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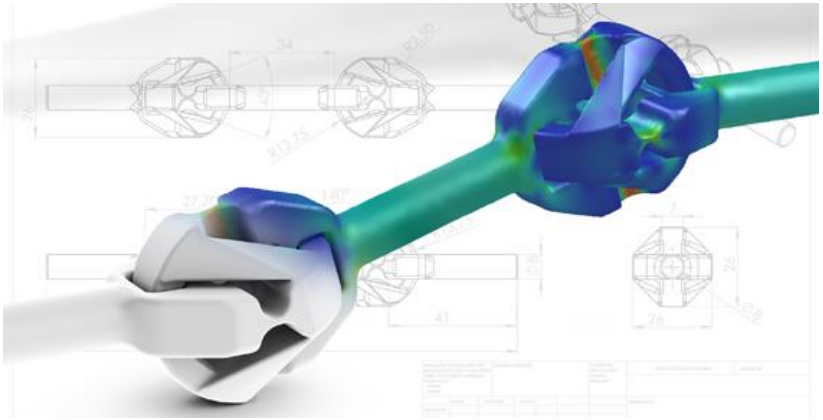
Rapid Product Development

- Rapid Product Development (RPD)

  Is the continuously accelerated process chain of the entire product development using modern methods and technologies such as CAD, CNC & rapid prototyping. *(Wikipedia)*



CAD & Computer simulation

Rapid Product Development

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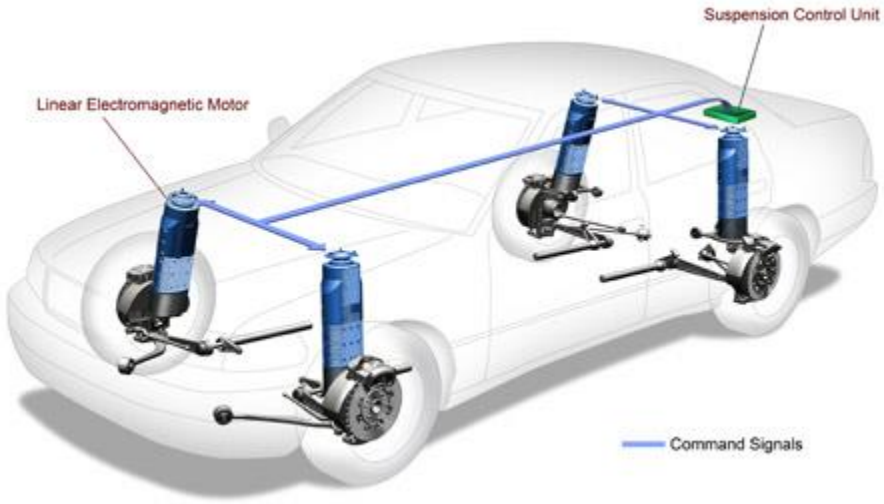
- Primary: Automotive industry



Full Computer-Aided-Design

Rapid Product Development

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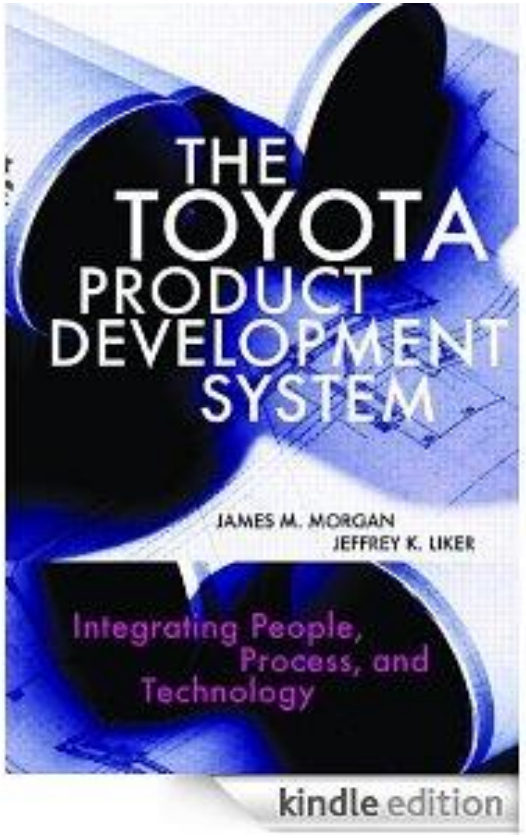
- Pioneer: Toyota



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- Primary: Automotive industry
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- Today: Best industrial practice
- Adapted by other industries

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Conventional vs. “Right First Time” workflow

