Virtual Integrated Design for Real Medicines

In silico Development Technology:

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

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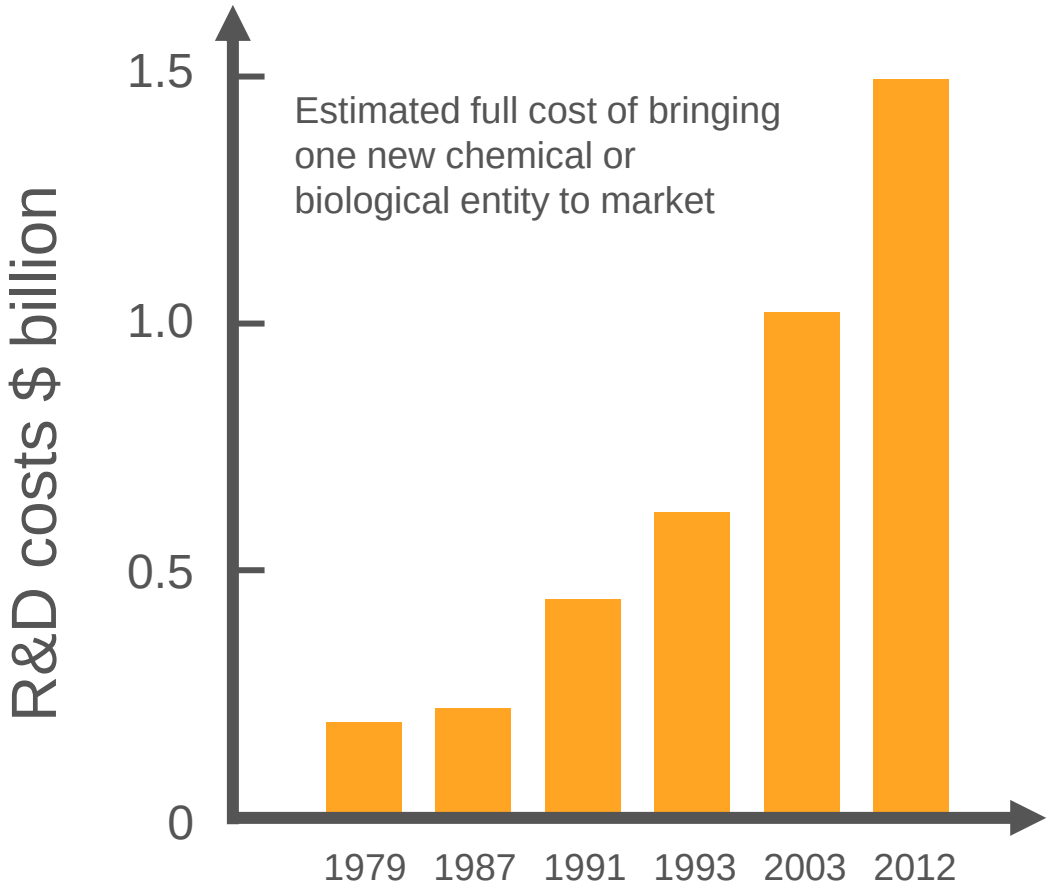
CINCAP LLC

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

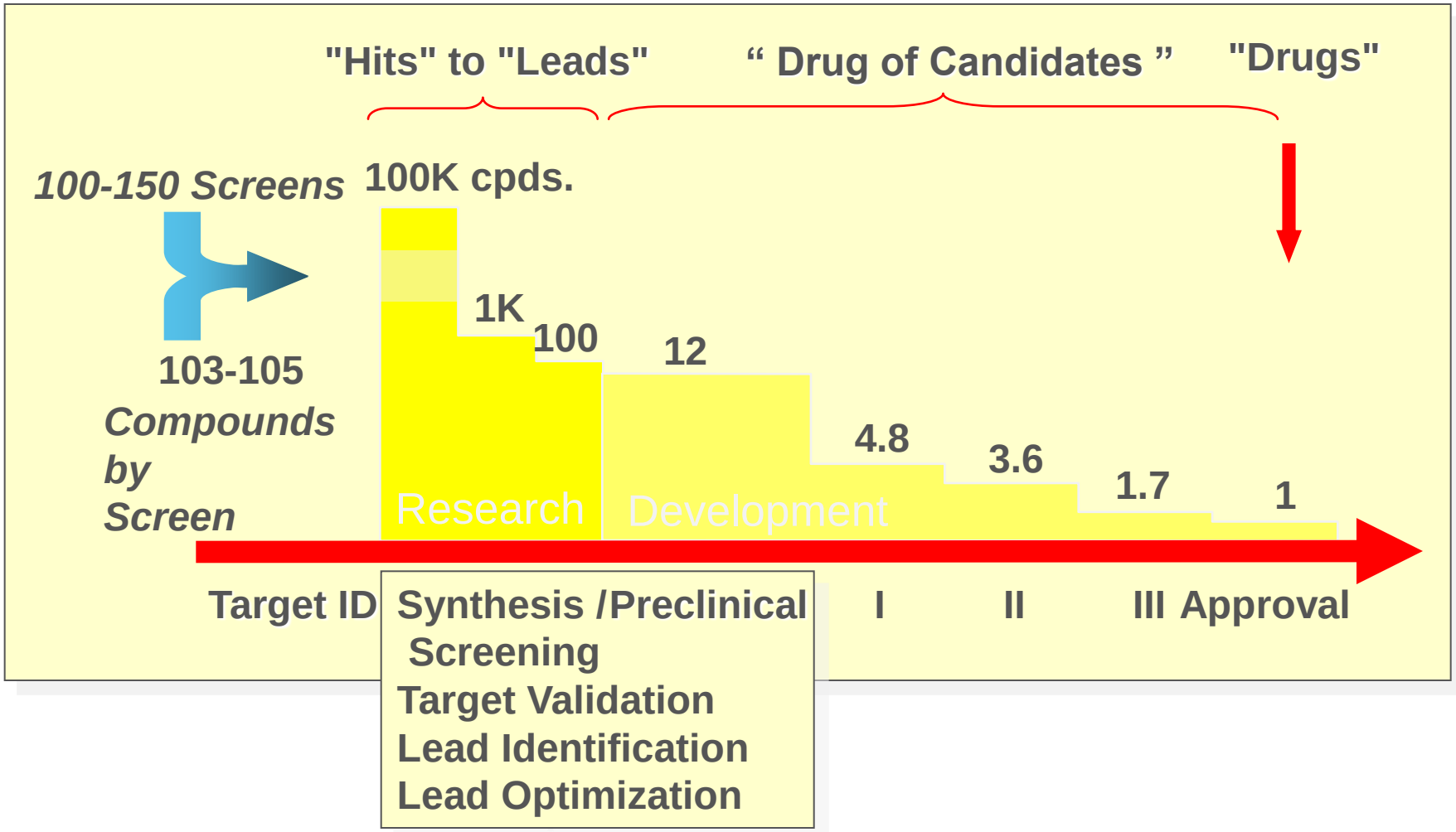
- Cost cutting
- Efficiency increase

AstraZeneca example:

