Virtual Integrated Design for Real Medicines

In silico Development Technology:

Virtual Design of Tablets (Dec 3, 2014, Loerrach)

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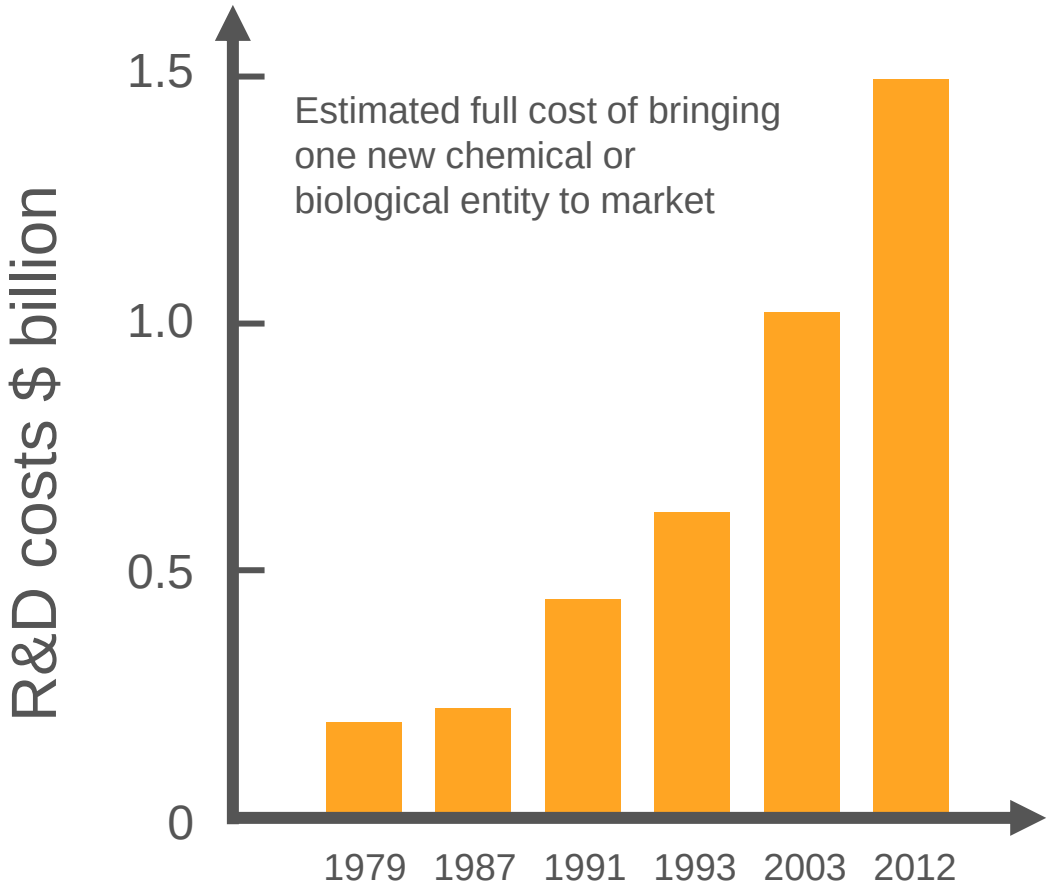
Today's Challenge: Accelerating R&D Costs