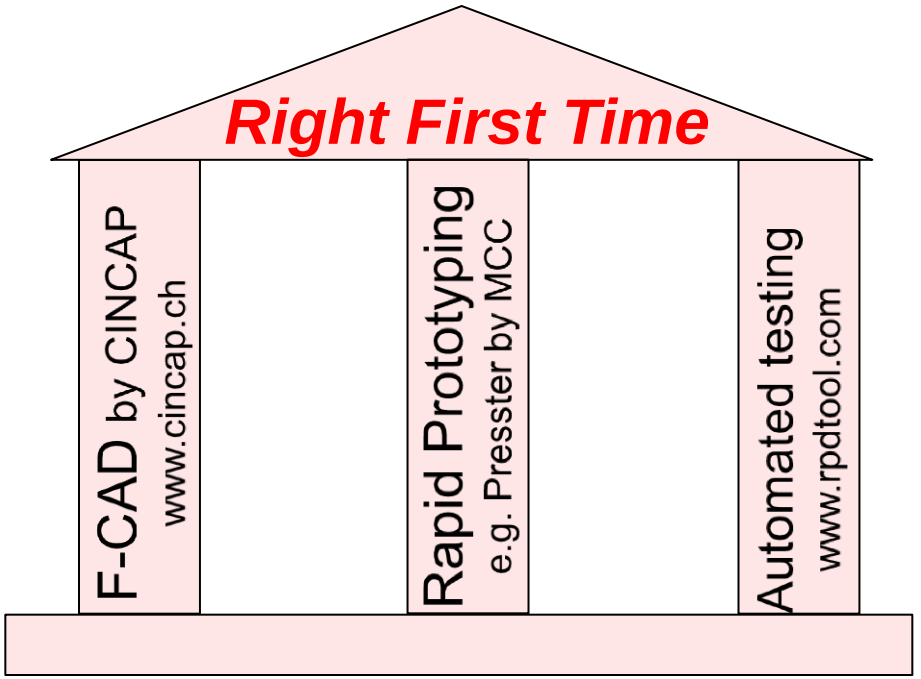
Right First Time workflow

Market ready tablet (diff. strengths)
by *F-CAD* <six-sigma quality>

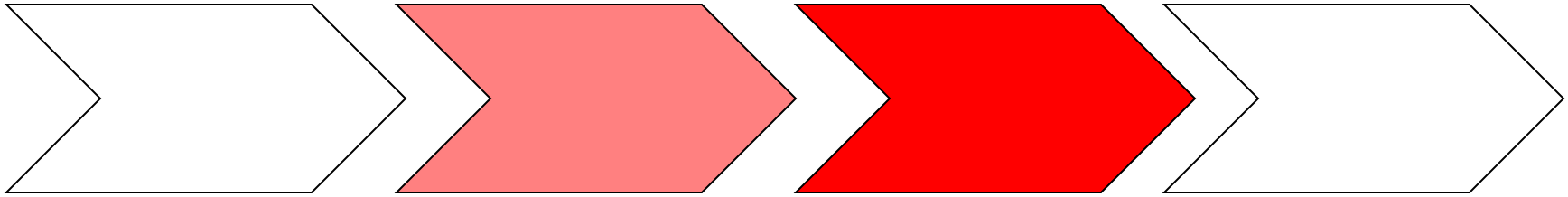
Small-scale Production for
the very first clinical trials

Scale-Up Exercise
(computer-assisted)

Mass-production of final
marketed form <six-sigma quality>



Right First Time-STAGE PLAN (all BCS)



Technical Development	• Preformulation • Early Formulation Development	• Formulation Development
Tox./Clinical Studies	*In vitro/animal* • Pharmocology • General Tox • Genotoxity/Other	*First in man* • Pharmocology • General Tox • Genotoxity/Other

Pre- & Early Formulation Development

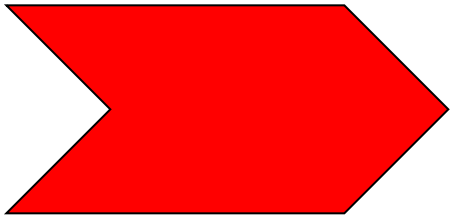
- Phys.-chem Characterisation
  - Solubility (aqueous, excipient)
  - Chemical & Physical stability (solid & solution)

- Solid state Development
  - Salt/polymorhphism screen
  - Amorphous form (solid dispersion, lyophilisation, micronisation)

- Solubilisation
  - Solubilizer/Precipitation retarder (cyclodextrin, micelle, liposome, mixed micelle, polymeric additives, excipient)

- Tox-Formulation

Formulation Development



- Phys-chem Characterisation
  - Accelerated Compatability / Stability
  - Galenical screening
- Rapid Prototyping
  - F-CAD
  - High speed tablet press simulator
  - Dissolution testing
- Phys-chem Characterisation
  - Dissolution
  - Accelerated chemical & physical stability
  - Packaging selection
- “Market ready” formulation
  - Production for clinical (phase 1)
  - ICH stability program

Meteorology - a scientific success story

Witterungsbeobachtungen.

Zürich 31. M./1. Juni	Barometerst. 470 M. Höhe	Meer reduz.	Thermometer Cels.-G.	Haarhygrometer.	Wind.	Witterung.
9h A.	717.0	758	16.3	68	NE 0	bed., schwacher Regen
7h V.	718.3	759	11.2	96	W 0	bedeckt, Regen.
1h Mt	719.2	760	15.0	79	W 0	bewölkt.

Telegraphischer Bericht des Pariser Observatoriums vom 1. Juni. Auf dem Kanal und dem Ozean Barometerstand gegen 761 mm. Schwacher Wind und schönes Meer. In der Gascogne stehen Gewitter zu erwarten.

Barometerstand: 747 in Hernösand; 750 in Christiansund, Ordö, Wisby und Bodö; 755 in Fano, Libau und Helsingfors; 760 in Shetland, Hamburg, Breslau, Paris, Bordeaux, Nizza Neapel und Constantine; 764 in Lissabon.

Aussichten für die Witterung des 2. Juni in der Nordost-Schweiz: Fortdauer der unbeständigen zu leichten Regenschauern geneigten Witterung; Aufheiterung steht erst bei weiterem Steigen des Barometers zu erwarten.

Anmerkung. Vielseitig geäußerten Wünschen entsprechend, führen wir mit heute in den täglichen Witterungsberichten zwei Neuerungen ein:

1) Die Reduktion der auf der Züricher Sternwarte (470 Meter über Meer) beobachteten Barometerstände auf das Meeresniveau, wobei wir jedoch die reduzirten Stände aus verschiedenen Gründen nur in ganzen Millimetern geben.

2) Die Prognose für die Witterung des folgenden Tages auf Grundlage der hierseitigen Beobachtungen und des Berichtes des Pariser Observatoriums.

Erstere soll zur Vergleichung des jeweilen hier beobachteten Barometerstandes mit den Daten der Pariser Depeschen, die für 7 Uhr Vormittags gelten, dienen und ist namentlich für diejenigen Leser von Werth, welche jene Daten mittelst der Isobaren kartographisch aufzeichnen.

In Betreff der Prognose halten wir eine nähere Erörterung, die in der Montagsnummer folgen soll, nicht für ganz überflüssig. R. B.

