SBA Academy: Dosage Form Design: From Classical to "Right, First Time" Workflow

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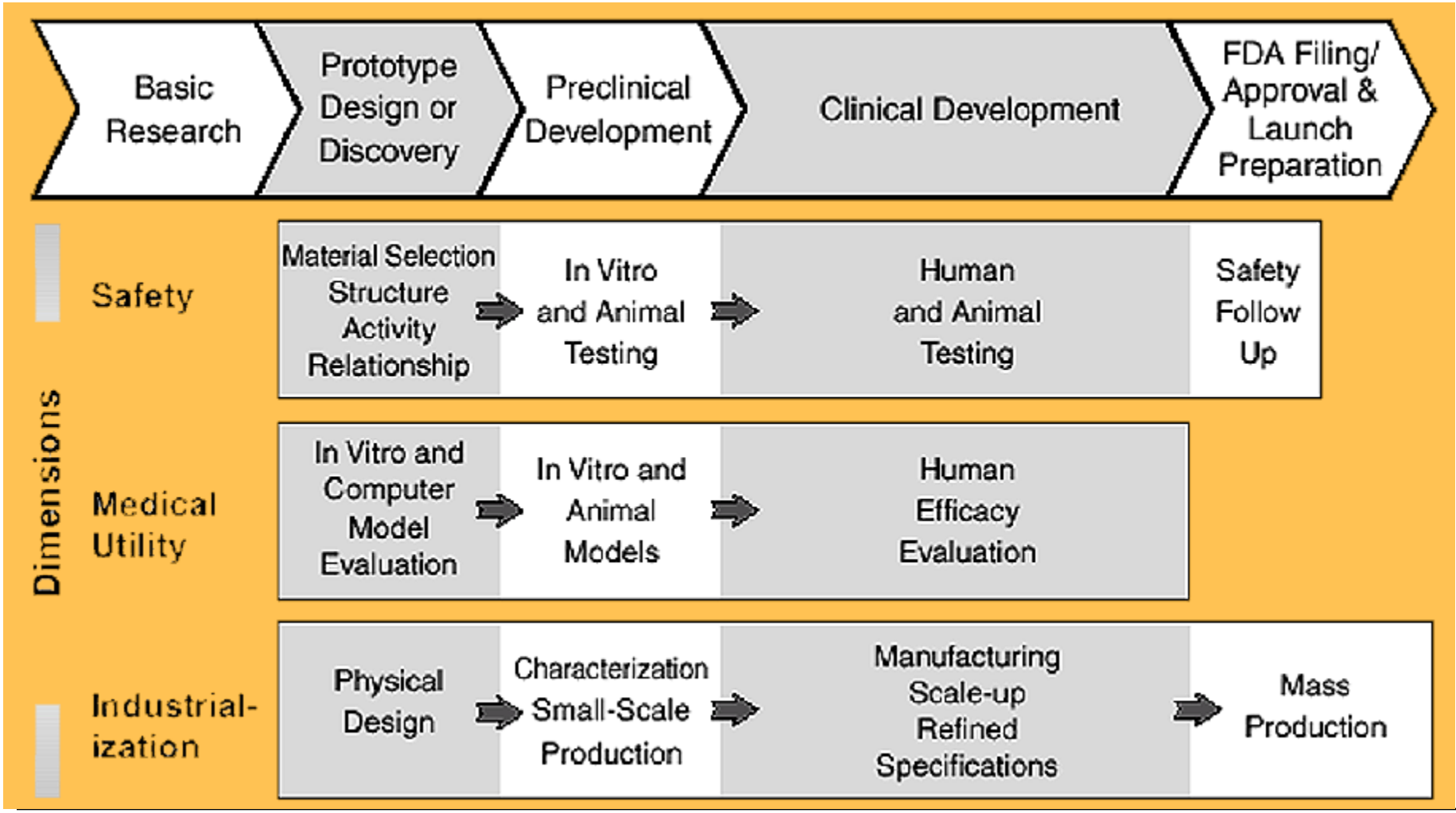
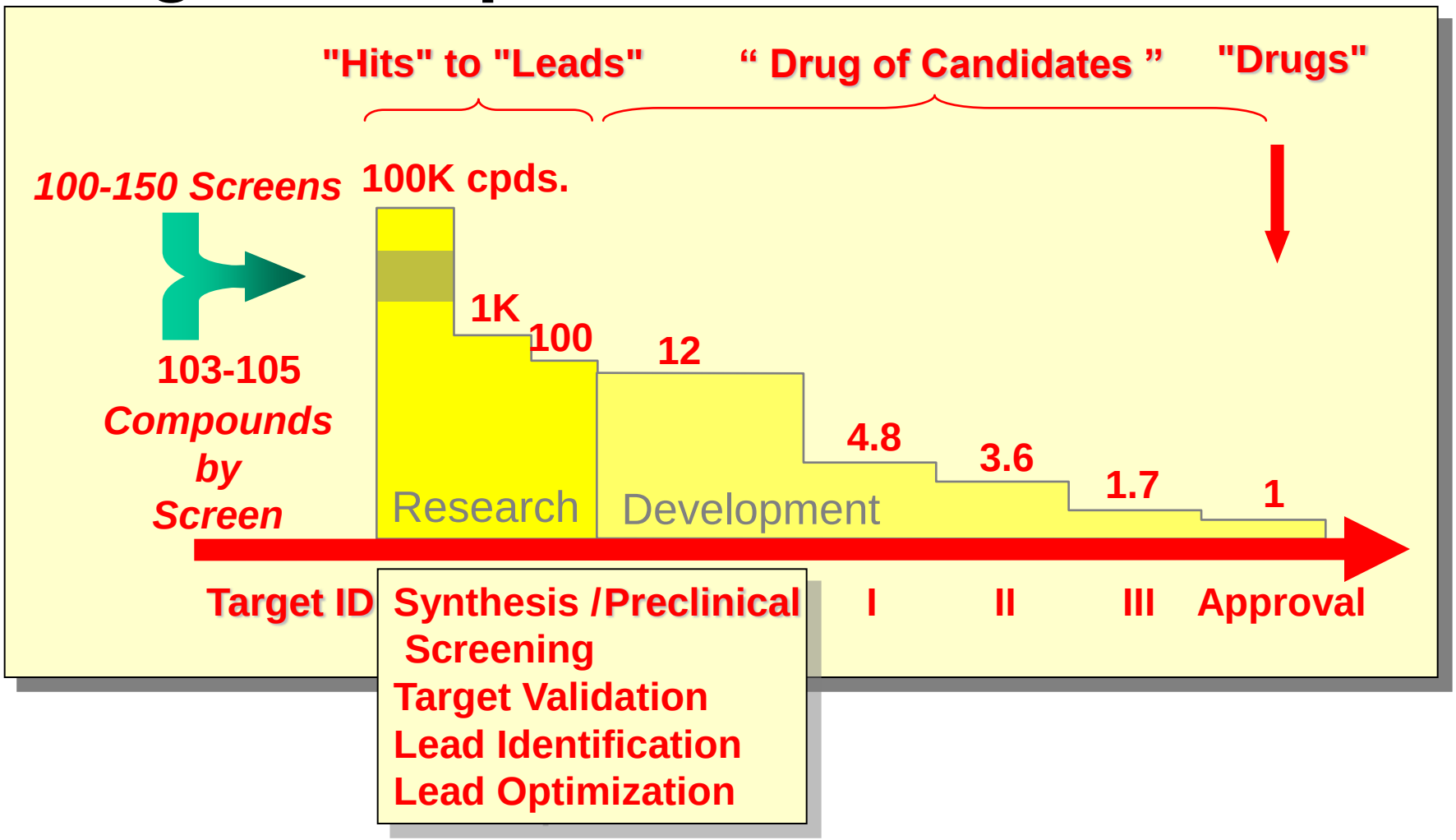
Drug Development: Critical Path Initiative (FDA)

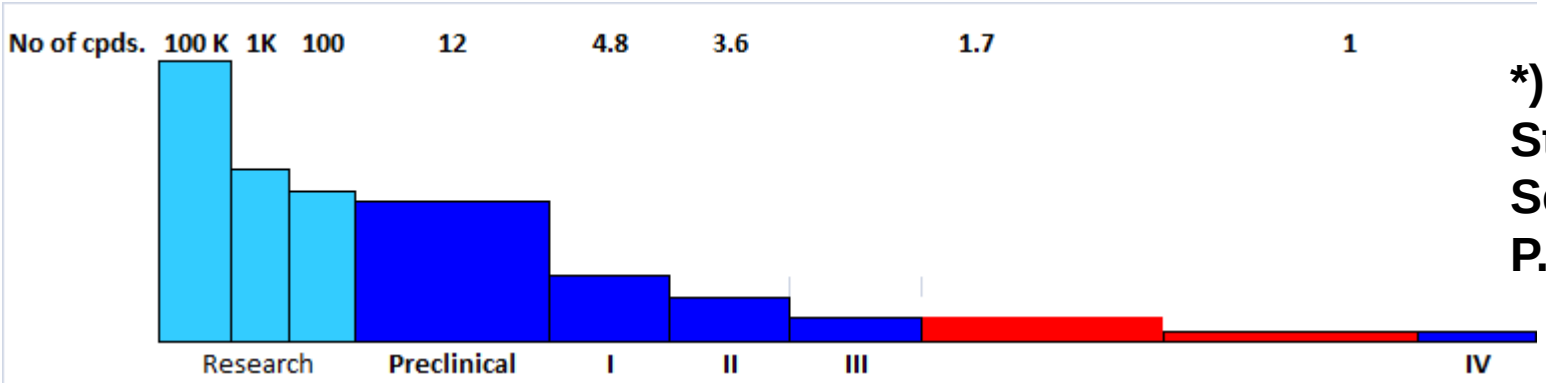


Drug Development



Drug Development

Conventional Workflow: Early development of a sterile dosage form for i.v. injection* -> Pharmacokinetic study, Bioavailability:

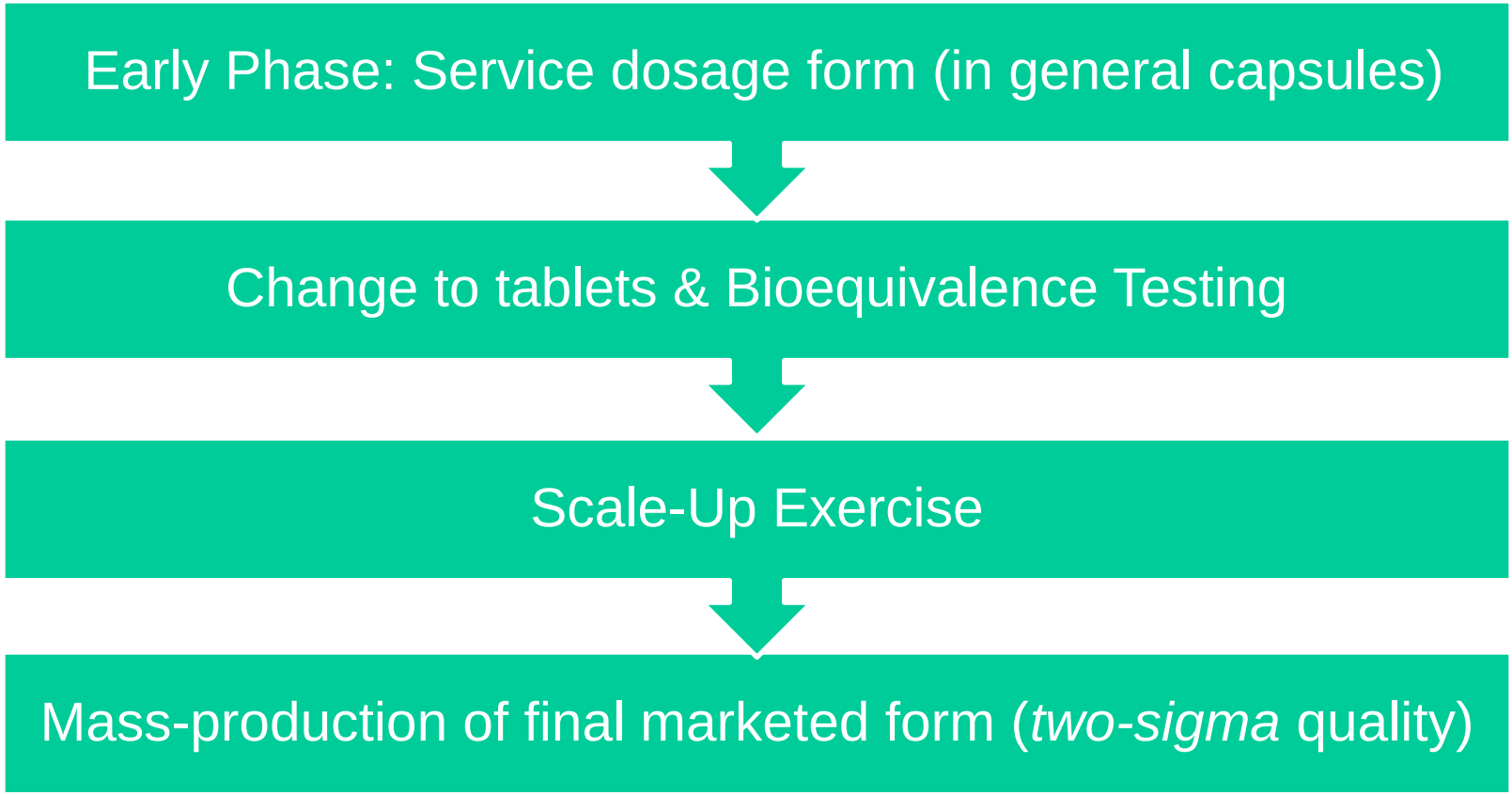


*)Oral solutions, Sterile Injections: See presentation P. Ruffieux

Change from a service dosage form, a capsule formulation to the final marketed dosage form, a tablet formulation at Phase II c → Bioequivalence Test is needed: ***Bioavailability of tablet and capsule should be identical***

Drug Development

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



Drug Development

Conventional Workflow: Development time up to 12 years!
Goal: Maximum -> 6 years

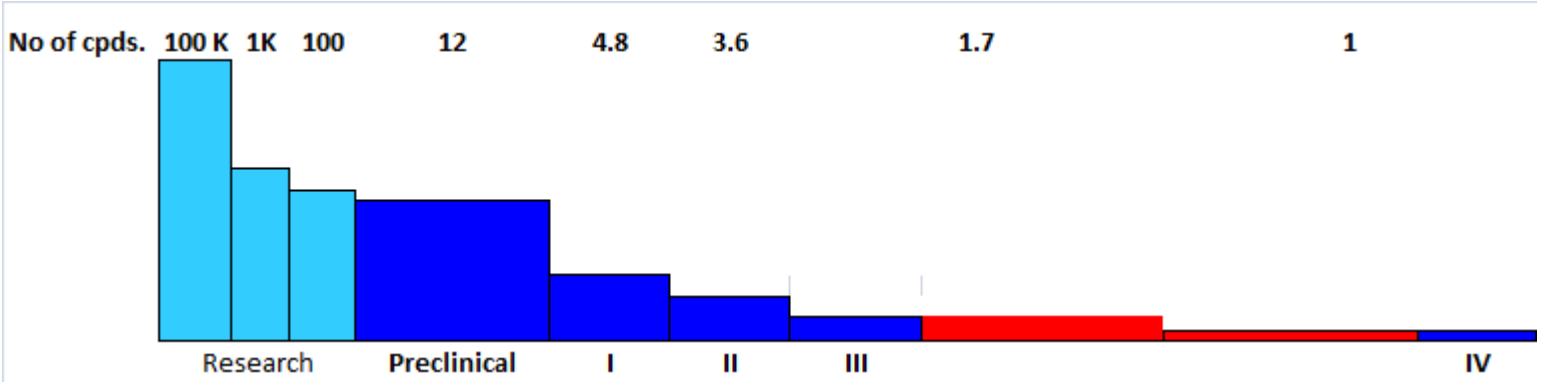
«Right, First Time workflow»
Sterile i.v. Injection is as a reference for the bioavailability always needed (see presentation Dr. P. Ruffieux)

Difference to the conventional, classical workflow:
Adoption of the workflow of the automotive and aircraft industry: Design and Test of the Vehicle (Drug Delivery System: Tablet) fully in-silico, i.e. computer-aided design and dissolution tests!

-> Save drug substance, laboratory work and optimize to Six-Sigma Quality -> reducing time to market!

Drug Development

Conventional Workflow: Late development of the final marketed dosage form -> Normally close to the end of phase II:



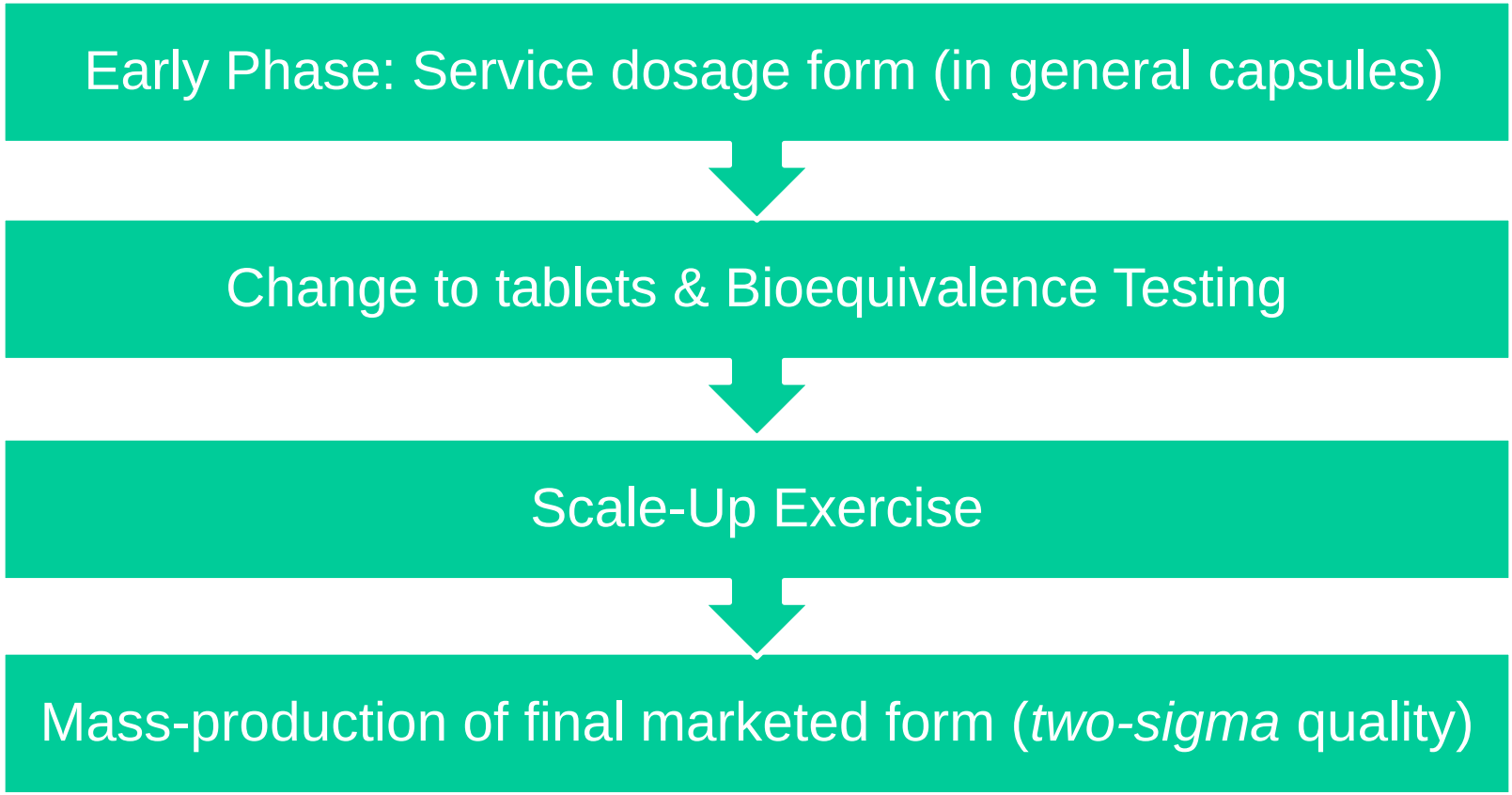
Rescue & repair actions

for non robust formulations

at a late stage!

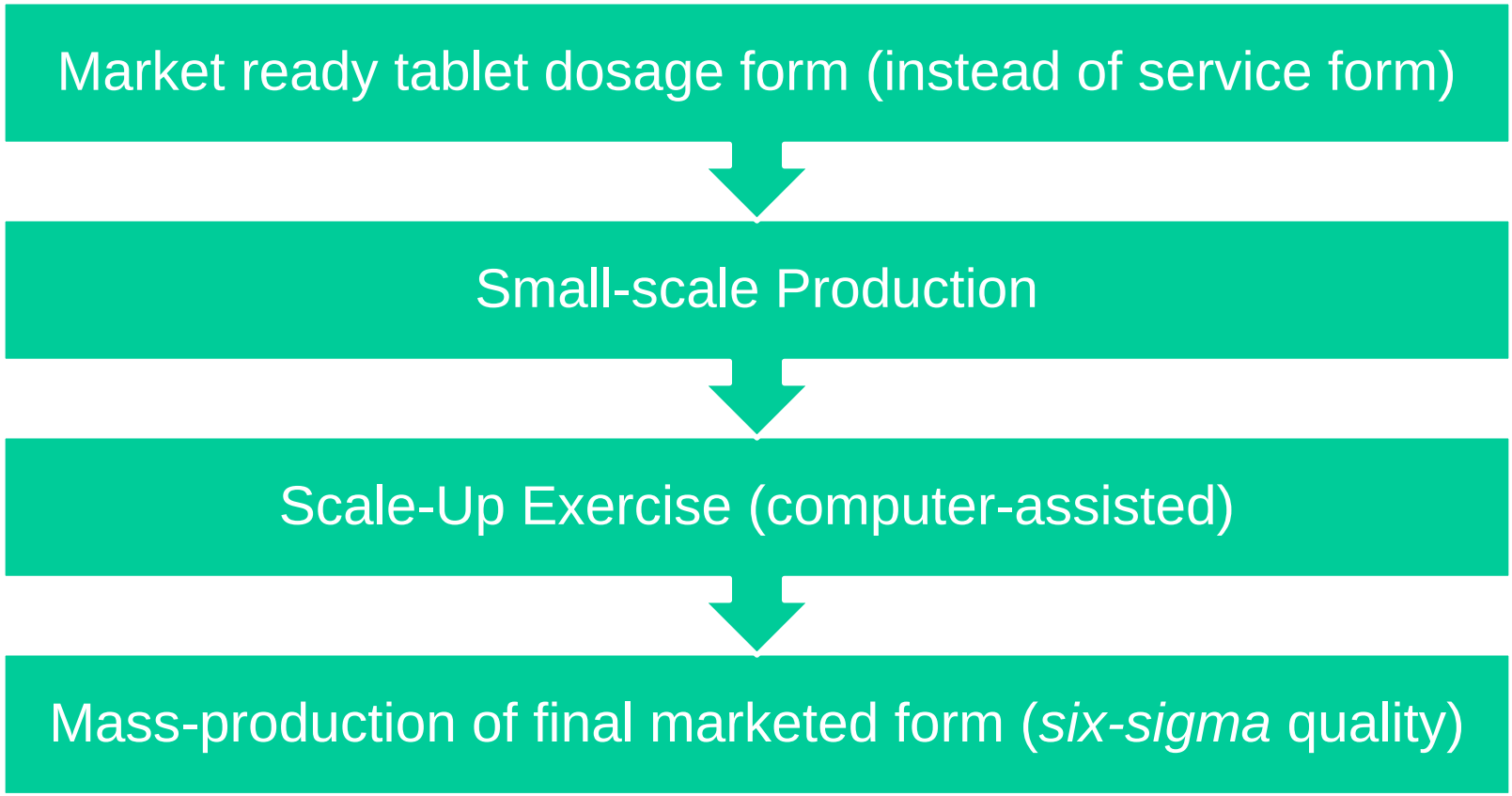
Drug Development

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



Drug Development

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



Drug Development: Preformulation Activities

1) **Physico-chemical characterization of the API such as** solubility & chem. stability (different media, pH, ionic strength), light sensitivity, intrinsic dissolution rate, polymorphy, crystalline structure, salts, pseudopolymorphic forms, particle size distr. (psd), shape, true density (!) etc.

2) **Drug-excipient chemical compatibility program** to select excipients for long term chemical stability of the API using a suitable **factorial design**, taking into account possible interactions between the API and excipients present in the formulation.

Drug Development: Preformulation Activities

Drug-excipient chemical compatibility program (Example)

Factorial design with 1% (w/w) API and functional excipients

Factor	*Level*		*Conc.(excipient)*
A	- 1	Lactose	69 % (w/w)
(Filler)	+1	Mannitol	69 % (w/w)
B	- 1	Stearic Acid	5 % (w/w)
(Lubricant)	+1	Magnesium Stearate	5 % (w/w)
C	- 1	Maize Starch	20 % (w/w)
(Disintegrant)	+1	MCC Sanaq burst*)	20 % (w/w)
D	- 1	PVP	5 % (w/w)
(Binder)	+1	HPC **)	5 % (w/w)
E	- 1	Dry (Dessicant added)	
(Storage Condition)	+1	High Humidity	

**) formerly: Gelatine

*) Polymorph of normal MCC,
see RFT/Computer-Aided Scale- up
SWISS PHARMA 32 (2010) 3-13

Factorial Design: Confounding E = ABCD (Stress test, 4 weeks, 50 °C)

	A	B	C	D	E	50°C	4°C
1 = e	-	-	-	-	+	59.6	100
2 = a	+	-	-	-	-	86.4	98.3
3 = b	-	+	-	-	-	95.0	98.7
4 = abe	+	+	-	-	+	**97.0**	96.5
5 = c	-	-	+	-	-	83.4	96.6
6 = ace	+	-	+	-	+	**53.8**	96.7
7 = ce	-	+	+	-	+	93.7	98.5
8 = abc	+	+	+	-	-	**99.7**	96.9
9 = d	-	-	-	+	-	54.1	97.9
10 = ade	+	-	-	+	+	**45.8**	99.0
11 = bde	-	+	-	+	+	92.8	95.3
12 = abd	+	+	-	+	-	96.1	98.0
13 = cde	-	-	+	+	+	**53.6**	98.7
14 = acd	+	-	+	+	-	64.7	99.6
15 = bcd	-	+	+	+	-	94.0	96.4
16 = abcd	+	+	+	+	+	**96.3**	97.2

Important Conclusion I

API-Excipients chemical compatibility program

-> the importance has been recognised

->to chose the right «robust material» to construct the «drug vehicle»

However, as literature shows, a corresponding

API-Excipients galenical compatiblity program is not existing!

-> The excipients are mostly chosen by the experienced formulator and carry the «Signature» of the formulator
Is this a good choice?