Source: http://www.efpia.eu/uploads/Figures_Key_Data_2013.pdf

Challenge

- Accelerating R&D costs
- Decreasing output

Companies' strategy

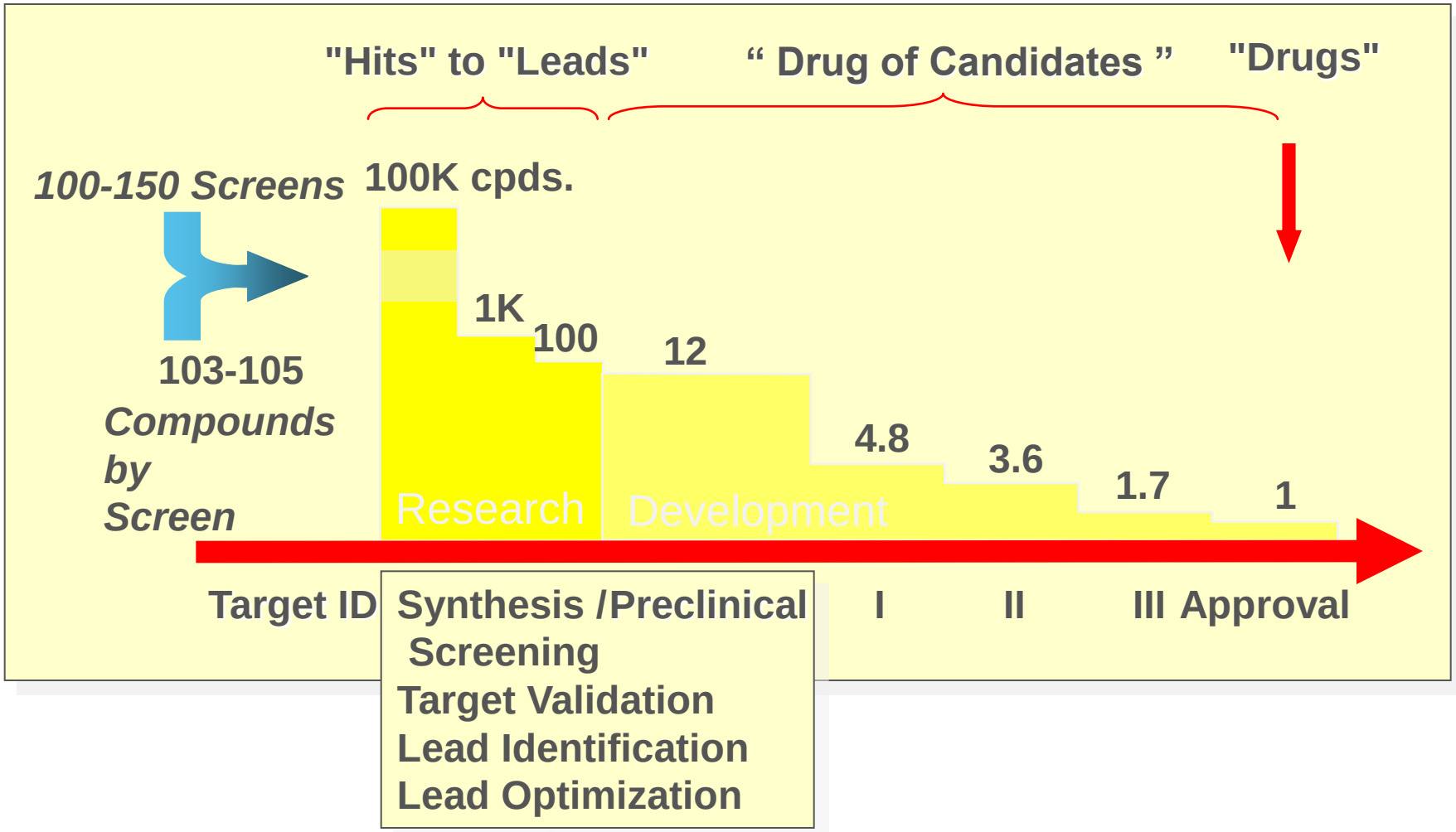
- Cost cutting
- Efficiency increase

AstraZeneca example:

- closing R&D in Macclesfield
- shedding 500 jobs
- moving 1600 jobs to Cambridge
- new global R&D center
- £330m ($550m) investment

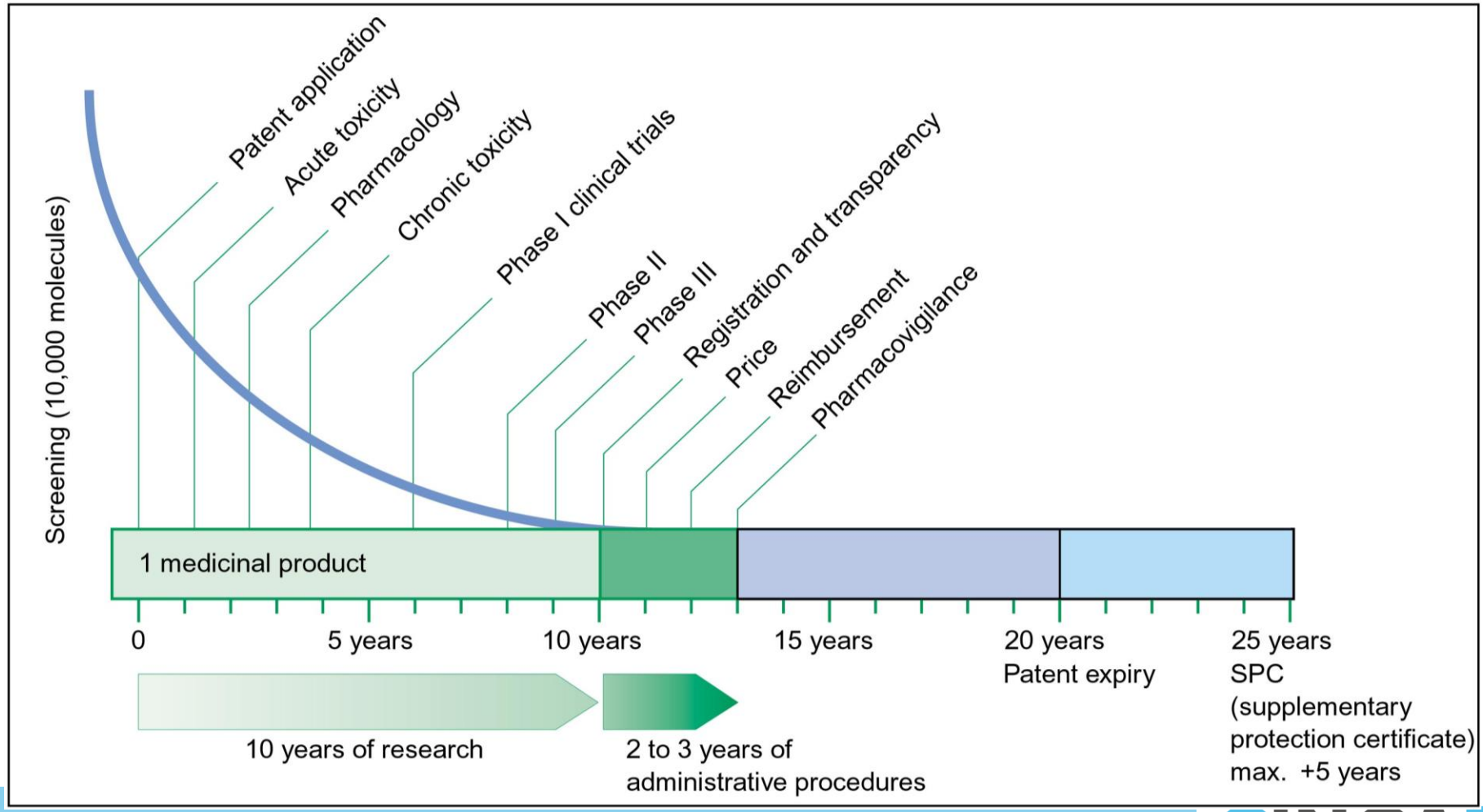
Source of Costs: Attrition rate

Attrition rate during the development of a medicinal product (Originator)