1 Juni 1878 1st public weather forecast for the nordwest of Switzerland for the next day:

„On-going unstable with trend to light rains. No improvement can be expeced prior climbing of barometer reading.“

Basis: 88 weather stations in Switzerland & weather report of French observatory

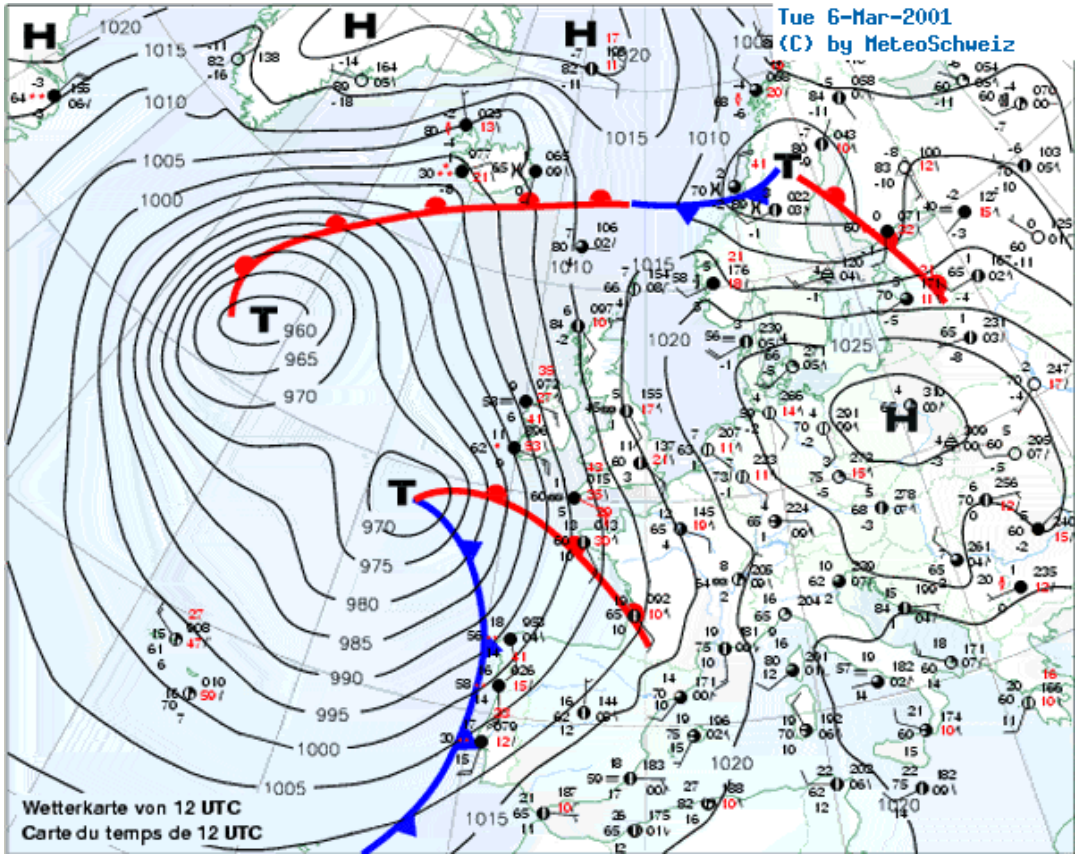
Workflow

- Data collection
- Data analysis
- Forecast

Source: Meteo Schweiz

2nd decade of 20th Century. **Automatisation in data acquisition and analysis**

Swiss Meteo office in 1980



Workflow

- Data colleting -> quantity & quality
- Data analysis -> improved models
- Forecast -> long, mid & short-term

Quelle: Meteo Schweiz

Compatibility study

- Study plan: Taken into account
  -pharmaceutical needs
  -physico-chemical properties & quality of api & excip.
  -properly designed (i.e. factorial)
- Composition and sample production:
  - composition as close to target formulation as possible (including quality of api and excipients)
  - sample production as close to planned manufacturing process as possible (solid state, homogeneity)

Compatibility study: Example

- Composition:

  API: 1 compound with target concentration of 1 %

  Filler: Two fillers (one with two qualities)

  Lubricants: Two lubricants

  Disintegrants: Two disintegrants

  Binders: Two binders

Compatibility study: Example

No of Experiment	api [%]	Fillers [%]			Lubricants [%]		Disintegrants [%]		Binders [%]	
		A	B	C	D	E	F	G	H	I
1	1	69			5		20		5	
2	1	69			5		20			5
3	1	69			5			20	5	
4	1	69			5			20		5
5	1	69				5	20		5	
6	1	69				5	20			5
7	1	69				5		20	5	
8	1	69				5		20		5
9	1		69		5		20		5	
10	1		69		5		20			5
11	1		69		5			20	5	
12	1		69		5			20		5
13	1		69			5	20		5	
14	1		69			5	20			5
15	1		69			5		20	5	
16	1		69			5		20		5
17	1			69	5		20		5	
18	1			69	5		20			5
19	1			69	5			20	5	
20	1			69	5			20		5
21	1			69		5	20		5	
22	1			69		5	20			5
23	1			69		5		20	5	
24	1			69		5		20		5

Set-up of compatibility study: Example

- Number of storage temperatures: 2 (50 & 60°C)
- Number of humiditiy: 2 (0 & 75%RH)
- Number of time points: 4 (0, 10, 20 & 30 days)

Number of test samples: 24 * 2 * 2 * 4 = 384

Amount of drug required: approx 200 - 400 mg

Set-up of compatibility study: Example

Automated solid dispensing of excipients (Placebo)