-> Necessity for a galenical API-Excipients Screening Program:

TECHNOLOGICAL (galenical) SCREENING PROGRAM -> Testing of API with appropriate amount of excipients -> Checking galenical performance with factorial design using PRESSTER equipment ->

Factor	*Level*		*Conc.(excipient)*	
A	- 1	Lactose	76 % (w/w)	with API *)
(Filler+Drug load)	+1	Mannitol	76 % (w/w)	with API *)
B	- 1	Stearic Acid	1 % (w/w)	*) **Recommended**
(Lubricant)	+1	Magnesium Stearate	1 % (w/w)	**2-3 drug (API) loads: Low dose & High dose**
C	- 1	Maize Starch	20 % (w/w)	
(Disintegrant)	+1	MCC Sanaq burst	20 % (w/w)	
D	- 1	PVP	3 % (w/w)	
(Binder)	+1	HPC	3 % (w/w)	
E	- 1	Low speed (**Presster**)	**Presster = Mechanical Simulator of Rotary High Speed Press**	
	+1	High speed (**Presster**)		

Factor	*Level*	*Conc.(excipient)*	*Drug Substance (API)*		
			Low strength	Mid strength	High strength
A (%, w/w)	- 1	Lactose (%)	71 + 10 API	41 + 40 API	11 + 70 API
(Filler + API)	+1	Mannitol (%)	71 + 10 API	41 + 40 API	11 + 70 API
B	- 1	Stearic Acid	1 % (w/w)		
(Lubricant)	+1	Magnesium Stearate	1 % (w/w)		
C	- 1	Maize Starch	15 % (w/w)		
(Disintegrant)	+1	MCC Sanaq burst	15 % (w/w)		
D	- 1	PVP	3 % (w/w)		
(Binder)	+1	HPC	3 % (w/w)		

Factor E
-1 Low speed
+1 High speed

Presster = Mechan. Simulator of Rotary High Speed Press

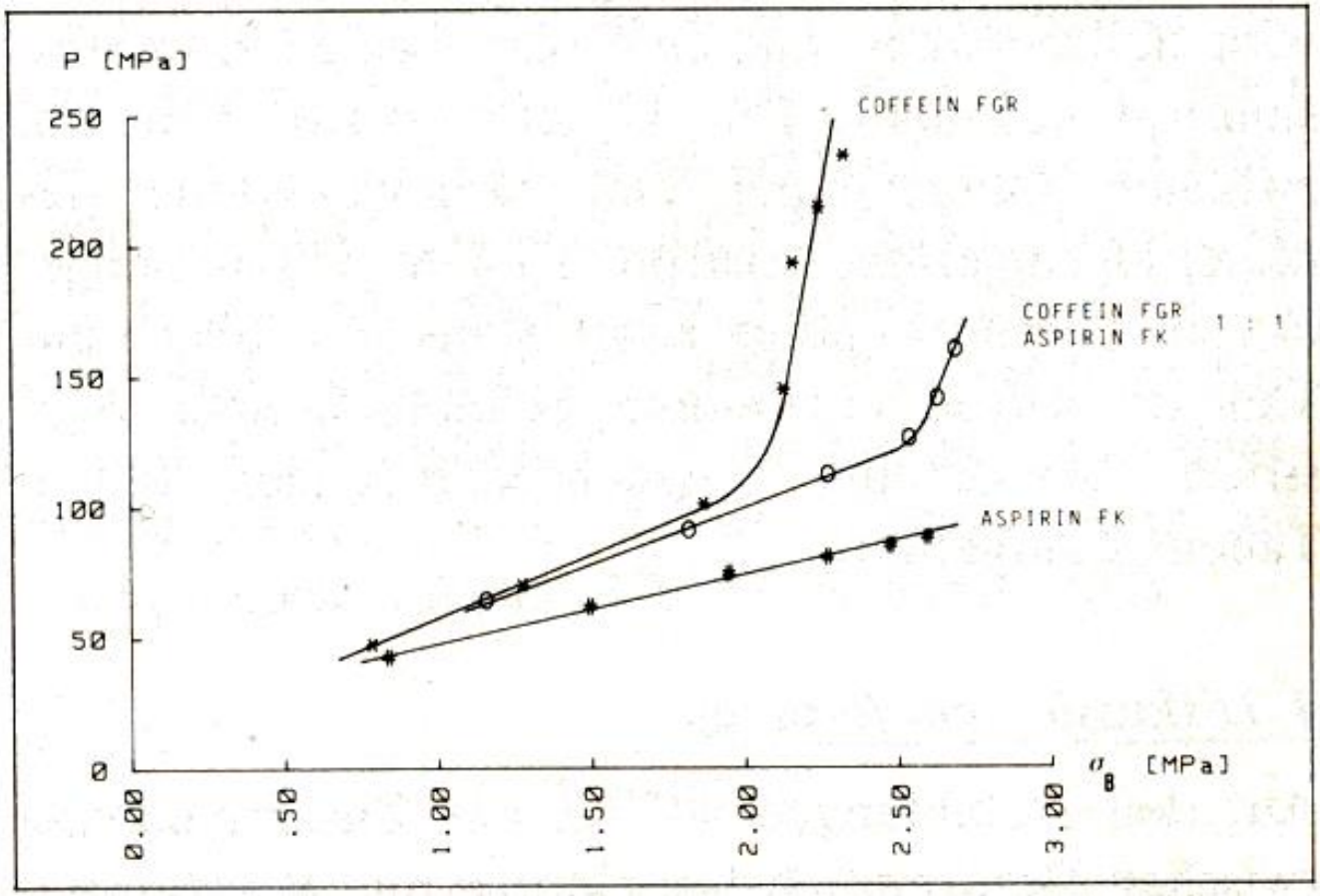
Example of a factorial design for a galenical drug-excipient screening program for the **best technological choice of the functional excipients**.

GALENICAL SCREENING PROGRAM -> Testing of API with appropriate amount of excipients -> Checking galenical performance with factorial design using PRESSTER equipment

GALENICAL SCREENING PROGRAM -> Testing of API with appropriate amount of excipients -> Checking galenical performance with factorial design using PRESSTER equipment

Result	D1.2	D1.3	D1.4	D2.2	D2.3	D2.4
UCPeak (kN)	58.9	37.1	13.1	39.7	19.1	5.5
LCPeak (kN)	55.5	37	14.1	39	19.8	6.2
Peak Ejecti (N)	134.2	78.8	121	2095.7	1306.3	493.8
Take-Off (N)	2.1	1.6	1.3	1.1	0.9	0.8
Weight (mg)	504.9	506.2	506.4	504.7	505.2	504.3
Thickness (mm)	4.52	4.58	4.8	3.64	3.82	4.27
Hardness (N)	>300	>300	>300	144	91	19
Disint. time (sec)	454	426	174	35	12	6

- Prediction of Capping Tendency Before Capping Really Occurs?
  → See paper Jetzer & Leuenberger Pharm. Acta Helv. 59, Nr.1(1984) 2-7



Ratio:
Indentation hardness
Tensile Strength

→ streight line
For no Capping Tendency

→ slope not constant
For Capping Tendency

Summary: Results of Presster

Typical Tabletting Problems & Results of Presster:

- **Lubrication problems - > High ejection force**
- **Sticking of tablets -> High take – off force**
- **Capping of tablets -> % of elastic energy high?**

- **Prediction of Capping Tendency Before Capping Really Occurs?**
  → See paper Jetzer & Leuenberger Pharm. Acta Helv. 59, Nr.1(1984)
- **->download at www.ifiip.ch**