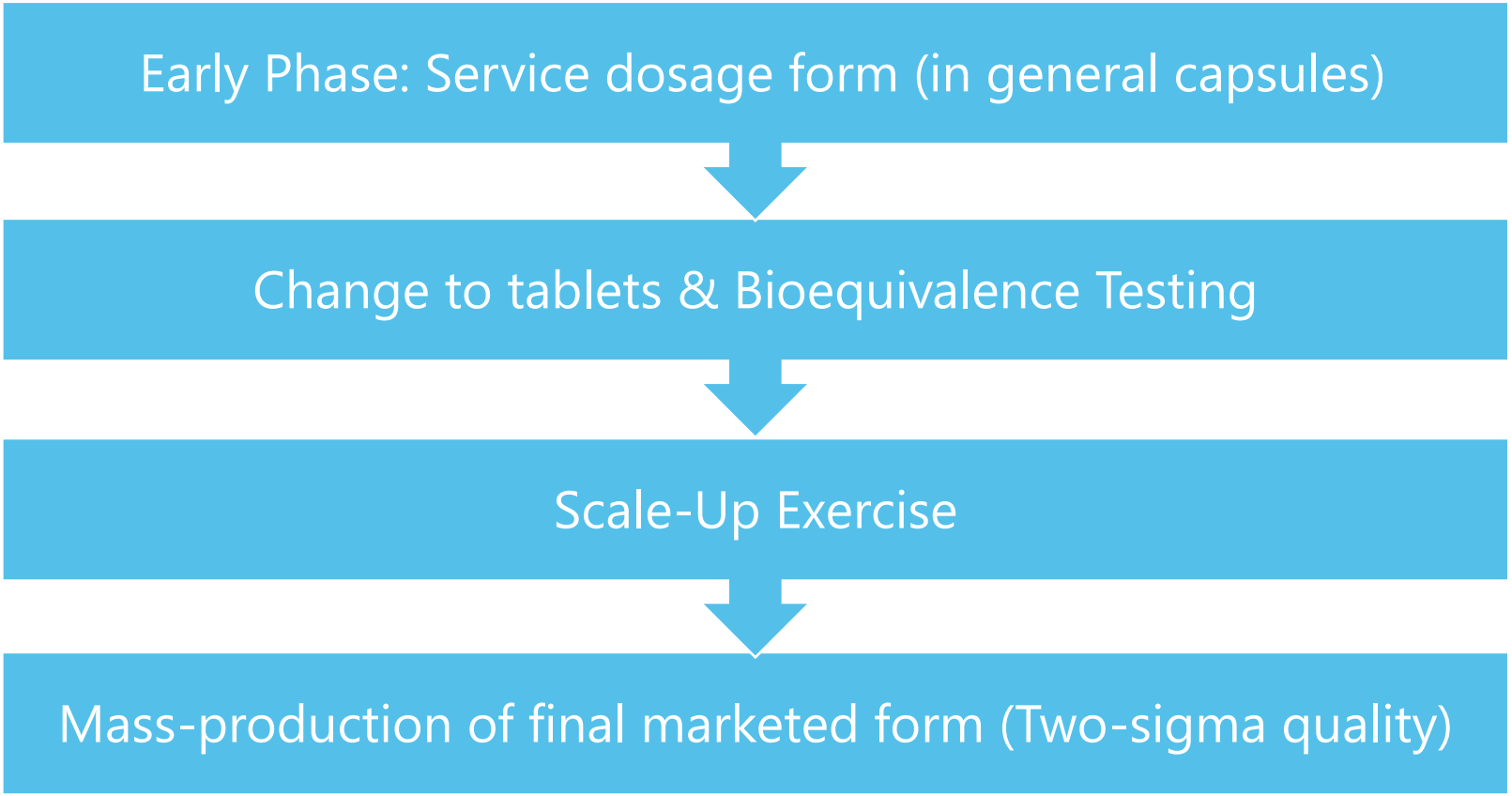
Development & Lifetime

Development and lifetime of a medicinal product (Originator)