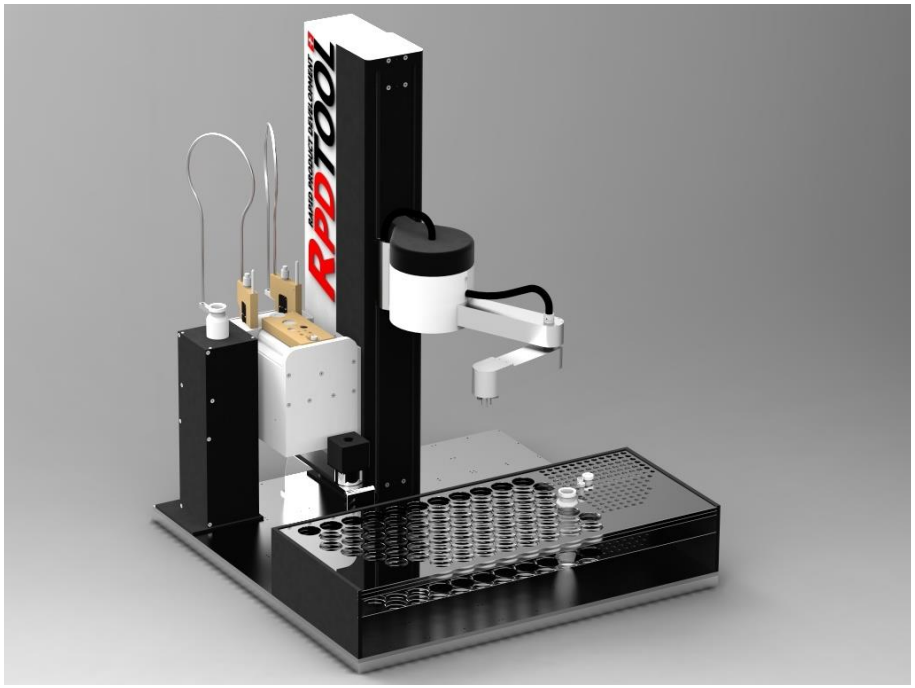
- Worflow:
  - Preparation of set of excipient mixtures (placebo-vials)
  - Dissolving of api in solvent
  - Dispensing of planned amount of api to placebo vials = > test vials.
  - Slow removal of solvent under appropriate vortexing of test vials
  - Dry test vials = starting samples of chemical and physical compatibility study

Compatability studies – mg scale production

Production of mg scale amount of test sample by simulation wet granulation.

- Worflow:
  - Preparation of set of excipient mixtures (placebo-vials)
  - Dissolving of api in solvent
  - Dispensing of planned amount of api to placebo vials = > test vials.
  - Slow removal of solvent under vortexing
  - Dry test vials = starting samples of chem. & phys. compatibility study

SamplePrep – chromatographic sample preparation



Stand alone

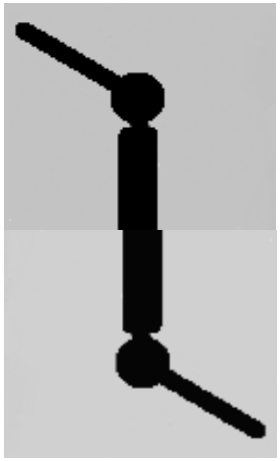
Connected to UPLC

Storage Cabinet

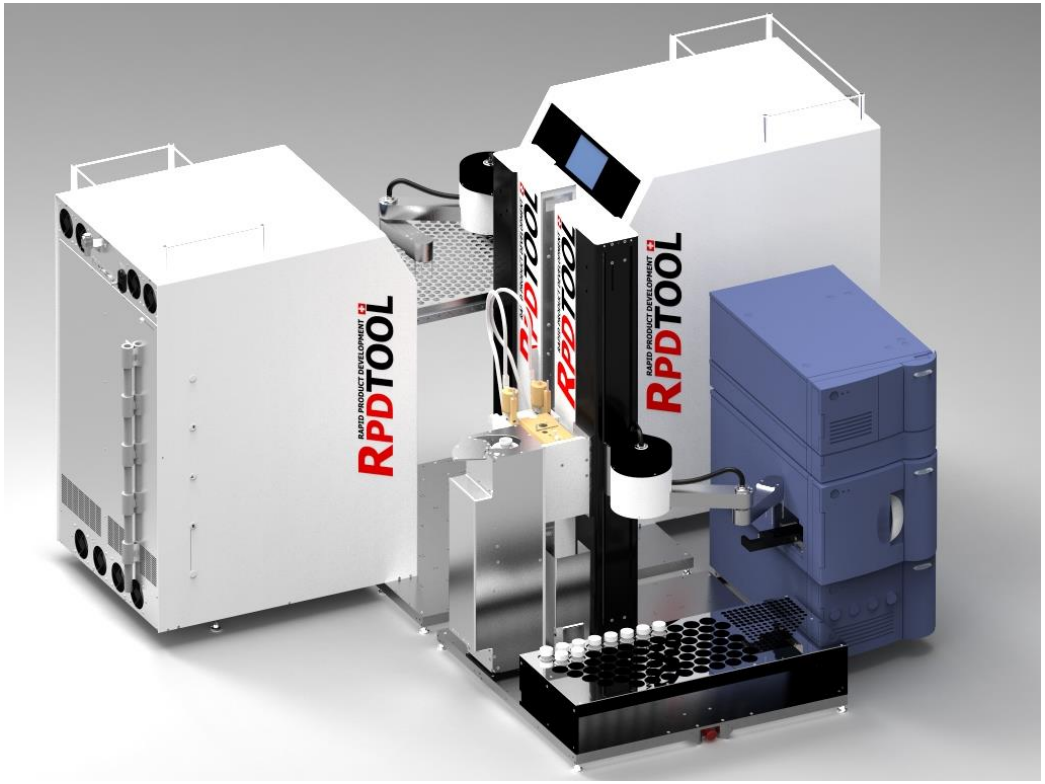
- 5 independent climate zones
  - Dimensions: h/w/d: 833/564/782 mm
  - 1 Peltier / 4 heat foil (0 – 100 °C)
  - Humidity control (0 – 90%RH)
  - Max. height of vial/blister: 75 mm
  - Storage capacity per drawer:
    e.g. 315 vials with d = 17 mm
- Accelerated stability studies
- Selection of packaging material

Automated storage stability: Multi robot system

Example: Chemical storage stability
(2 SP, 2 MCC & 1 UPLC/MS)



back to back



Compatibility study - evaluation

- Focus on key degradation products:

  Example: Imp 1, Imp 2 & Σ Imp

- Evaluation of degradation factors (example)

  $Imp\ 1 = f_a*[A]*t+f_b*[B]*t+f_c*[C]*t+f_d*[D]*t+f_e*[E]*t+f_f*[F]*t+$
  $f_g*[G]*t+f_h*[H]*t+f_i*[I]*t + f_t*t$

- Statistic software for model evaluation recommended

  (i.e. SAS, S-plus,...)