→ Ratio Indentation Hardness/Tensile Strength not constant

Next Slide: Effect of tabletting speed

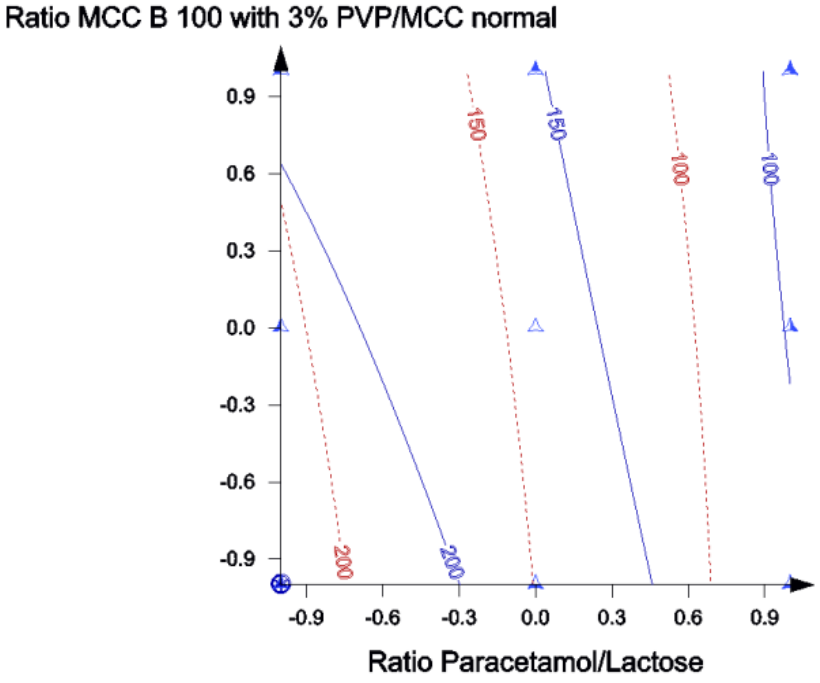
Slow: 10 800 TPH **Fast: 108 000 TPH**

A (API/Filler) **API/Lactose** **3 Levels (-1,0,+1)**

C&D (Disintegrant & Binder) MCC Sanaq burst (incl. PVP) **3 Levels (-1,0,+1)**

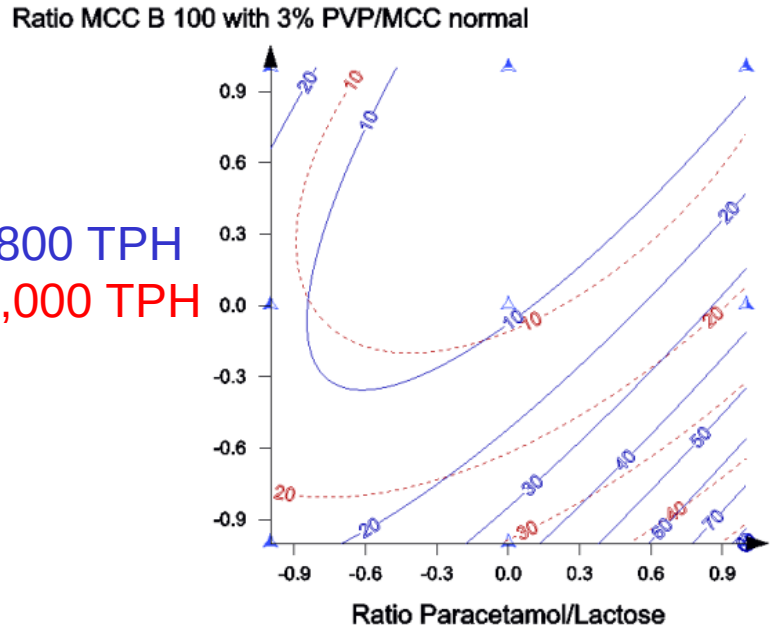
B (Lubricant) Magnesium Stearate 0.5 % (w/w) **= const**

E Effect of type of Press (Speed) **2 Levels (-1,+1)**



Tablet «Hardness» [N]

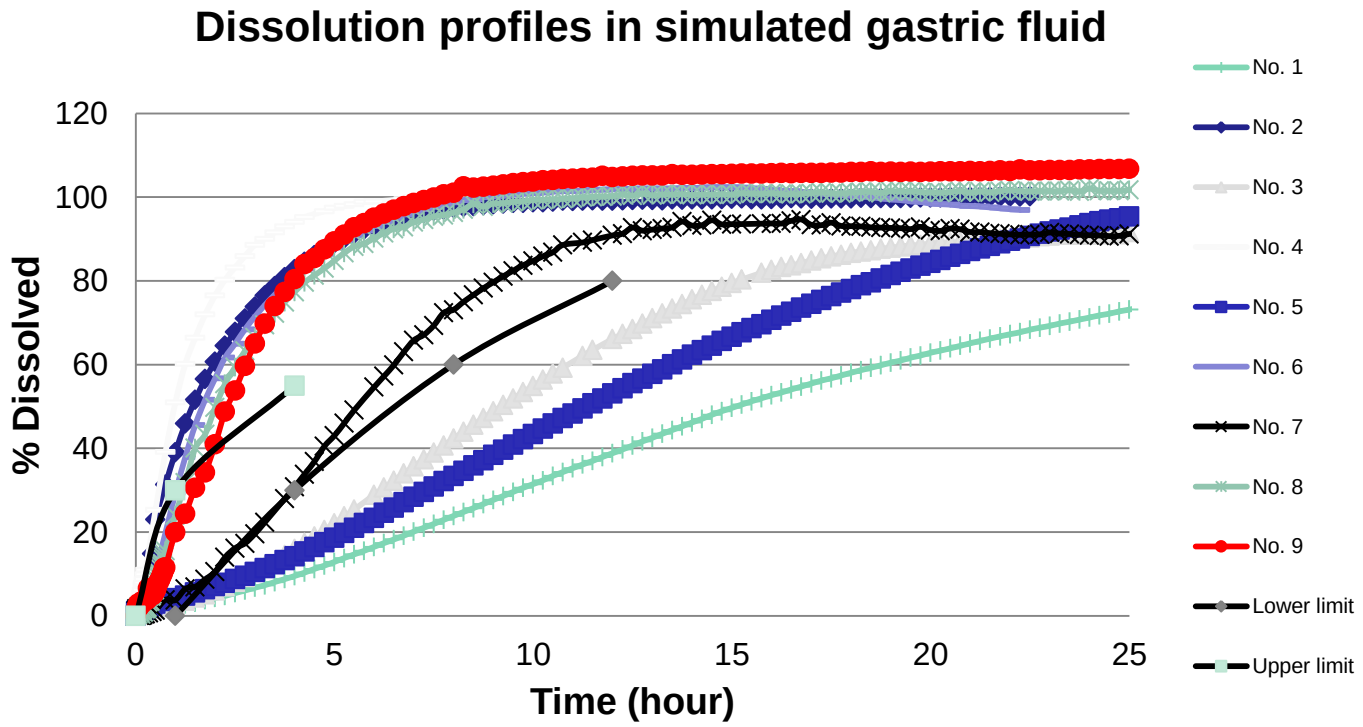
Blue: 10,800 TPH
Red: 108,000 TPH



Tablet «disintegration time» [s]

9 Nifedipine 80 mg Extended Release Formulations: In-vitro Dissolution Rate

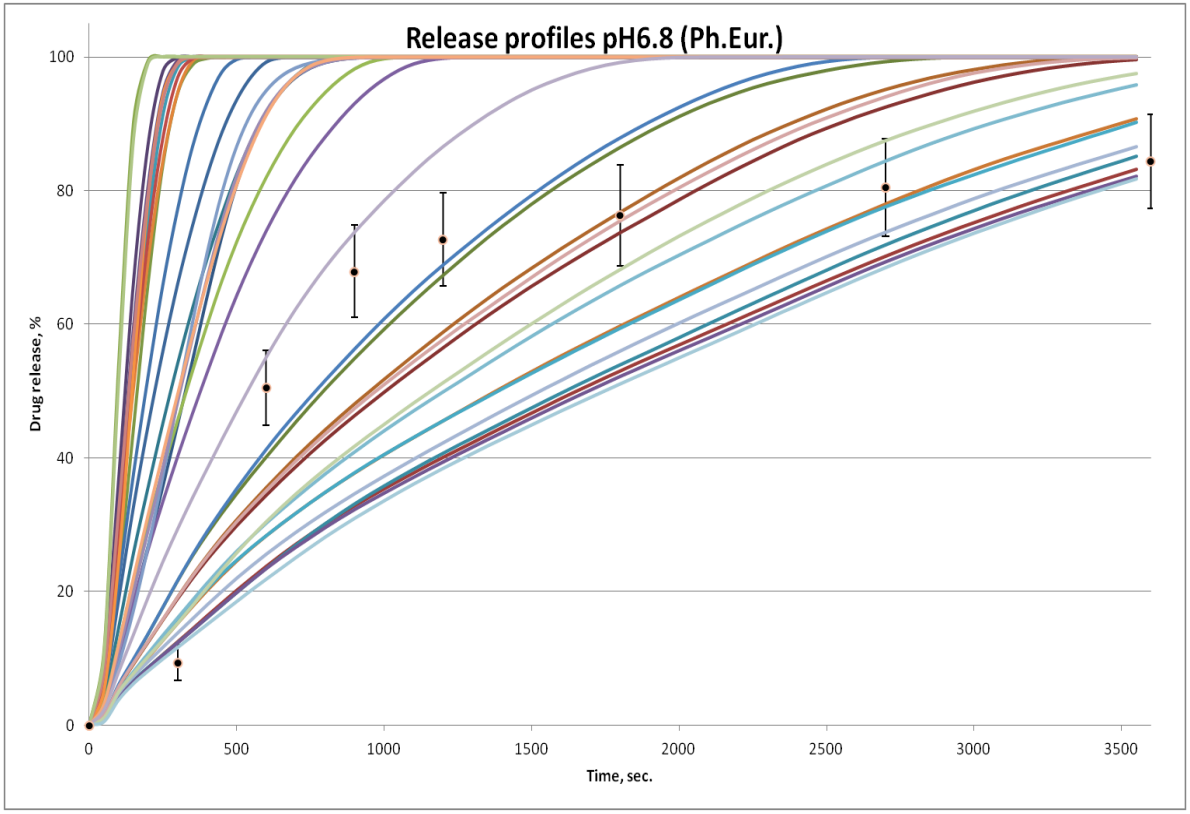
(Design Space Exploration according to ICH Q8 R2, tablets prepared with Presster)



Lower and upper limit: USP Specifications for a 60 mg Nifedipine Extended Release Formulation

Dissolution Rate (Goal: same profile of simple capsule and final tablet form.)