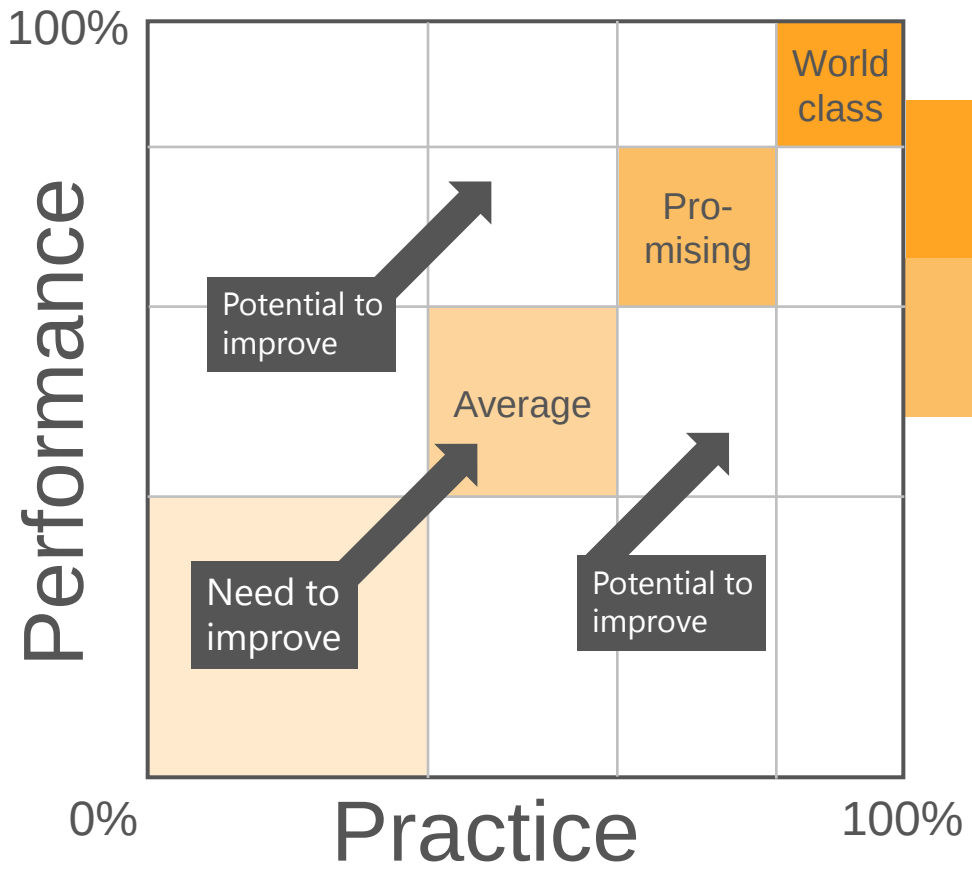


What is “Right, First Time” ?

Conventional Workflow: Early development (Clinical Phase I) with a service dosage form, i.e. a „simple“ capsule formulation (Two-Sigma).



Tomorrow's Chance: Improvement Potential of low quality formulations (2-Sigma)



	2004*	2013°
↑	15	30
↑	76	155
$bn	**91**	**184**

* Source: Roger S. Benson, Jim D.J. McCabe. From Good Manufacturing Practice to Good Manufacturing Performance. Pharmaceutical Engineering July/August 2004, Volume 24, Number 4

° Estimate according to the market development (IMS)

“Right, First Time”: Six -Sigma

Right First Time Workflow: Start with final marketed tablet formulation already at Clinical Phase I (!!!)

Market ready tablet dosage form (instead of service form)

↓

Small-scale Production

↓

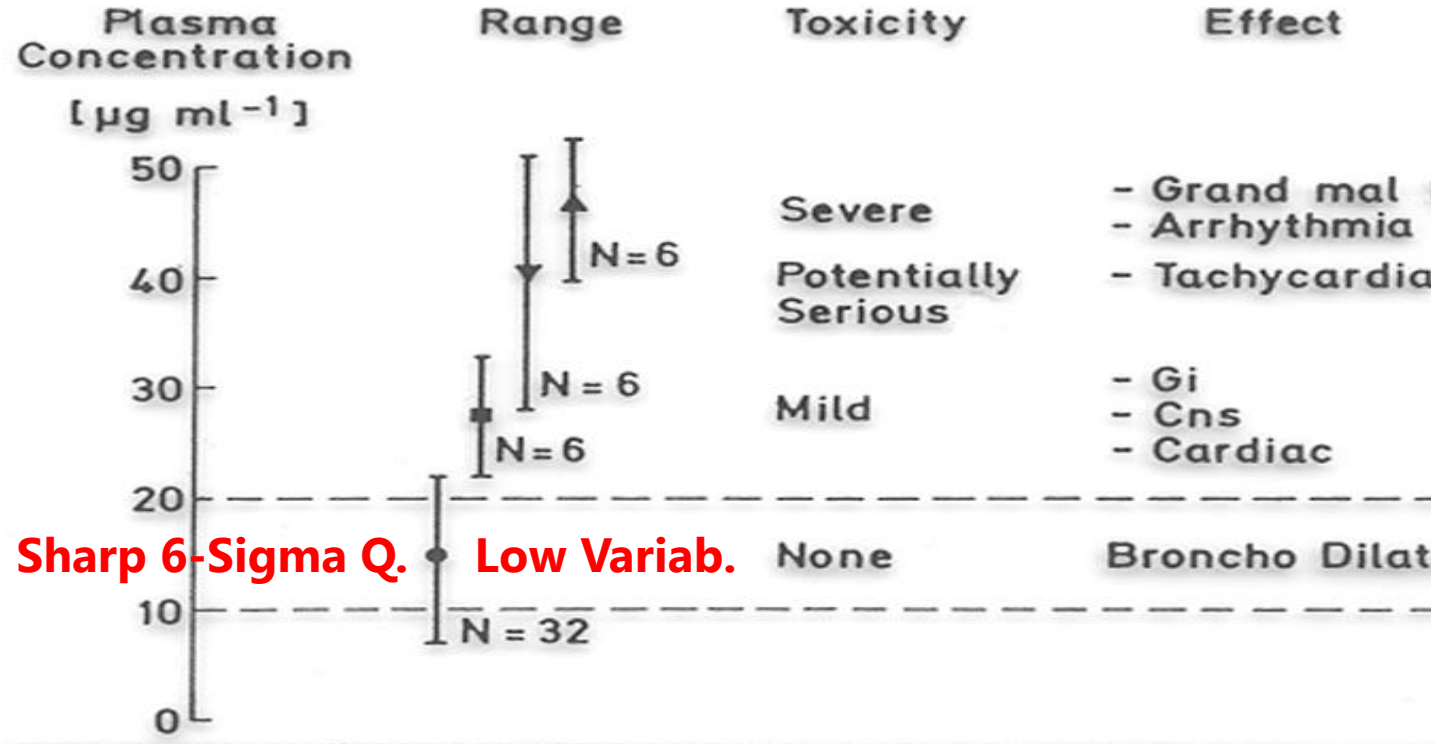
Scale-Up Exercise (computer-assisted)