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

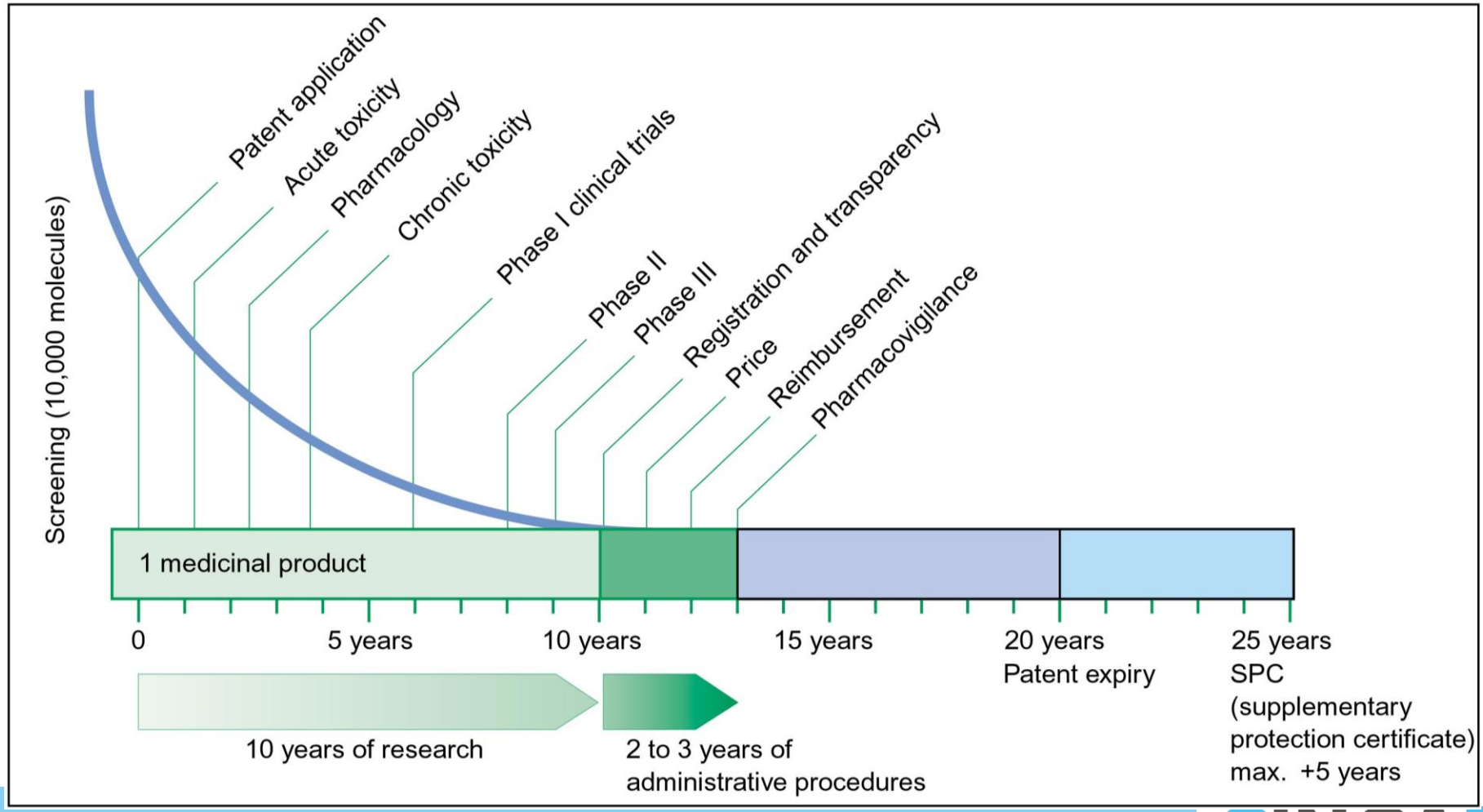
Source of Costs: Attrition rate

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



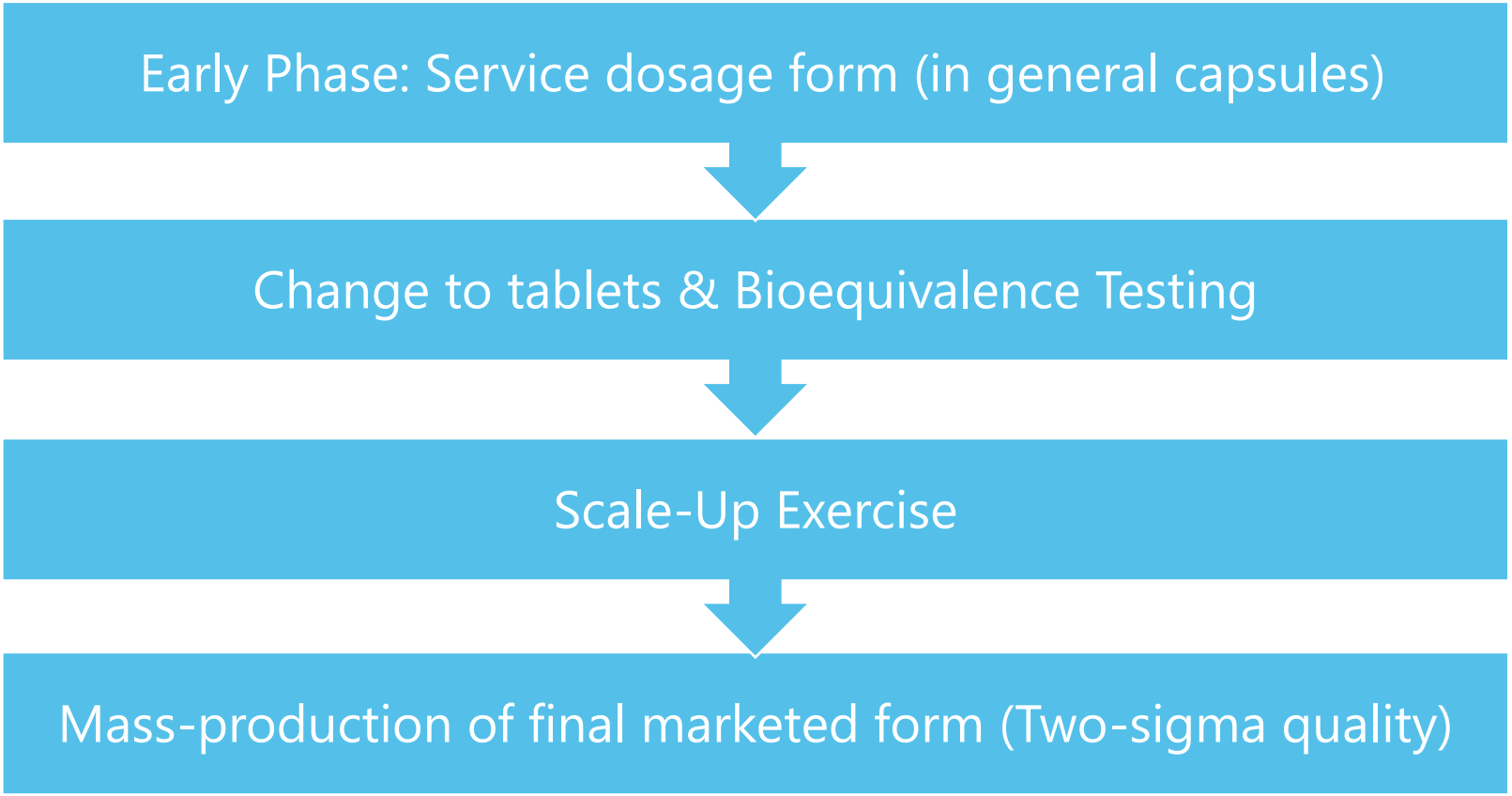
Development & Lifetime