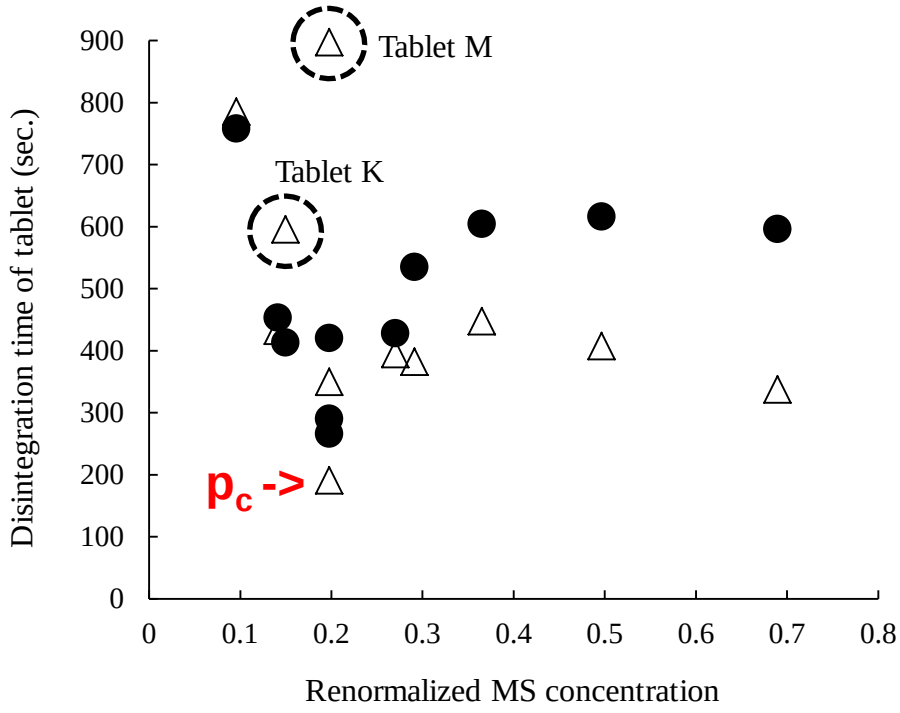
In silico Design Space Exploration according to ICH Q8 R2 for 35 Formulations



In-vitro Dissolution rate profile with error bars: Capsule Service Dosage Form (poor Quality) to be changed to a tablet: 35 F-CAD in-silico tablet Formulations -> search for the same profile at pH 1.2, pH 4.5. and at pH 6.8 for sufficient Bioequivalence !

Percolation Theory and F-CAD:

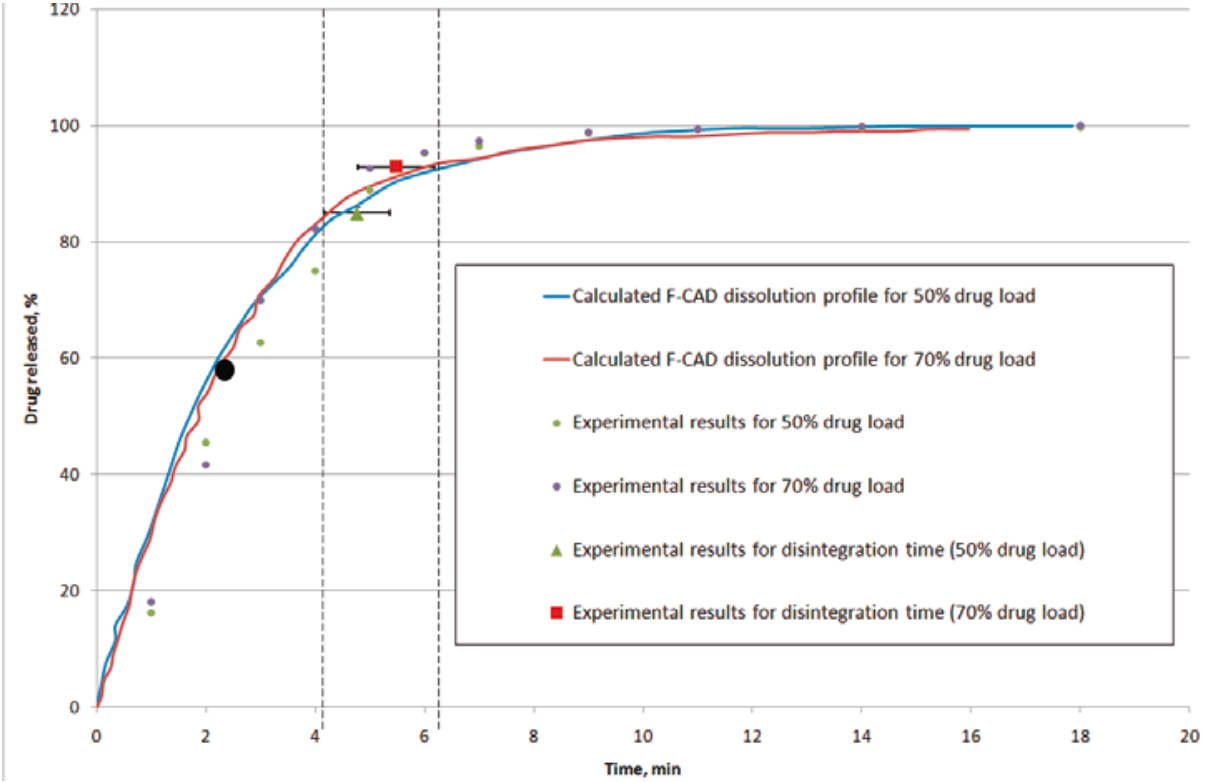
F-CAD is cabable to detect Percolation Threshold $\mathbf{p_c}$ in a tablet formulation, which can be the source of the variability of a tablet property such as the disintegration time ,
see PhD Thesis Go Kimura ,eLink:
at http://edoc.unibas.ch/diss/DissB_9886



Experimental disintegration time (●) and F-CAD values (△) as a function of the renormalized MS (= Maize starch as disintegrant) concentration.

The above «canyon» in the response surface is Difficult to detect with a classical experimental design without taking into account the power equation : $\mathbf{X = S (p - p_c)^q}$

«Time elapsed» till the water molecules have reached the center of the tablet



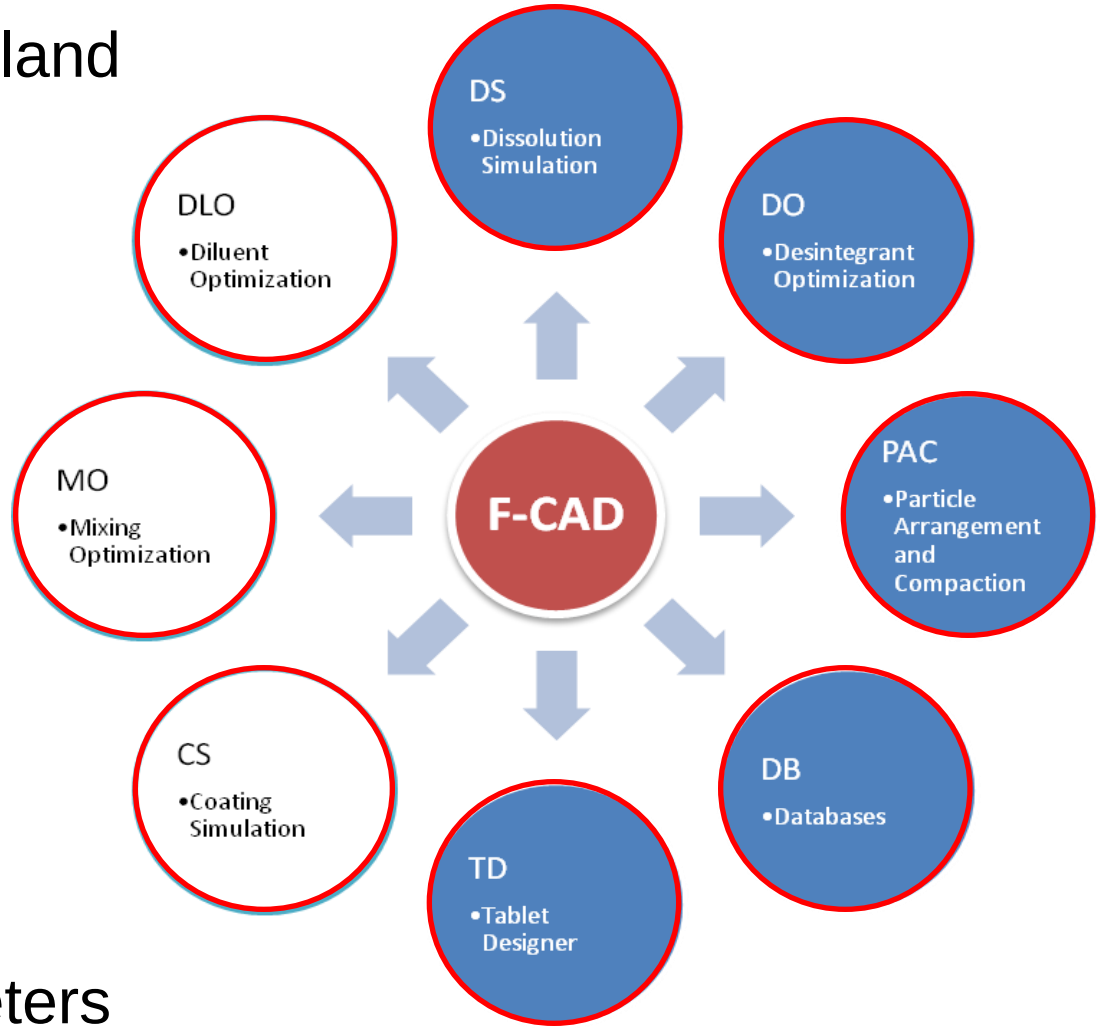
- «Time elapsed» as surrogate for the disintegration time