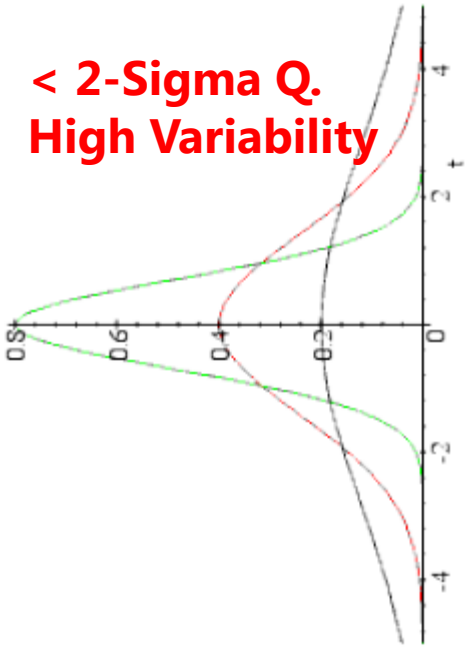
↓

Mass-production of final marketed form (six-sigma quality)

Benefit of Six –Sigma Form:

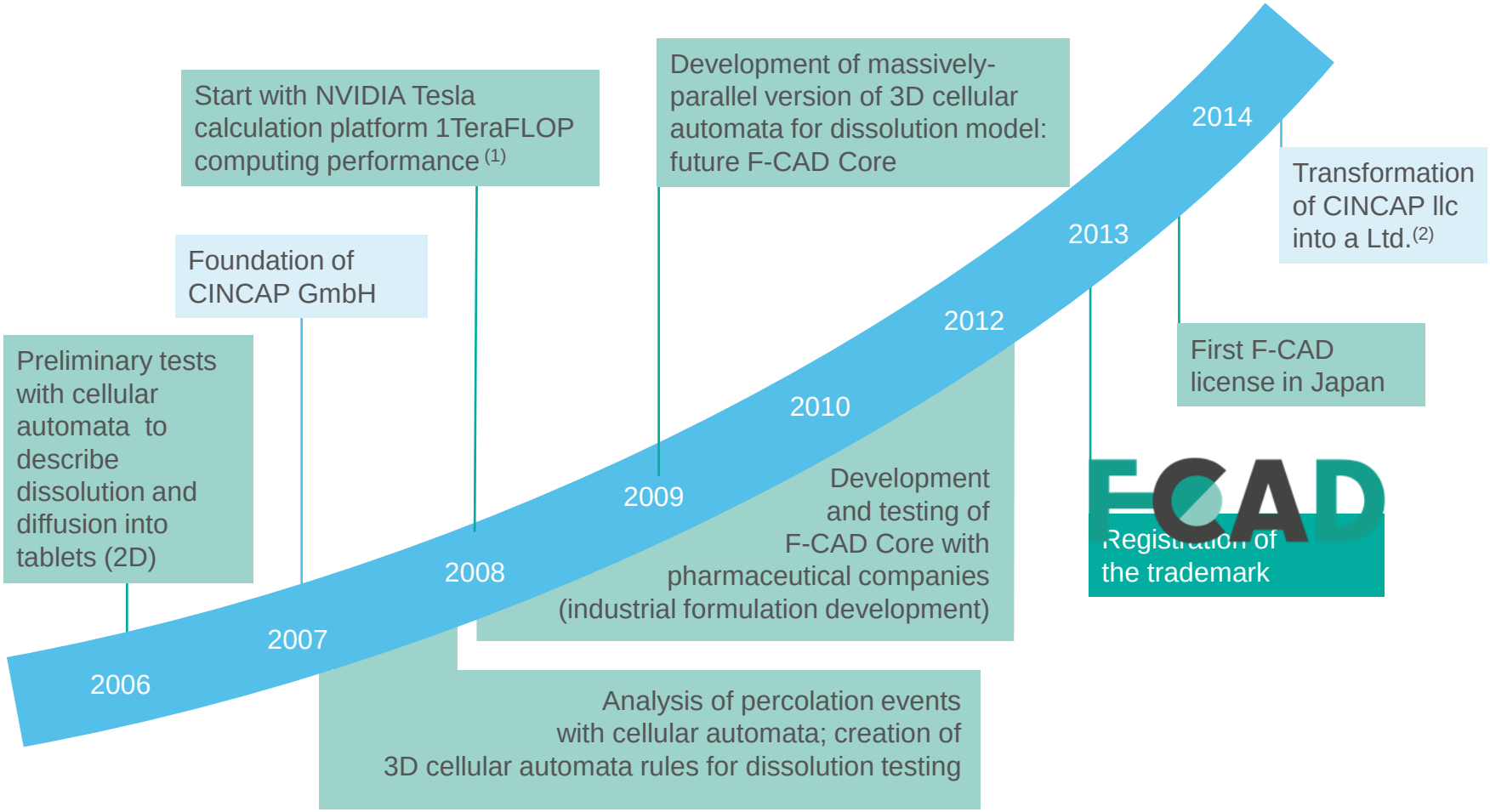
INNOVATION OF CINCAP: Top Quality Formulation (6-Sigma) already for Clinical Phase I to prevent false decisions during screening:





Plasma concentrations of theophylline related directly to the appearance of adverse reactions. Bronchodilation is the therapeutic effect of this drug

CINCAP Development



Remarks: (1) At this time the computing platform with the highest processing capacity in Switzerland; (2) Ongoing

Performance benchmarking of CA-based models and standard modeling methods

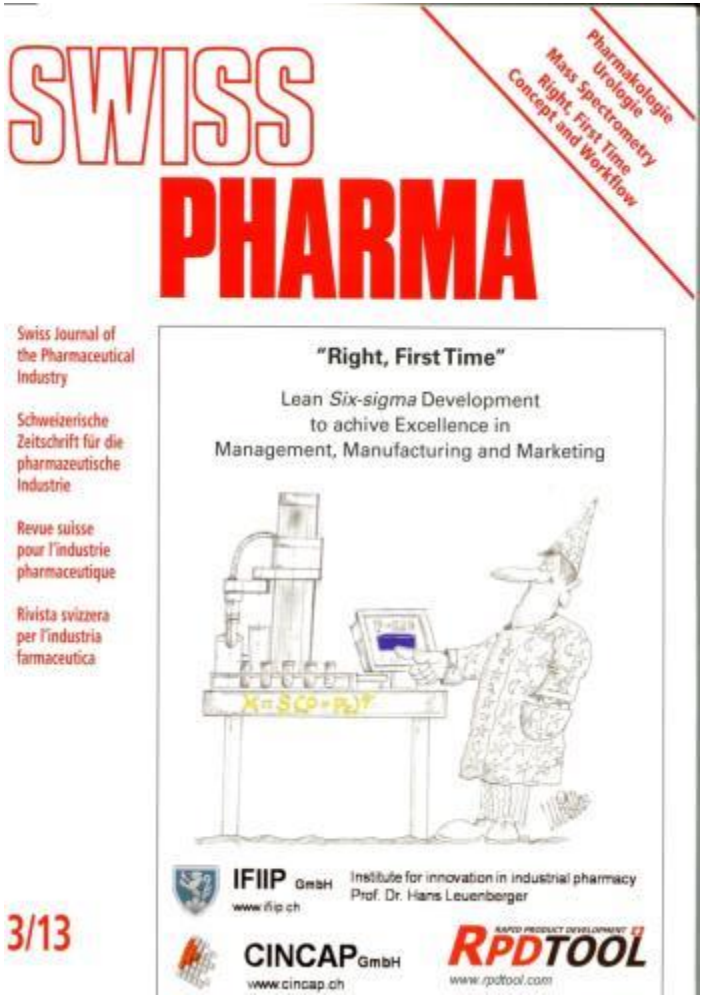
	CA-based models	DEM/FEM
Dissolution Simulation	yes	Yes
Swelling/diffusion	yes	Limited
Effect of granulation/milling	yes	Yes
Compaction Simulation	yes	limited
Memory usage	Extremely low	High
Particles per simulation	up to 1 000 000 000	Ca. 1 000 000 max.
Calculation speed	Up to 250x faster than real experiment	Extremely slow (days for simulation)
Hardware costs	Moderate/Low	Extremely high
Usage complexity	Simple and straight forward	Special training is essential

The Quality Benefit

	Conventional Production Process	FCAD
Sensitivity of formulation	**Experience-based** A time-consuming and expensive collection of a huge number of laboratory tests	**Calculated** by integrated tests during the Virtual Integrated Design
PAT* Production Process	**Risk** Any deviation along the PAT registered production process may cause a loss of batch	**Flexibility** Process variability insignificant for the quality of the final product is defined and registered
Quality	2σ	6σ

* Batch master file (“in-process control information”)

Right, First Time



Publication

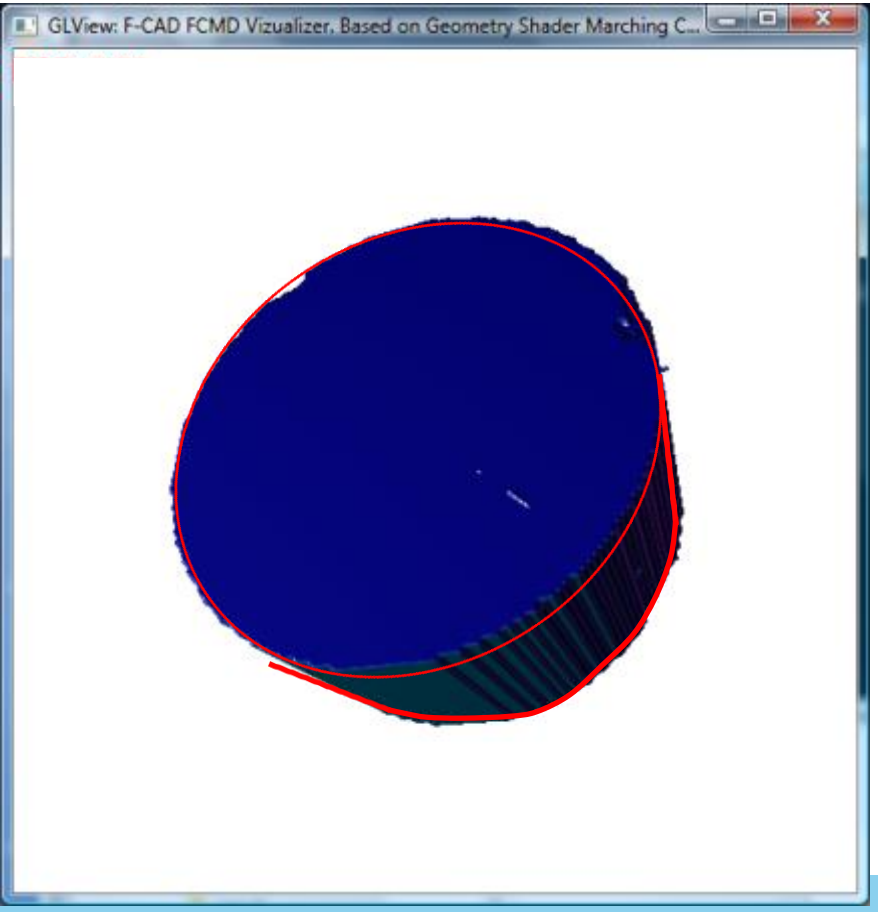
"Right, First Time"
Concept & Workflow
in SWISS PHARMA 3/13