Development and lifetime of a medicinal product (Originator)

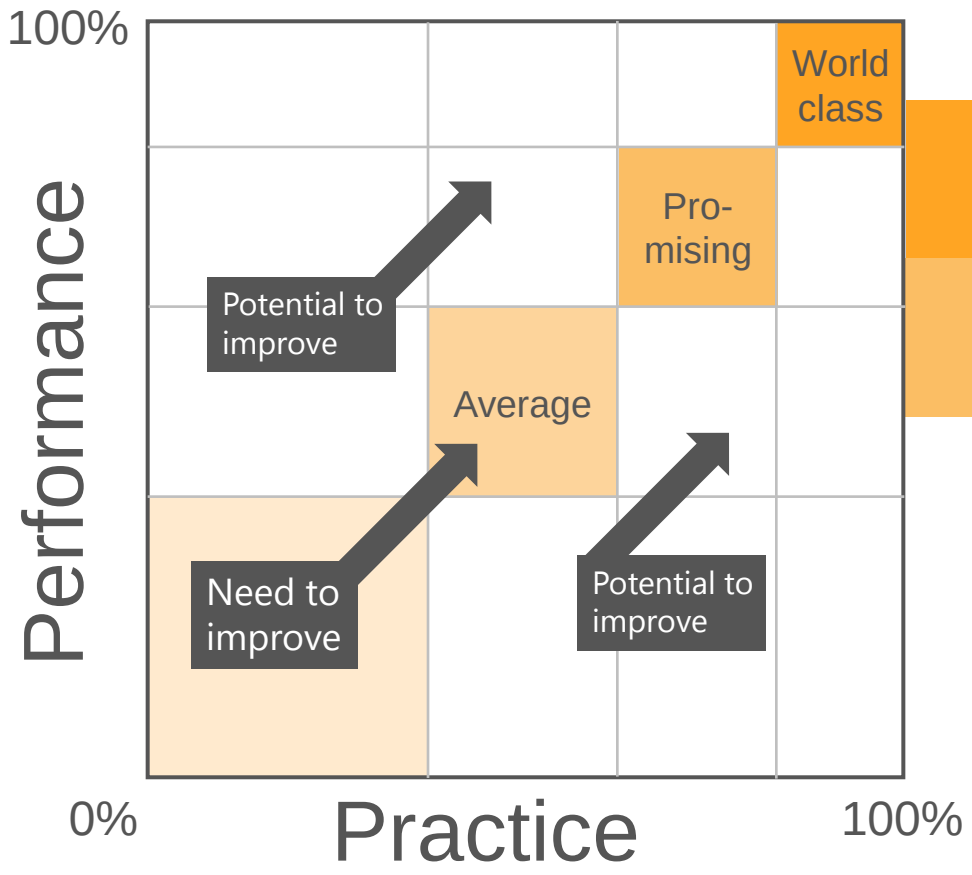


What is “Right, First Time” ?

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

↓

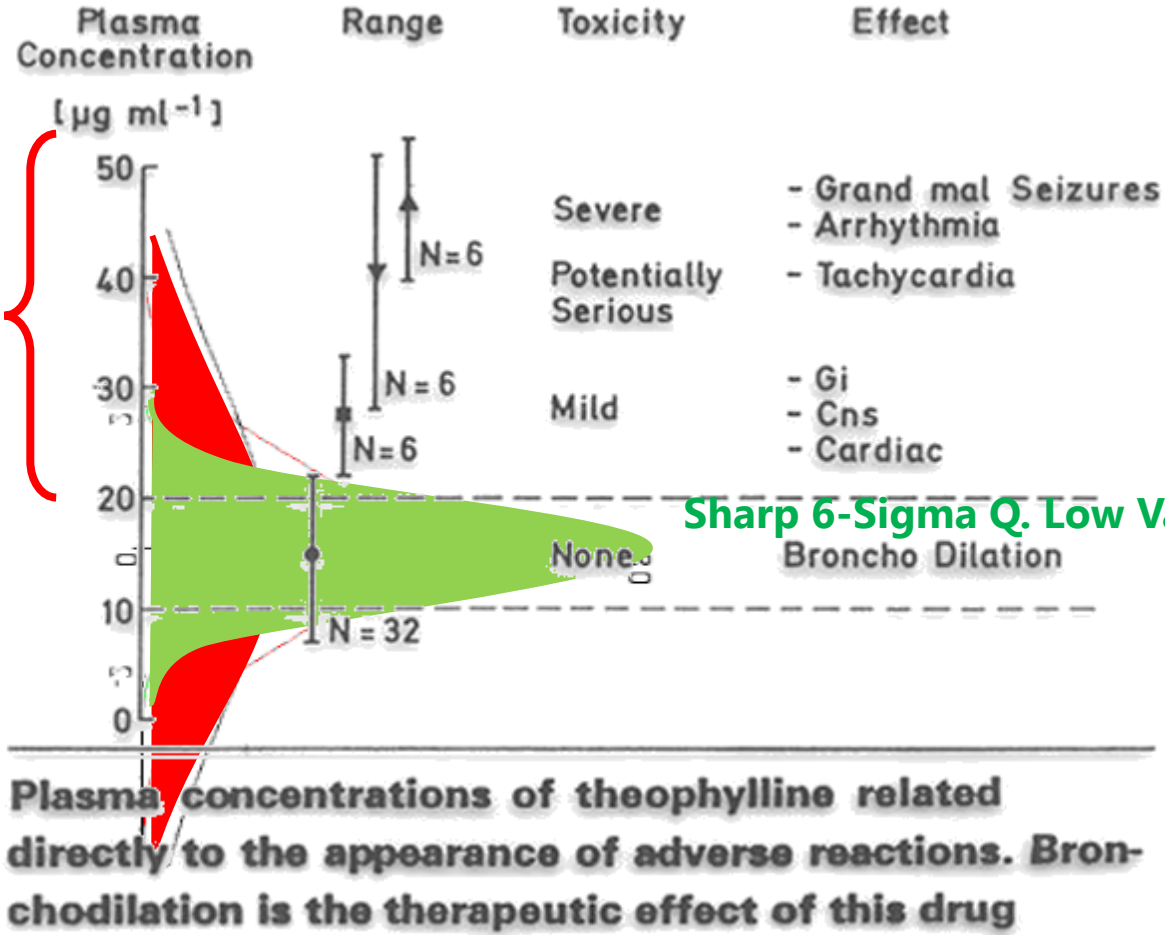
Scale-Up Exercise (computer-assisted)