Computer-Aided Formulation Design developed by Dr. Maxim Puchkov (CINCAP GmbH)

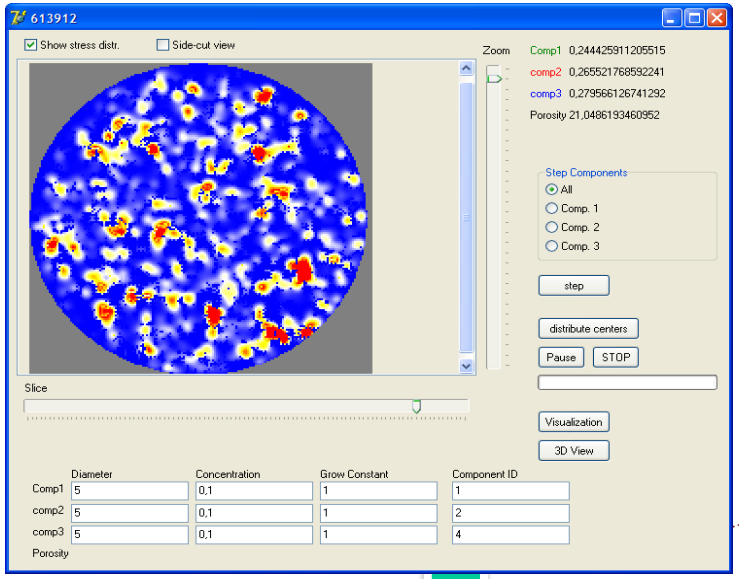
F-CAD is the ultimate set of modeling and computational tools to assist in formulation design of pharmaceutical solid dosage forms with the goal to save money by replacing lab work with "in-silico" experiments

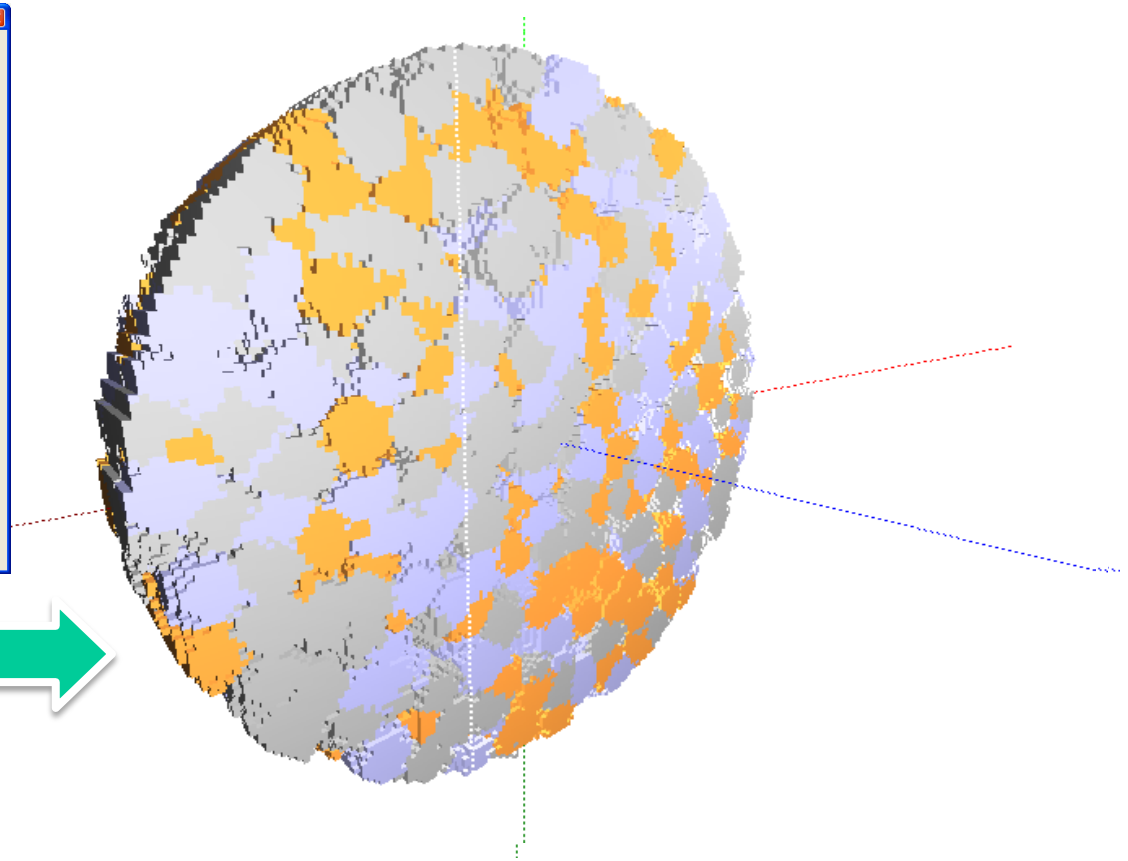
F-CAD by CINCAP, Switzerland

- Dissolution simulation
- Desintegration simulation
- Particle arrangement
- Tablet design
- Coating simulation
- Mixing optimization
- Diluent optimization
- Storage of data and parameters