⇒ **See**
www.ifiip.ch/downloads

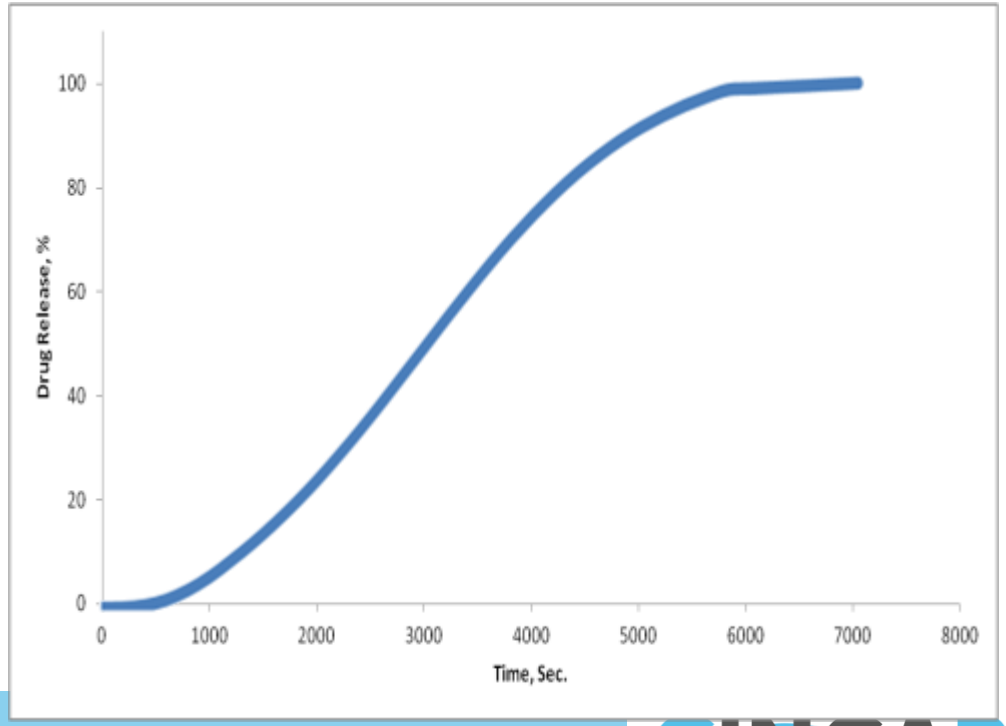
Virtual Integrated Design: from Lab to CAD

In-silico test of the dissolution profile

In-silico design of n formulations, i.e. design space exploration according to ICH Q 8 (R2)



- Calculation of dissolution profile



Benefits: Time + Quality + Security etc

1. Time: shortening time to market

- Faster time to develop final solid formulation
- Reduction of the number of lab tests
- Clinical testing with the marketable formulation
- Tablet design redundant after clinical trials phase 2c
- Bioequivalence test redundant after clinical trials phase 2

2. Security: enhancement

- Calculated risk of process deviation
- Final formulation during all 3 clinical trials phases

3. Reverse Engineering: possible for known excipients

4. Quality: improvement

- Sensitivity of formulation (ICH Q8/R2)
- Computable consequences of production deviations
- Storable and retrievable expert knowledge

Services, which can be offered by CINCAP

For Originator Companies

- Full license for F-CAD platform for a “Right, First Time” R&D and support
- Market ready tablet formulations already for Clinical Phase I
- Support to realize workflow “Right, First Time”
- In-silico scale-up support, manufacturing “Right, First Time”
- Support to facilitate and speed-up registration process
- Full support for Life Cycle Management and Formulation Patent Extension

For Generic Companies

- Fast copy of originator formulation by reverse engineering
- Sensitivity analysis of robustness of originator formulation according to ICH Q8 (R2)
- Support to improve robustness and bioequivalence testing with originator formulation
- No difference in development time for a fast or slow release tablet formulations!
- F-CAD enables to create combination medicines from the original drugs.

For Start-up drug substance & Virtual Pharma Companies

- Contract R+D & Manufacturing of Clinical Samples (according to ICH Q8)
- Support for formulation patents (tested in-silico)
- F-CAD enables to optimize portfolio.

