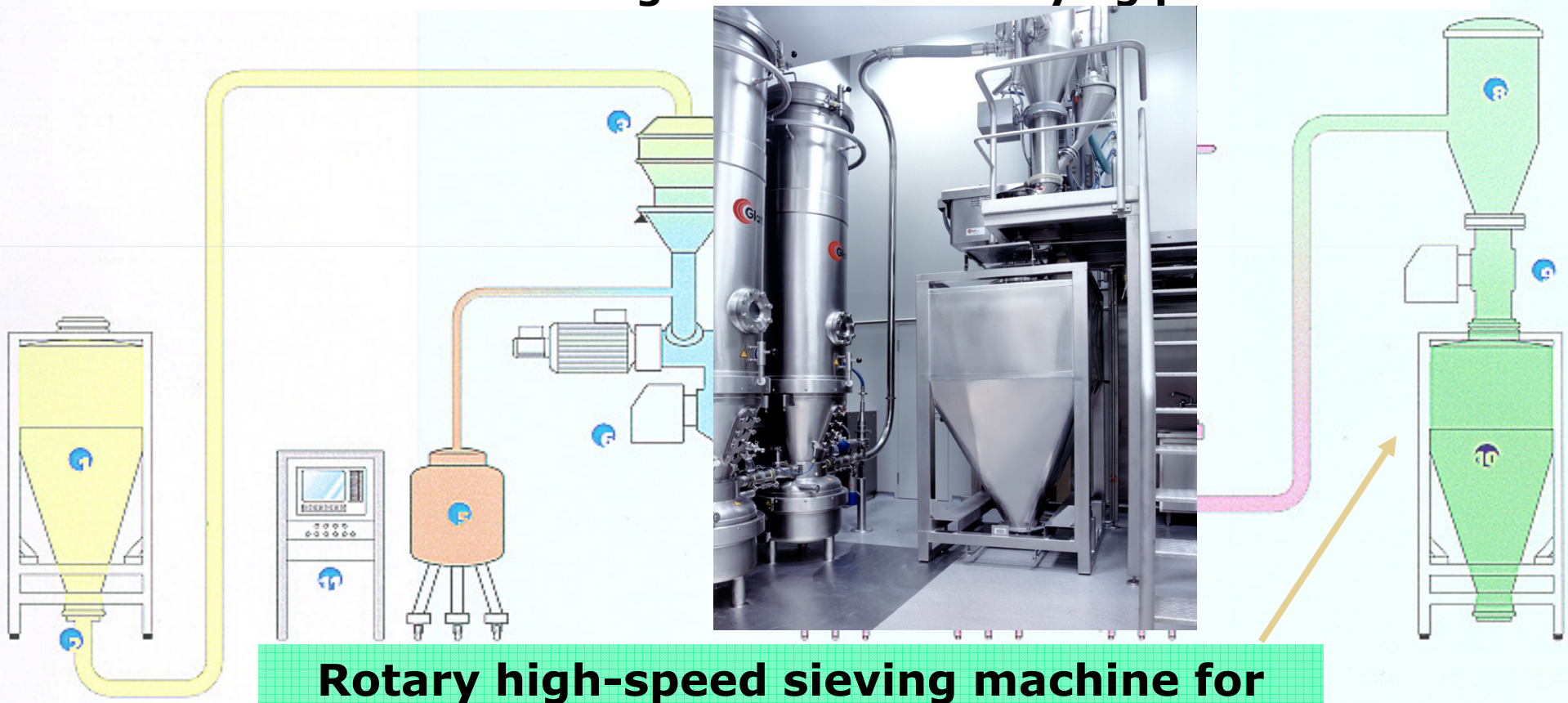


Three sequential fluid-bed dryers

Case Study for Innovation

Glatt Multicell GMC 30

Semi continuous granulation and drying process

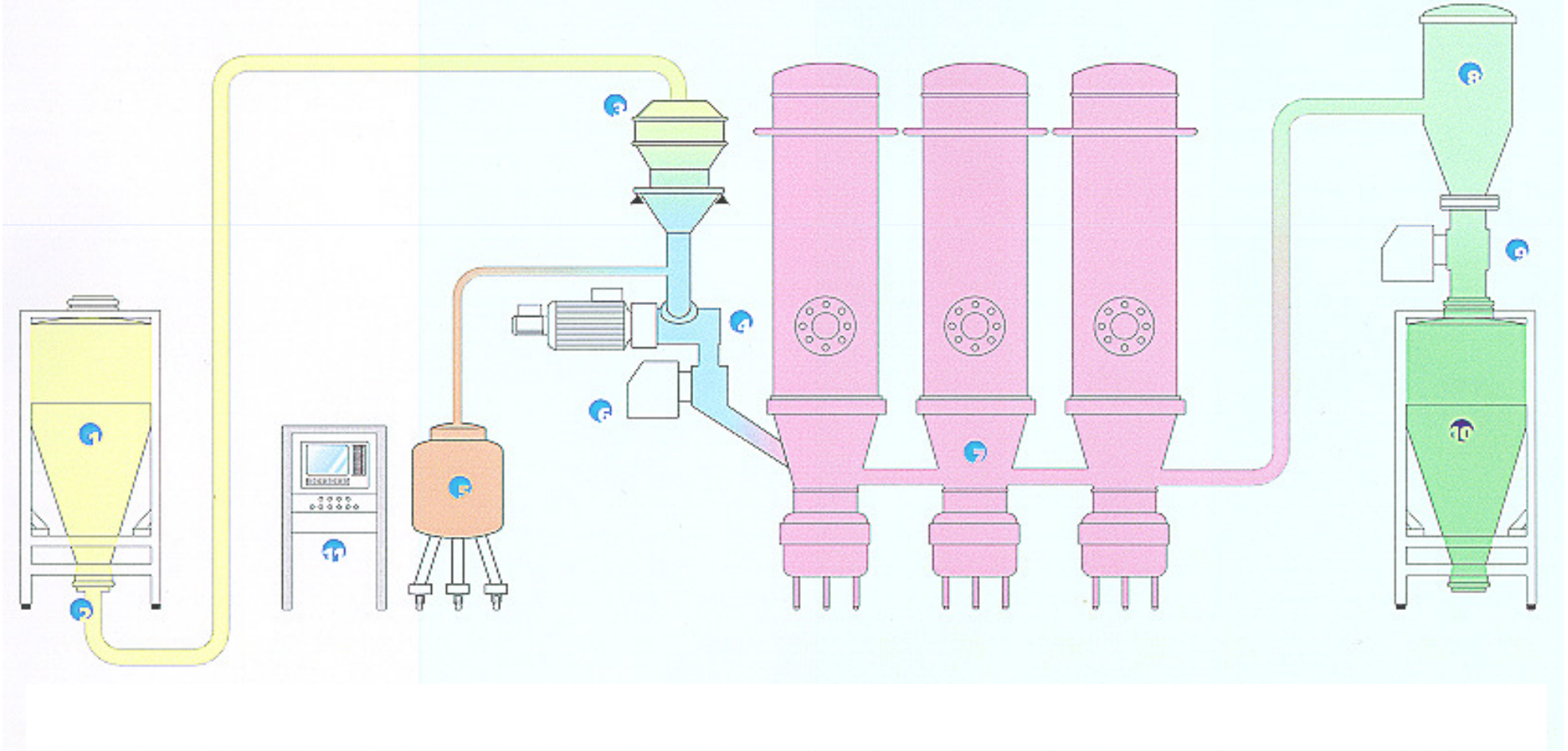


Rotary high-speed sieving machine for dry sieving and final product container

Case Study for Innovation

Glatt Multicell GMC 30

Semi continuous granulation and drying process

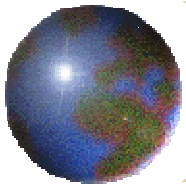


Highlights of the Glatt MULTICELL™ CONCEPT

- 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%