F-CAD PAC – Particle Arrangement and Compaction

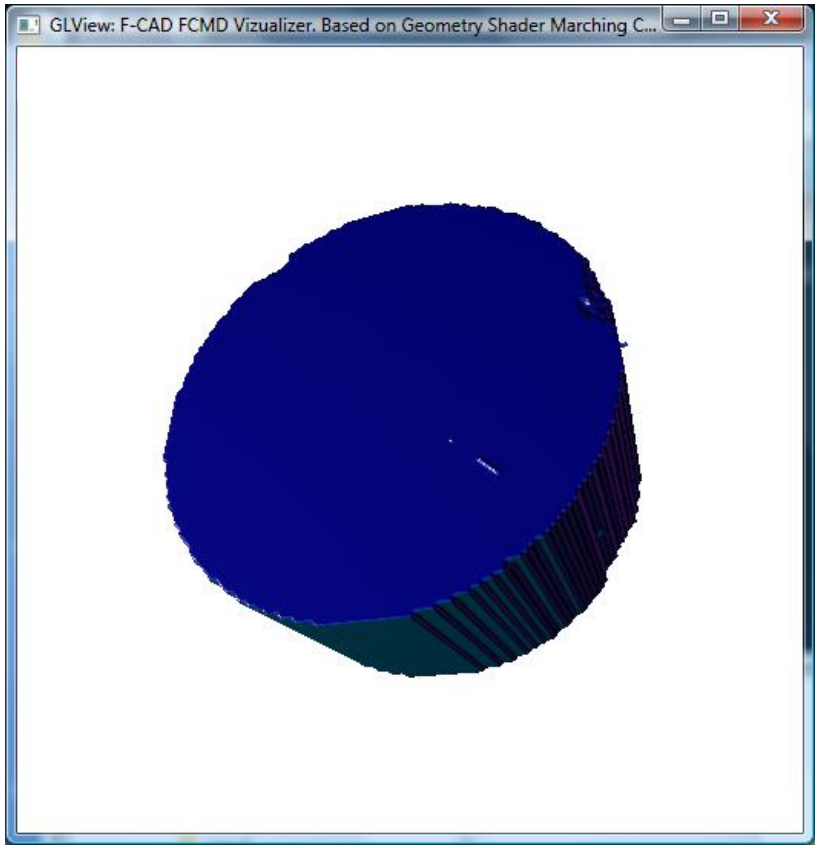




Example: Development of a new formulation

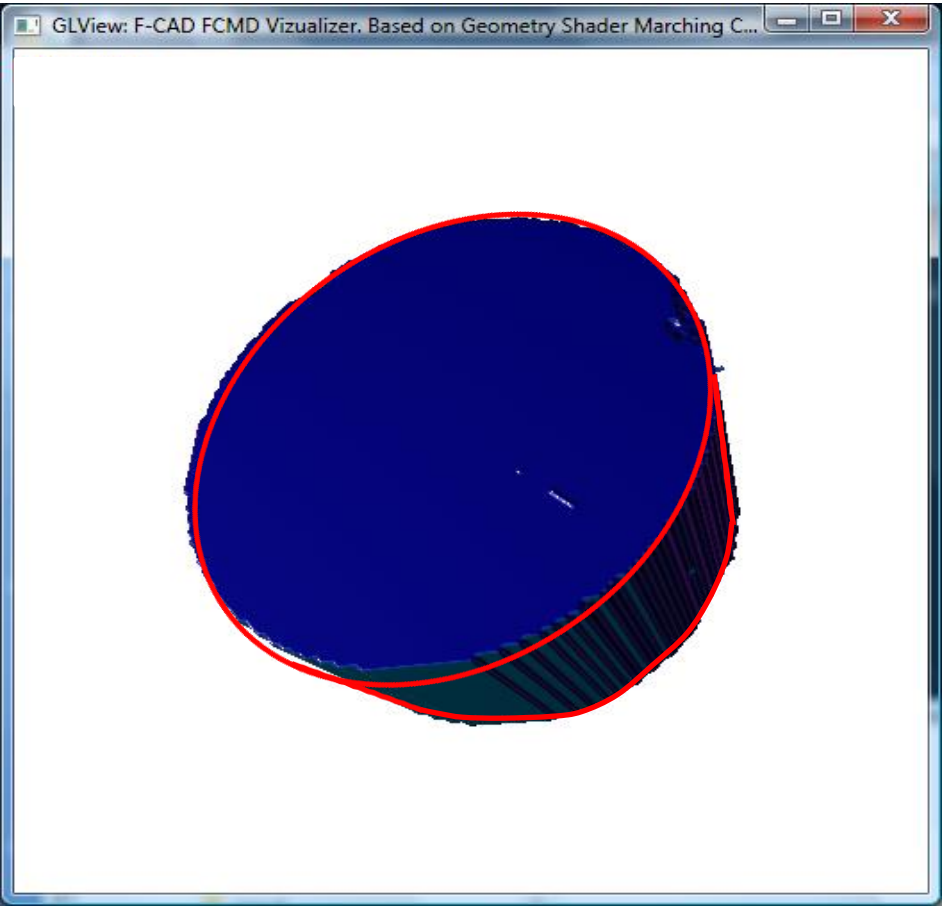
RFT workflow

N in-silico formulations

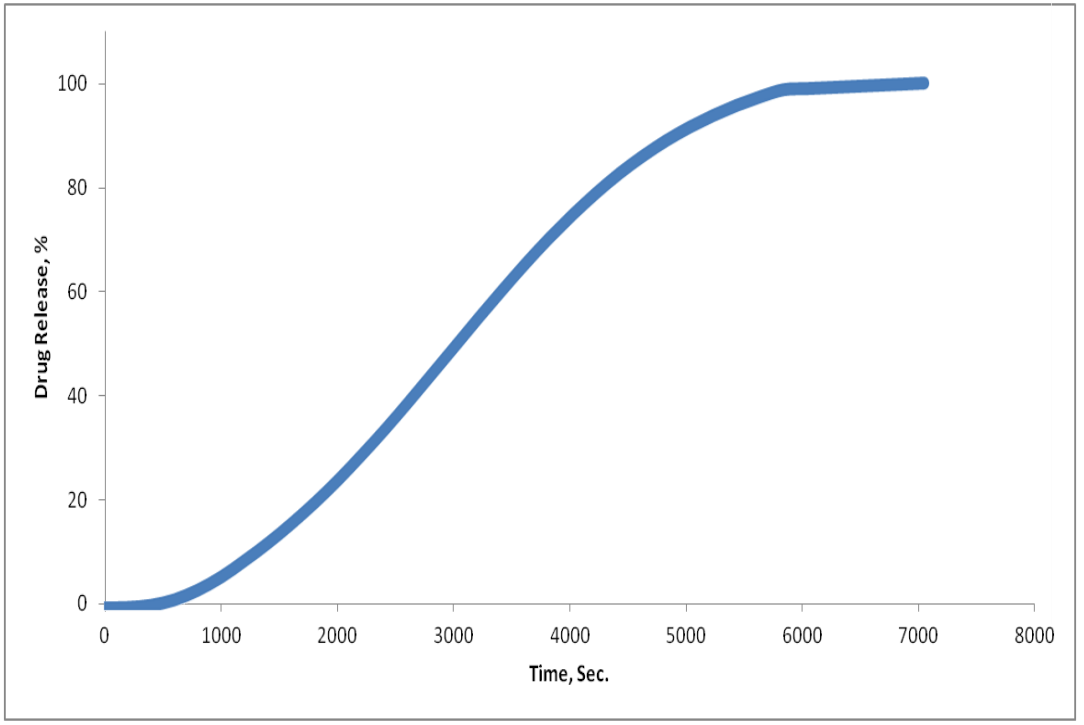


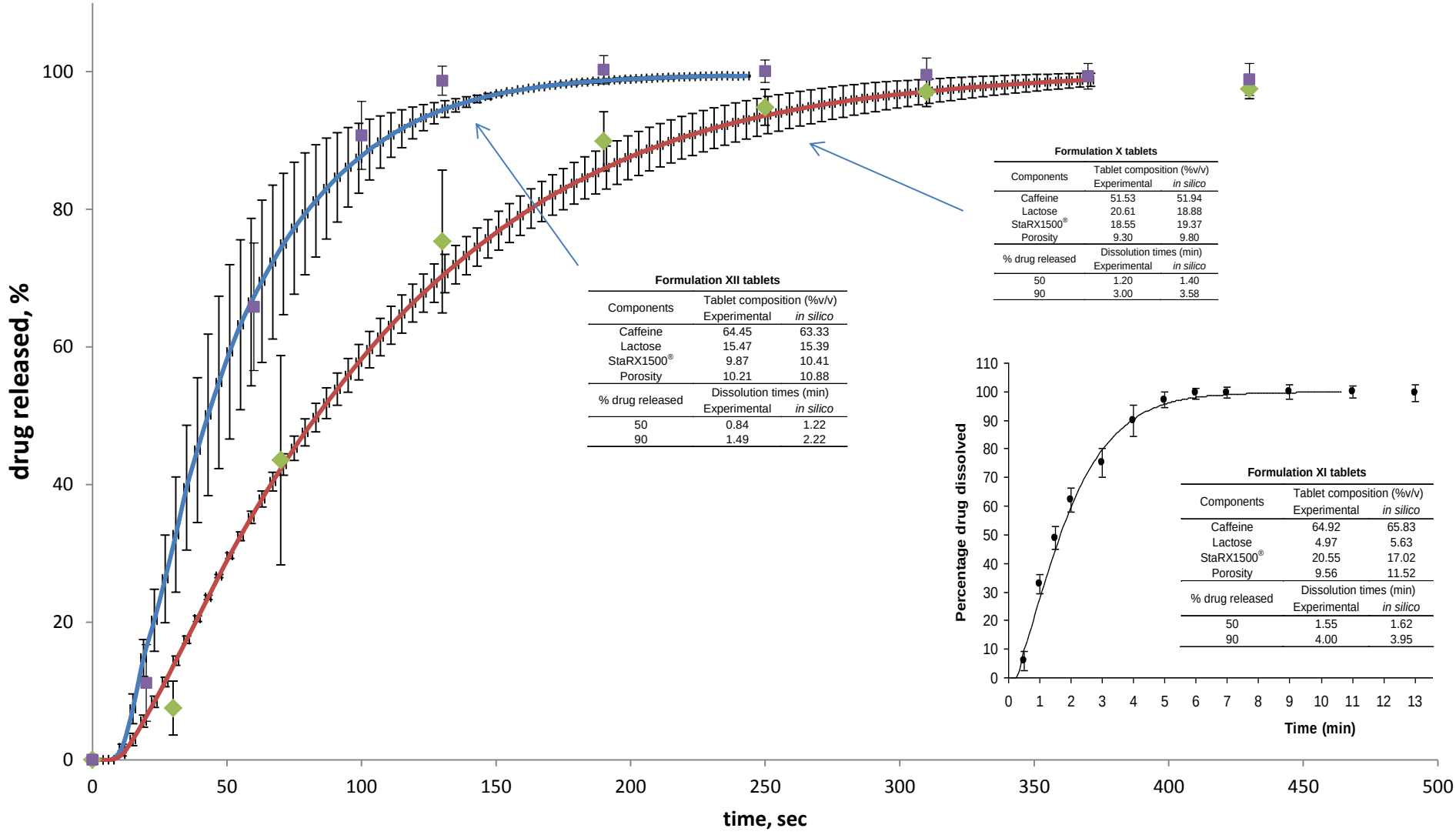
Example: Development of a new formulation

In silico development: Calculation of a set of *N* formulation prototypes



- Calculation of dissolution profile





Formulation XII tablets

Components	Tablet composition (%v/v) Experimental	*in silico*
Caffeine	64.45	63.33
Lactose	15.47	15.39
StaRX1500®	9.87	10.41
Porosity	10.21	10.88
% drug released	Dissolution times (min) Experimental	*in silico*
50	0.84	1.22
90	1.49	2.22

Formulation X tablets

Components	Tablet composition (%v/v) Experimental	*in silico*
Caffeine	51.53	51.94
Lactose	20.61	18.88
StaRX1500®	18.55	19.37
Porosity	9.30	9.80
% drug released	Dissolution times (min) Experimental	*in silico*
50	1.20	1.40
90	3.00	3.58

Formulation XI tablets

Components	Tablet composition (%v/v) Experimental	*in silico*
Caffeine	64.92	65.83
Lactose	4.97	5.63
StaRX1500®	20.55	17.02
Porosity	9.56	11.52
% drug released	Dissolution times (min) Experimental	*in silico*
50	1.55	1.62
90	4.00	3.95

"Krausbauer E.: Contributions to a science based expert system for solid dosage form design. PhD Thesis; University of Basel: Basel, 2007."

- **Audience Q&A**

Thank you for your attention!

Footnote:
«Right, First Time» Concept and Workflow – A paradigma shift for a lean & smart *six-sigma* development will be published as an article, resp. invited contribution by PHARM TECH JAPAN in Japanese and in English by SWISS PHARMA 3/2013
See also: www.pharmatrans-sanaq.com *– Scientific Forum 2013, May 23/24, Basel*