↓

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

Benefit of 6-σ Formulation

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

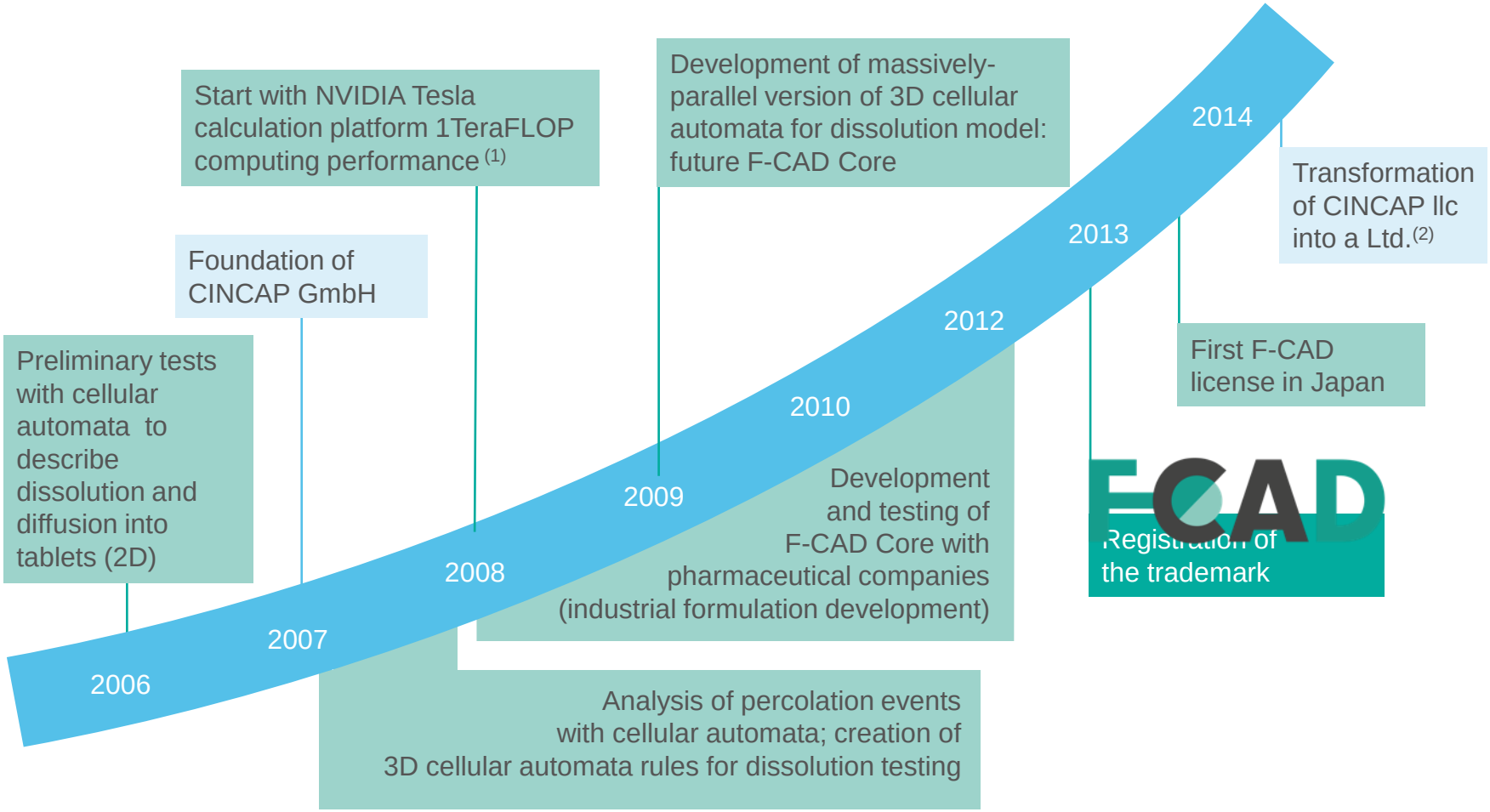


2-Sigma Formulation

Sharp 6-Sigma Q. Low Variab.