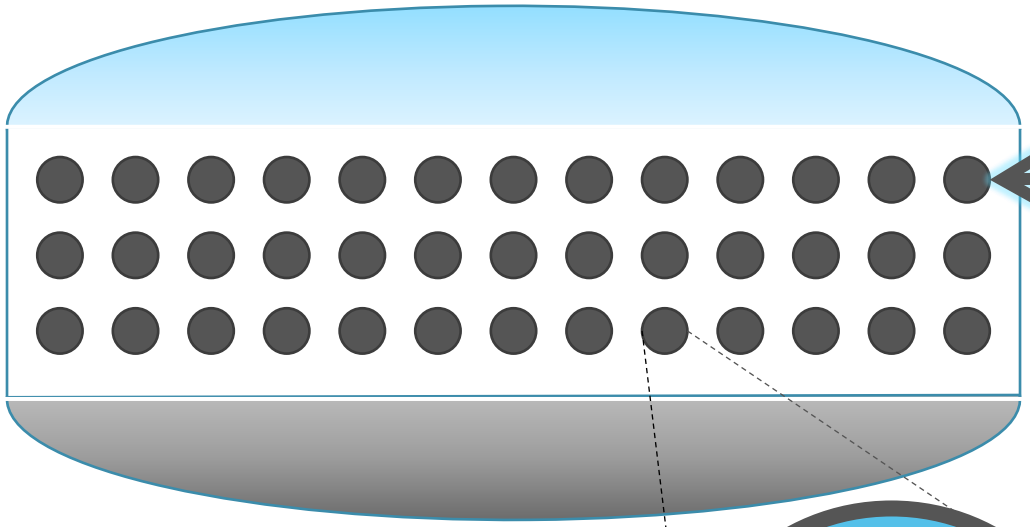
Example of Combi-Dosage Form

Total drug load with 6 API: 96.5mg

Nano-milled

Drug 3 **10mg**
Drug 4 **50mg**
MCC 60mg
AcDiSol 5mg

Layer 1



Drug 2 **10mg**

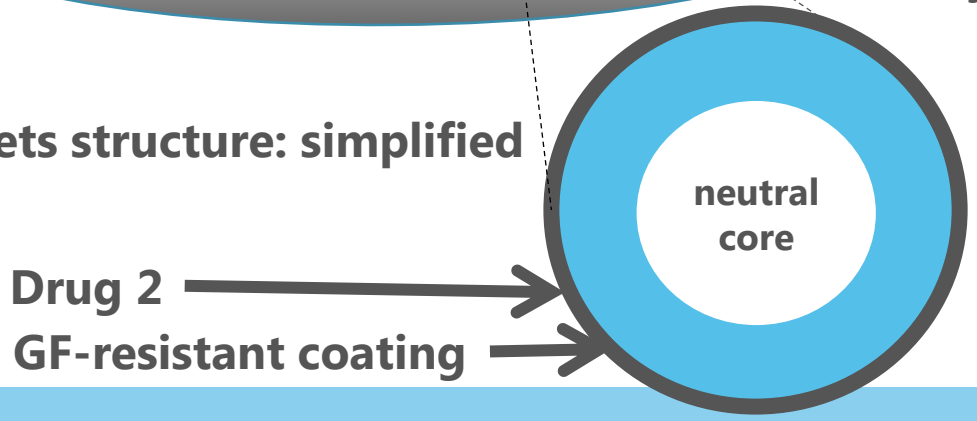
Layer 2

Drug 5 **12.5mg**
MCC 120mg
AcDiSol 10mg

Layer 3

Drug 1 **10mg**
Drug 6 **2mg**
MCC 132.5 mg
AcDiSol 5mg

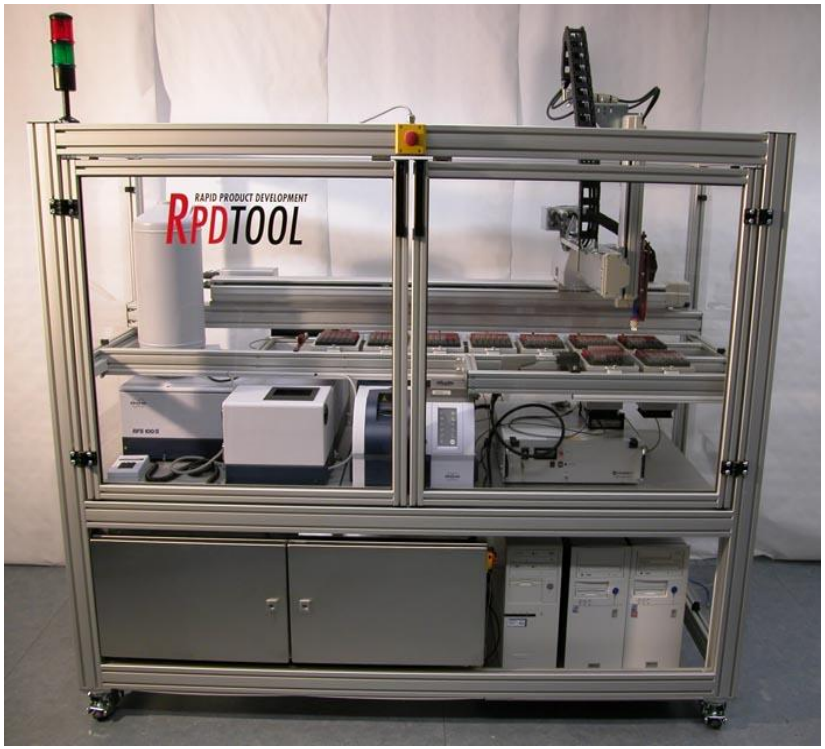
Layered pellets structure: simplified



CINCAP

Automated Stability/Compatibility testing e.g. for Combi-dosage forms

RPD Tool Technologies GmbH, Muttenz



Our Aspiration