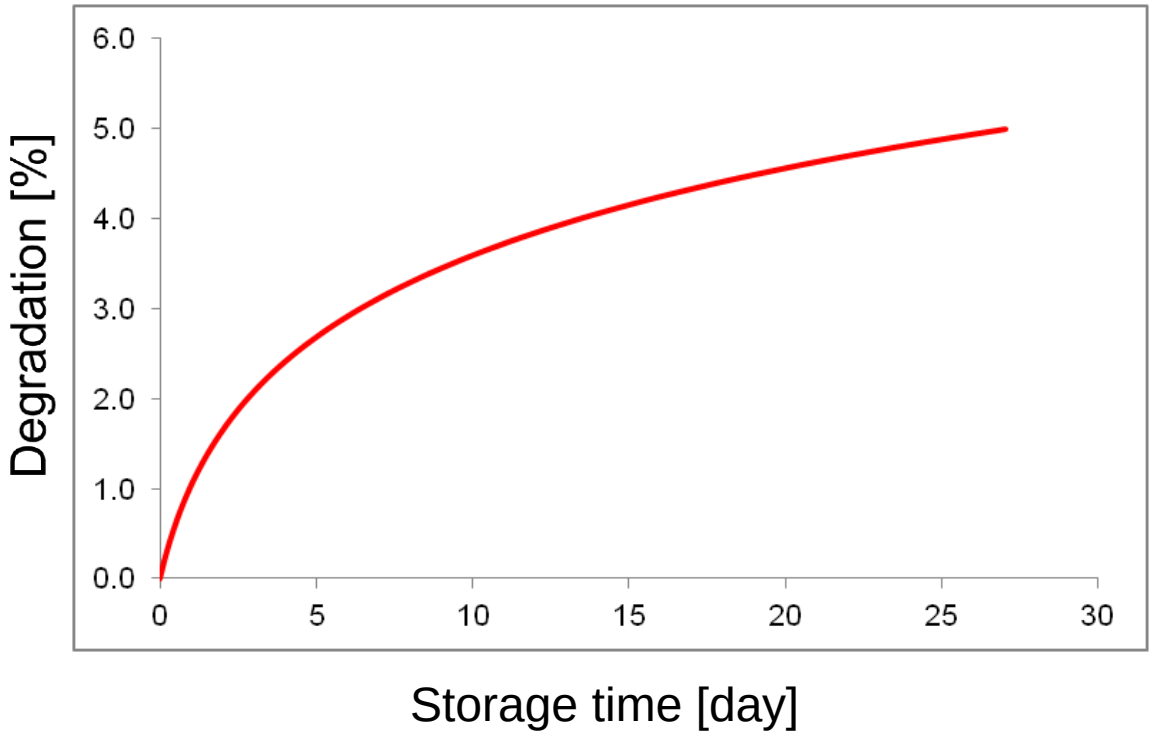
Accelerated stability study (tablet prototypes)

- Compatibility study: Selection of excipients
- Accelerated stability studies: Estimation of shelf live and packaging
- Evaluation of accelerated stability studies
  - Quantification of degradation kinetic
  - Modified Arrhenius equation

  $ln k = ln A - Ea/(RT) + B(RH)$

Evaluation of Accelerated Stability Data

- Complex reactivity in solid state due to different microenvironments



Evaluation of Accelerated Stability Data

- Approximation: Superposition of zero order kinetics:

$$[x_t] = \sum_i k_i \cdot x_i \cdot t$$

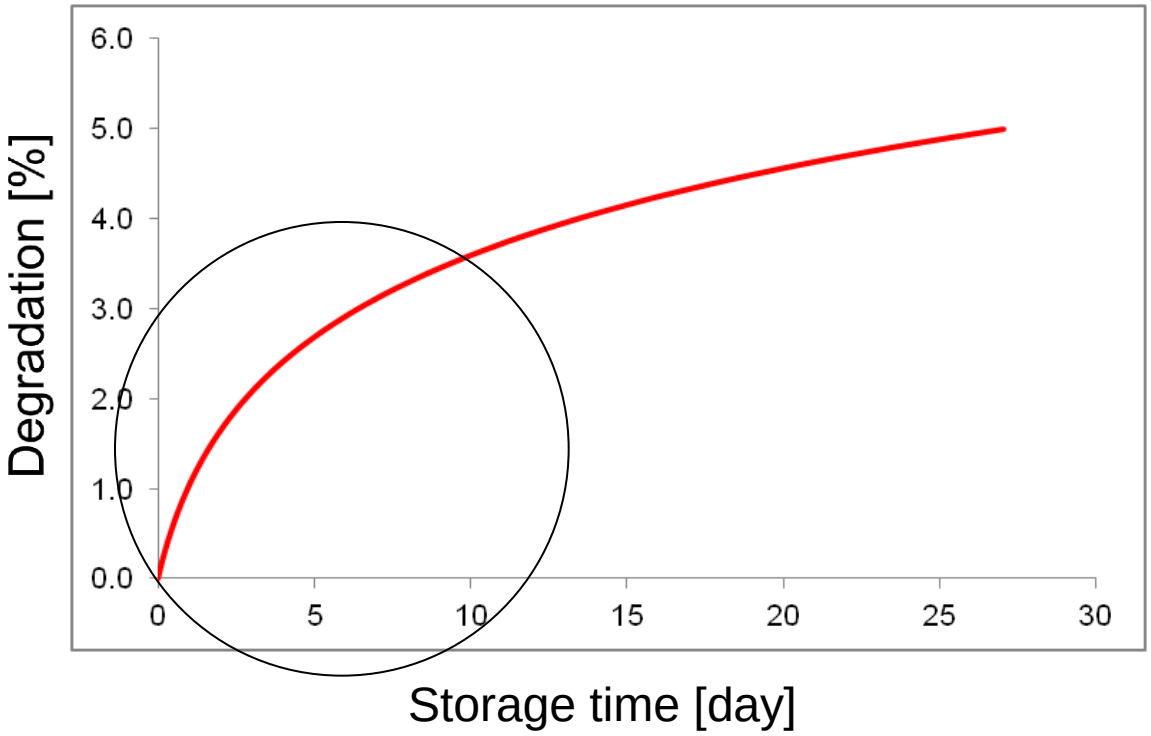
With x_i....mole fraction of api state *i* (1 if $c_i > 0$, 0 else)