< 2-Sigma Q. High Variability

CINCAP Development

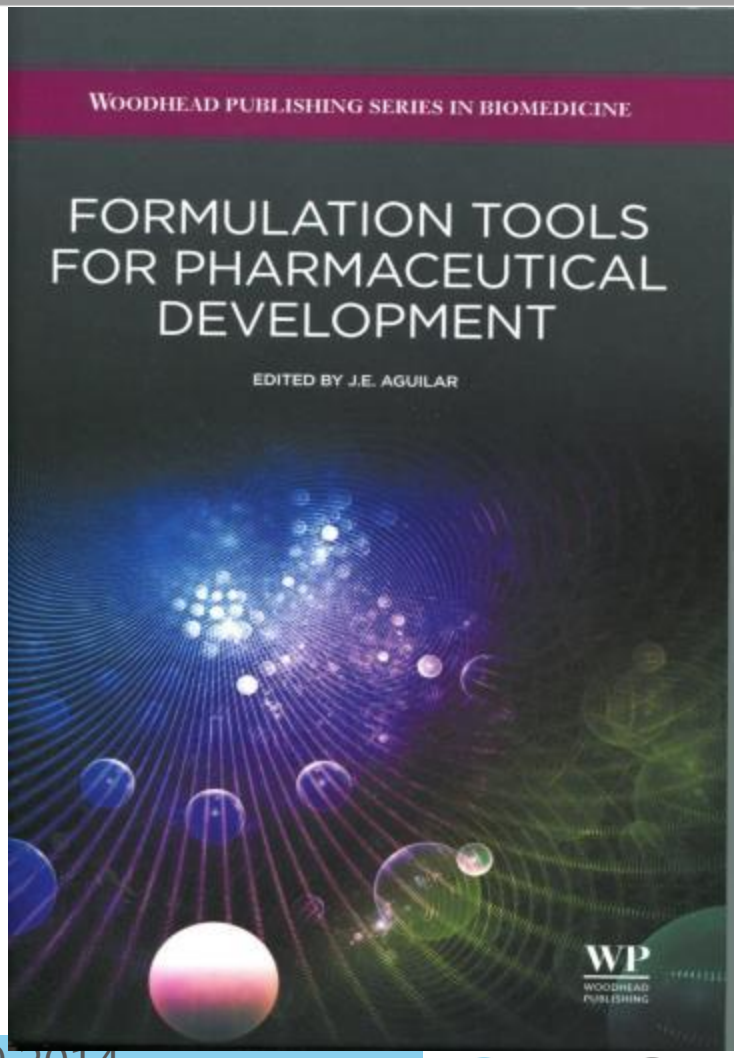


Remarks: (1) At this time the computing platform with the highest processing capacity in Switzerland; (2) Ongoing

Eine "Extrapolation"
der Biopharmazie im Hinblick
auf die Pharmatechnologie
führt zum Schwerpunkt

Computational (Bio)Pharmacy incl.
Computational Pharmatechnology

i.e. Formulation Tools such as
"Expert" Systems, in silico design



Performance benchmarking of CA-based models and standard modeling methods

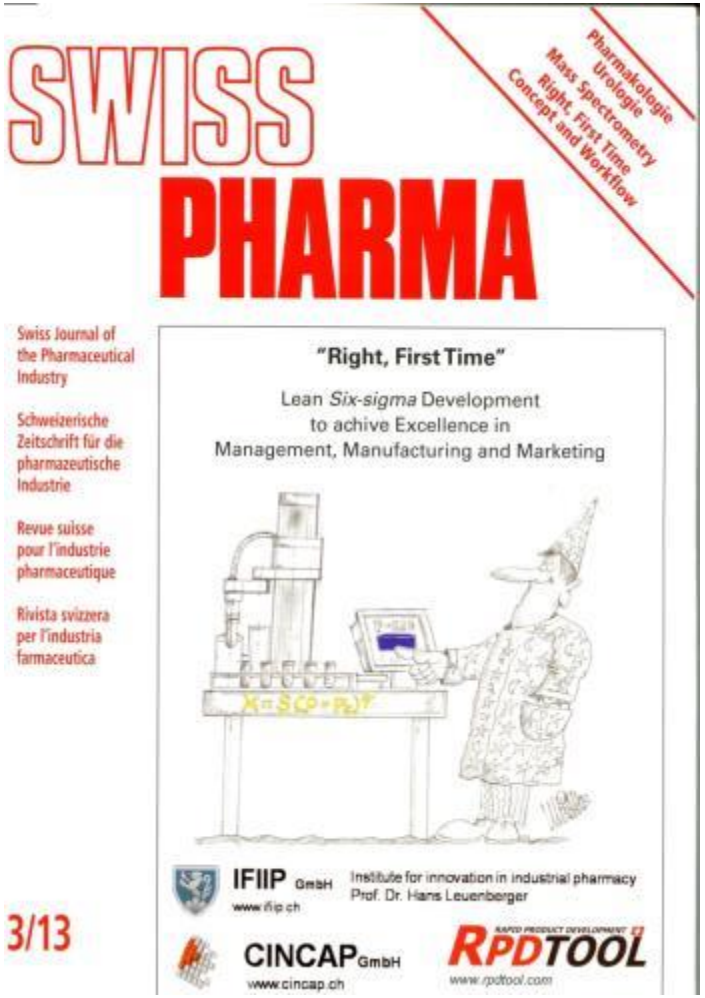
	CA-based models	DEM/FEM
Dissolution Simulation	yes	Yes
Swelling/diffusion	yes	Limited
Effect of granulation/milling	yes	Yes
Compaction Simulation	yes	limited
Memory usage	Extremely low	High
Particles per simulation	up to 1 000 000 000	Ca. 1 000 000 max.
Calculation speed	Up to 250x faster than real experiment	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

Personal Message from Janet Woodcock concerning the article "Right, First Time" in SWISS PHARMA 3/13

"Thank you very much for sending me your provocative article on right first time. It is very timely and I certainly hope we will see widespread adoption in industry. I'm not sure many in industrial pharmacy are aware how predictive in silico approaches have become. FDA is certainly supportive

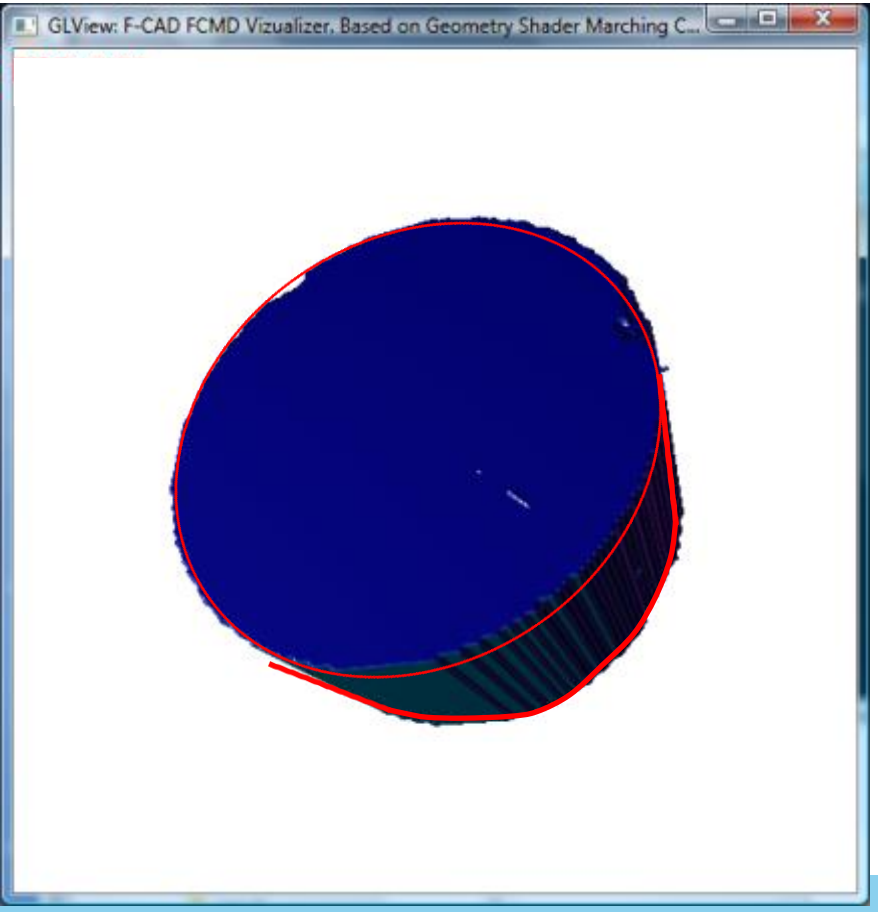
Email to Prof. Hans Leuenberger on May 8, 2013

Janet Woodcock, MD Director,
Center for Drug Evaluation
and Research

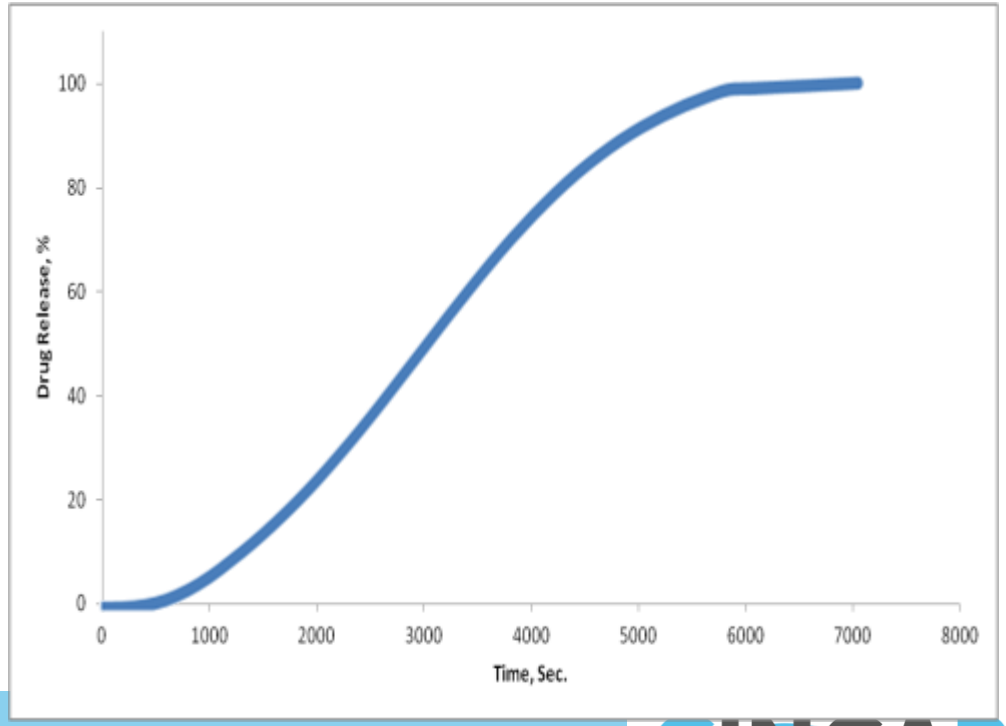
Virtual Integrated Design: from Lab to CAD

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.