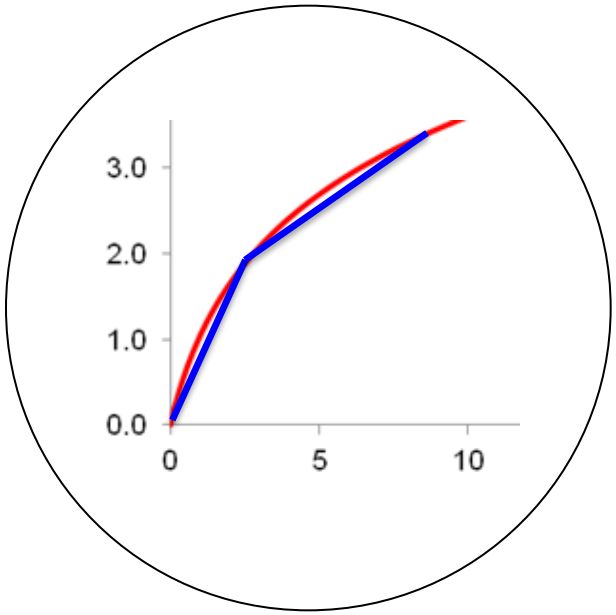
c_t....concentration

k_i.....reaction constant

Evaluation of Accelerated Stability Data

- Complex reactivity in solid state due to different microenvironments





Composition of zero order kinetics

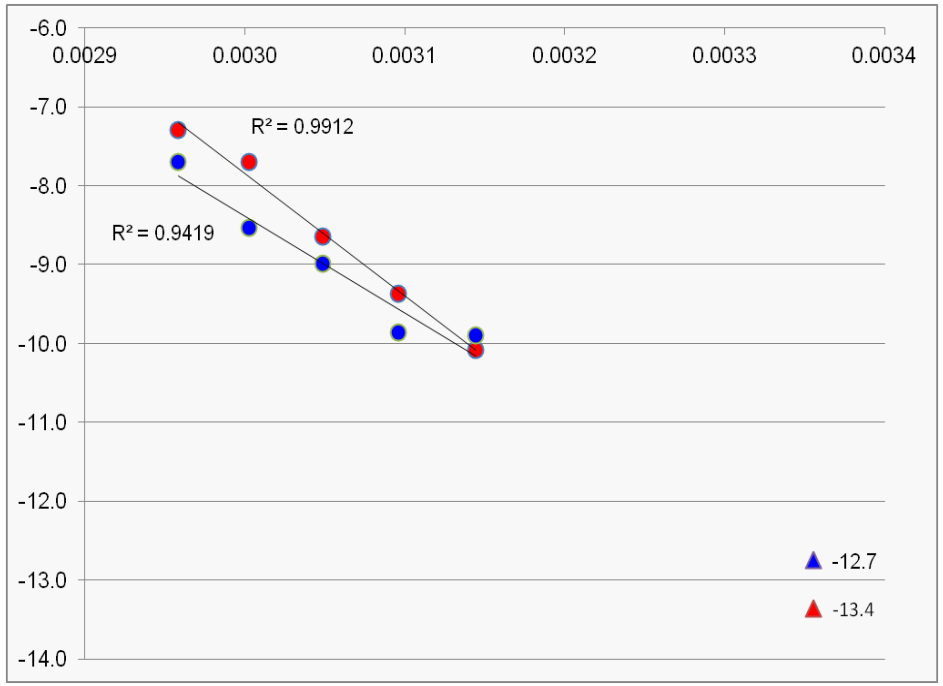
Example: Accelerated stability

Temperature	Storage Time													
[°C]	0	2	4	6	8	10	12	16	21	28	32	45	62	92
40°C	X										X	X	X	X
45°C	X						X	X	X	X	X	X	X	
50°C	X				X	X	X	X	X	X	X	X		
55°C	X			X	X	X	X	X	X					
60°C	X		X	X	X	X	X							
65°C	X	X	X	X	X									

Example: Accelerated stability

Temperature	Storage Time [day]													
[°C]	0	2	4	6	8	10	12	16	21	28	32	45	62	92
40°C	0.00%										X	X	X	X
45°C	0.00%						0.05%	X	X	X	X	X	X	
50°C	0.00%				0.07%	0.09%	0.10%	X	X	X	X	X		
55°C	0.00%			0.12%	0.16%	0.18%	0.21%	X	X					
60°C	0.00%		0.18%	0.27%	0.39%	0.47%	0.55%							
65°C	0.00%	0.12%	0.27%	0.37%	0.45%									
Temperature	Storage Time													
[°C]	0	2	4	6	8	10	12	16	21	28	32	45	62	92
40°C	0.00%										X	X	X	X
45°C	0.00%						0.06%	X	X	X	X	X	X	
50°C	0.00%				0.05%	0.07%	0.09%	X	X	X	X	X		
55°C	0.00%			0.06%	0.09%	0.12%	0.15%	X	X					
60°C	0.00%		0.07%	0.12%	0.18%	0.22%	0.27%							
65°C	0.00%	0.10%	0.18%	0.25%	0.30%									