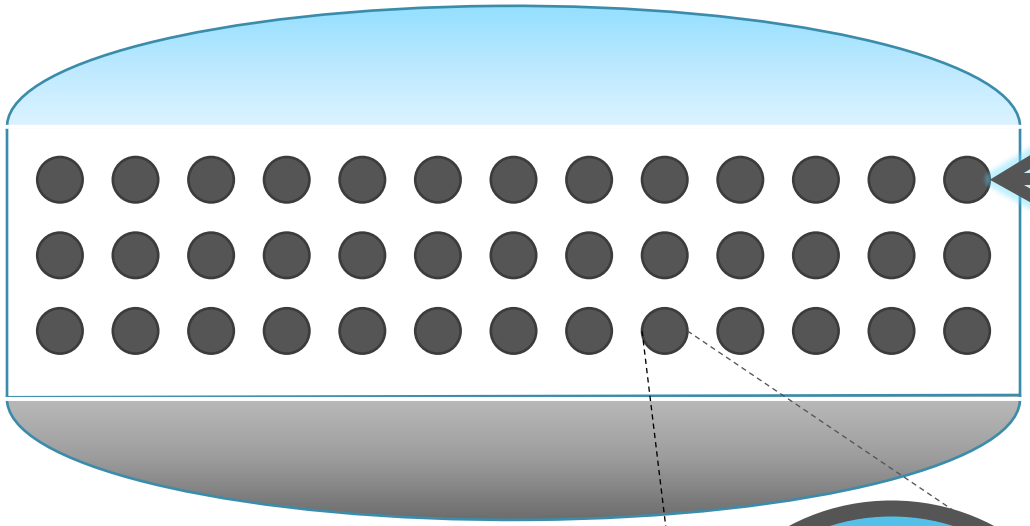
Example of Combi-Dosage Form

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**

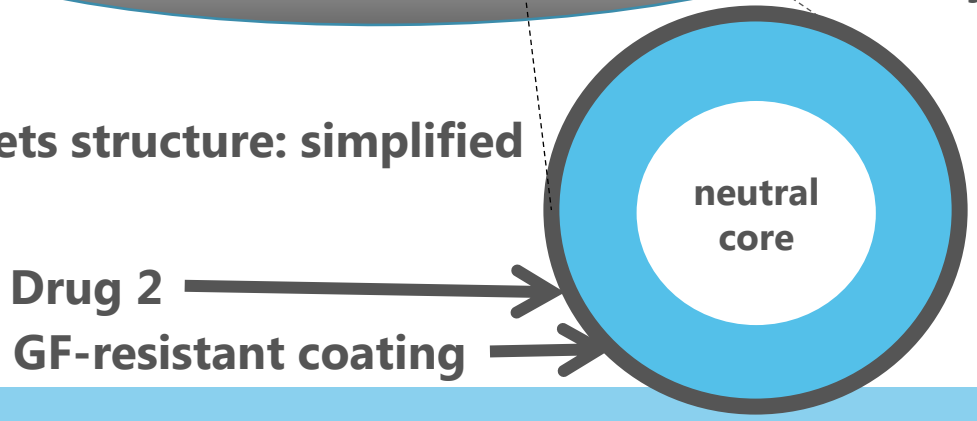
Layer 2

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

Personal Message from Janet Woodcock

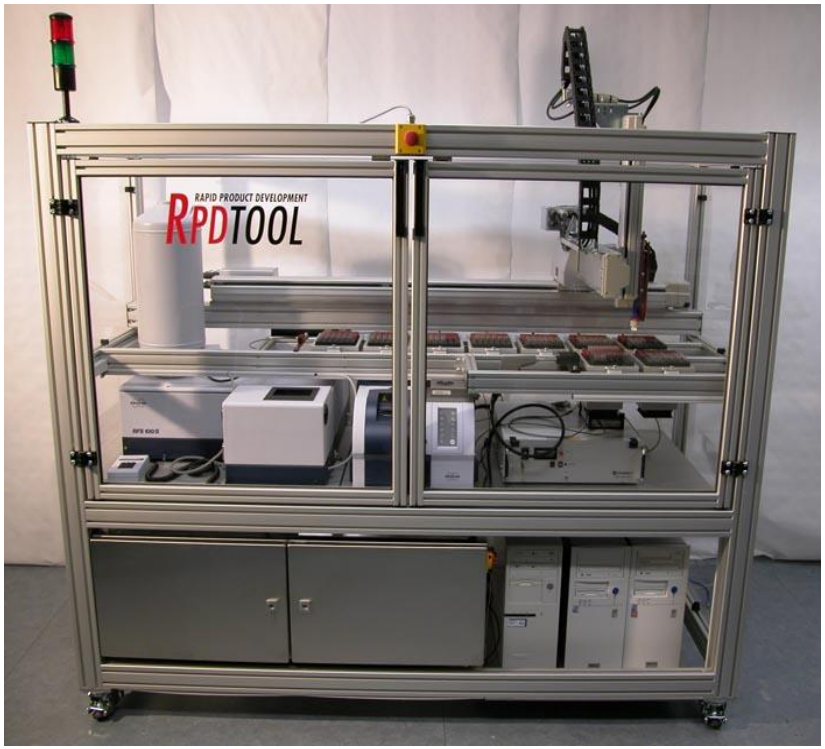
"Wow, very interesting. Getting to single tablets for the elderly (and others) will require this sort of dosage/manufacturing flexibility. Hope you get uptake!!jw"

Email to Prof. Hans Leuenberger on June 26, 2014

Janet Woodcock, MD Director,
Center for Drug Evaluation
and Research

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

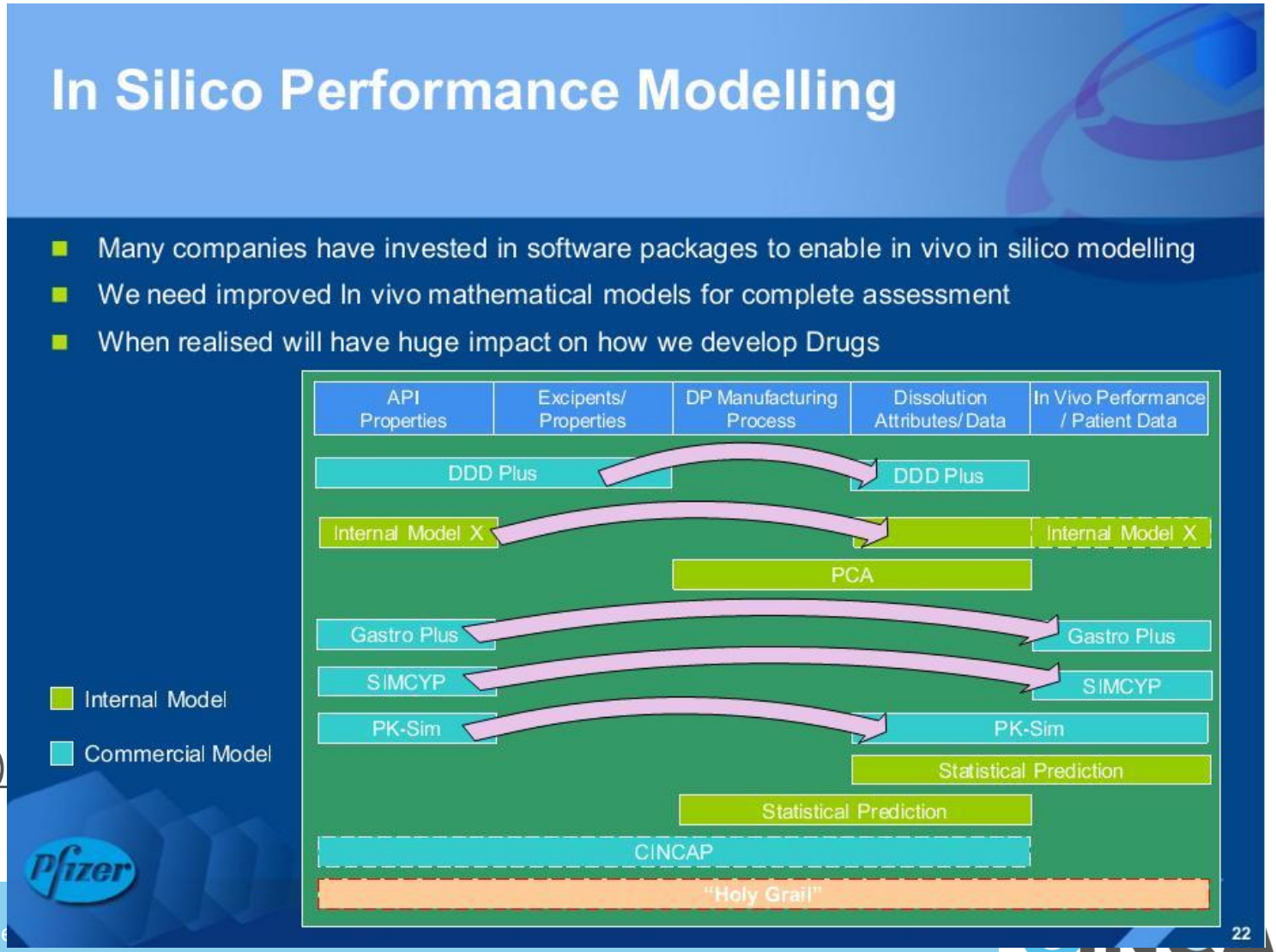
RPD Tool Technologies GmbH, Muttenz



Galenus Privatstiftung

Fördernde Kraft in der Pharmazeutischen Technologie

F-CAD of CINCAP: (2nd from Bottom) Covers Already A major Part of the Holy Grail (bottom) Slide Sally Greb Pfizer (http://pasg.org.uk/..)



Our Aspiration

Wyss Multiscale Modeling Center for Sustainability and Security, Basel

Outlook by Extrapolation from the past*):

- **The centuries of chemistry, physics and biology followed by**
- **The century of nanoscience and nanotechnology**
  => Convergence of Chemistry, Physics and Biology! Followed by:
- **The century of in-silico models of complex systems**
  =>Convergence of all sciences and scales, i.e. natural, medical & humanities!

=> Ignition and Implementation of this new Megatrend by the Basel Wyss Institute!

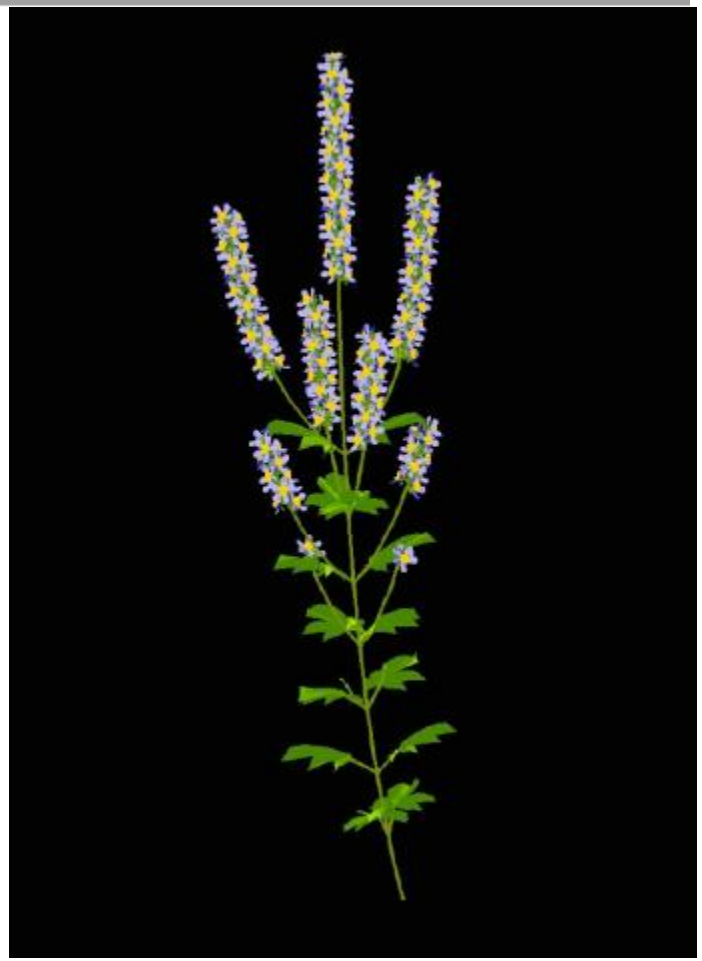
***) The Rise and Fall of Megatrends in Science,** Margit Leuthold, Hans Leuenberger, Ewald R Weibel, Schwabe Verlag Basel, 2002

An *L-system* or *Lindenmayer system*, after Aristid Lindenmayer (1925–1989), is a formal grammar (a set of rules and symbols) most famously used to model the growth processes of plant development, though able to model the morphology of a variety of organisms. Przemyslaw Prusinkiewicz & Aristid Lindenmayer, "The Algorithmic Beauty of Plants," Springe 1996. http://en.wikipedia.org/wiki/L-System

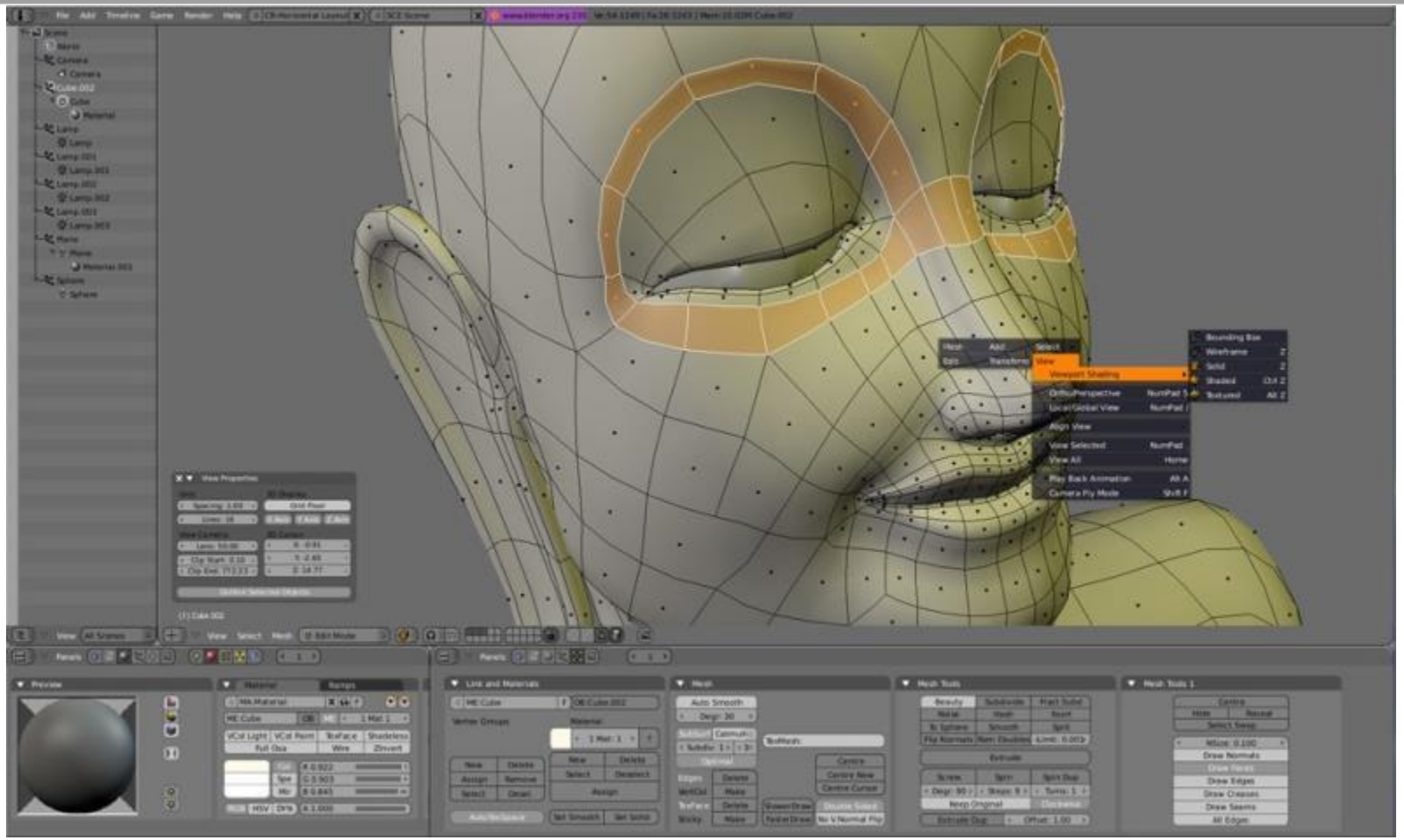
To the right: A model of a member of the **mint** family that exhibits a basipetal flowering sequence.

Cauliflower (approximate self-similarity)

<jupiterimages.com>



http://algorithmicbotany.org/papers



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