Example: Accelerated stability



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50°C	0.00%				0.07%	0.09%	0.10%	0.14%	0.17%	0.21%	0.25%	X		
55°C	0.00%			0.12%	0.16%	0.18%	0.21%	0.29%	0.35%					
60°C	0.00%		0.18%	0.27%	0.39%	0.47%	0.55%							
65°C	0.00%	0.12%	0.27%	0.37%	0.45%									
Temperature	Storage Time													
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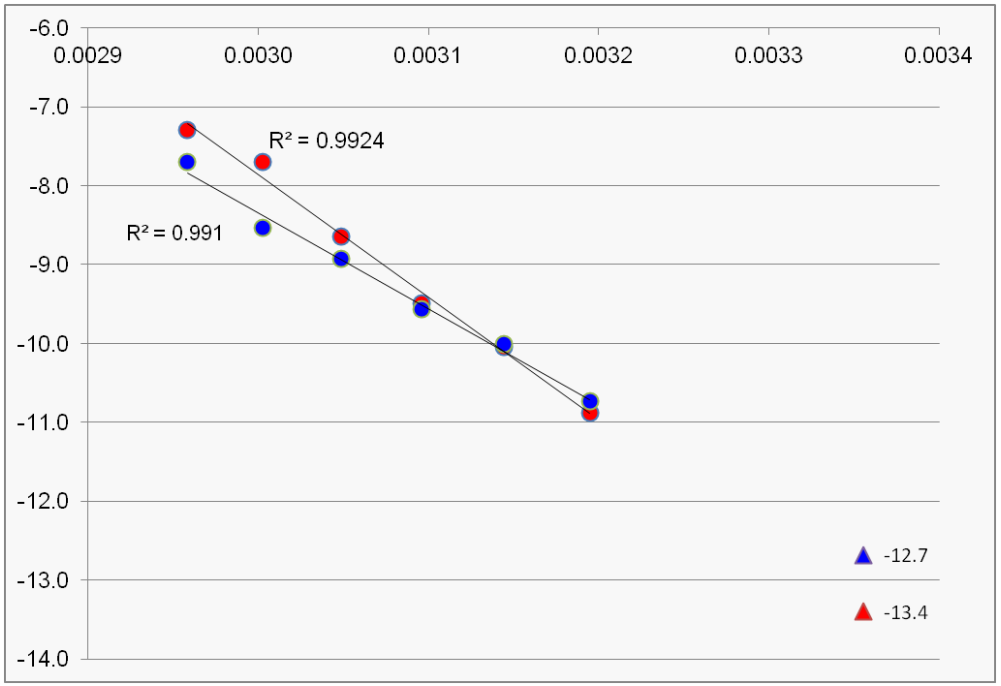
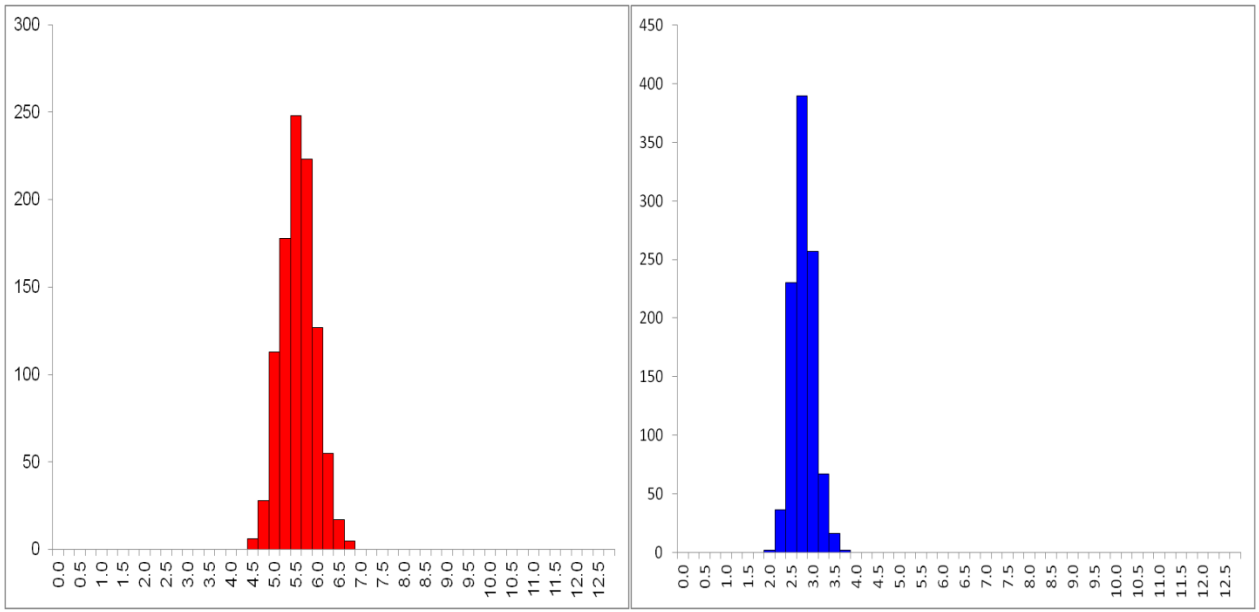
40°C	0.00%										0.07%	X	X	X
45°C	0.00%						0.06%	0.08%	0.10%	0.12%	0.15%	X	X	
50°C	0.00%				0.05%	0.07%	0.09%	0.11%	0.15%	0.18%	0.21%	X		
55°C	0.00%			0.06%	0.09%	0.12%	0.15%	0.21%	0.29%					
60°C	0.00%		0.07%	0.12%	0.18%	0.22%	0.27%							
65°C	0.00%	0.10%	0.18%	0.25%	0.30%									

Example: Accelerated stability

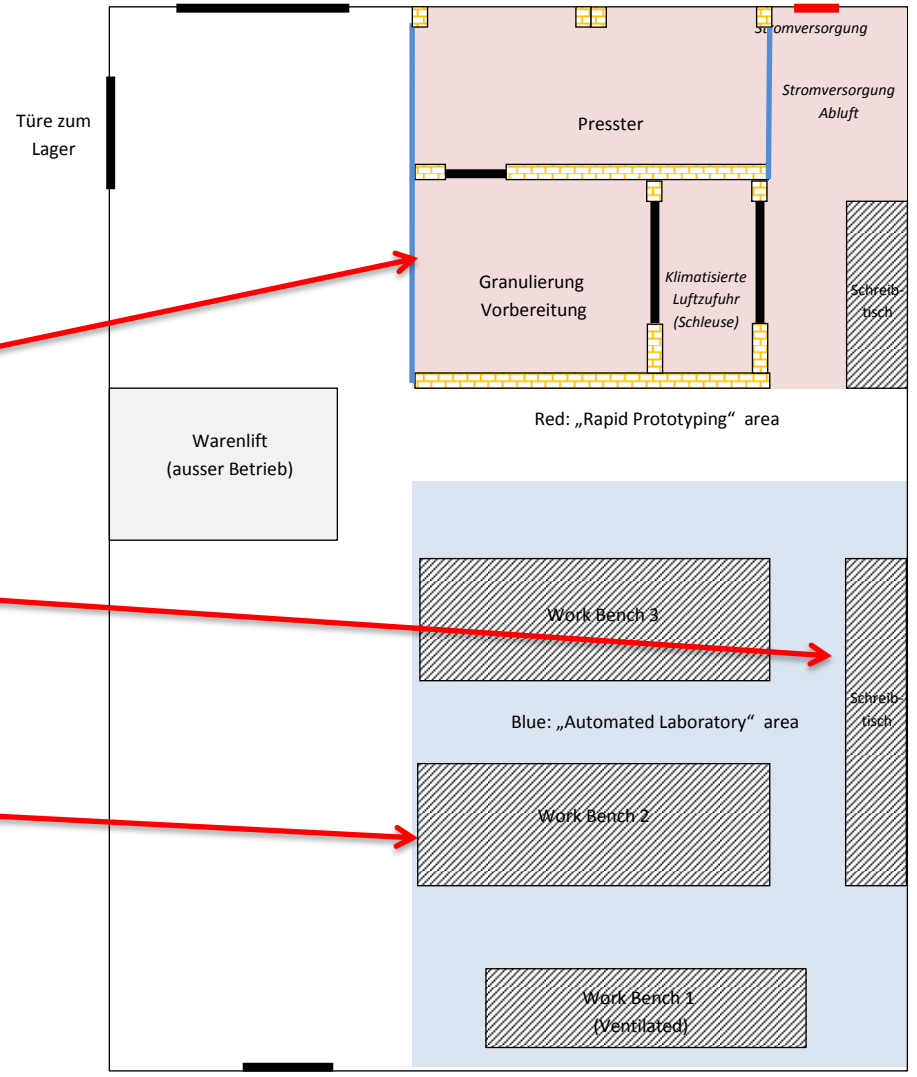


Example: Accelerated stability

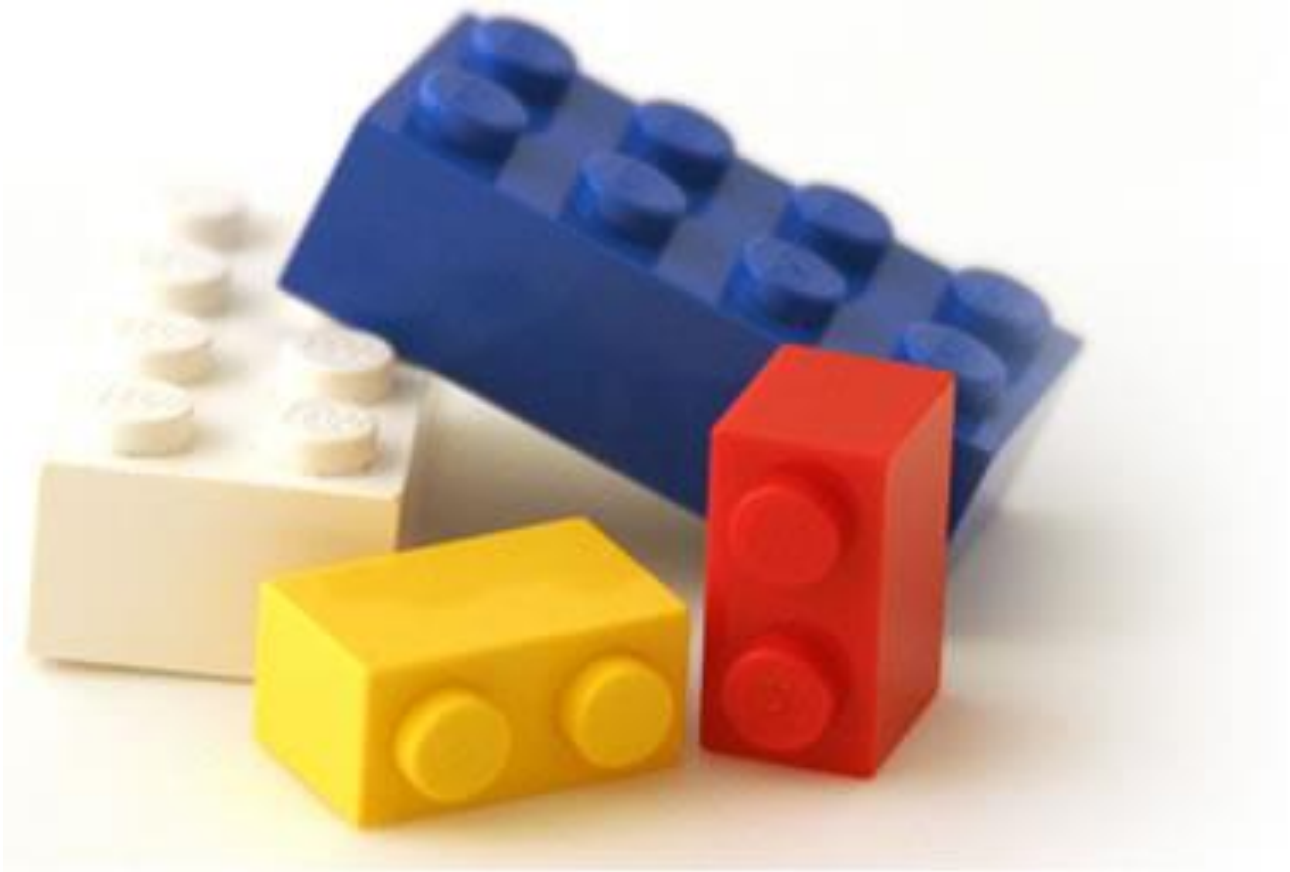


RFT-Lab

- Rapid Prototyping Area
- Computer simulation
- Automated Workflows



RFT-Lab



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