How will the Quality by Design Initiative Affect Formulation Development and Manufacturing?

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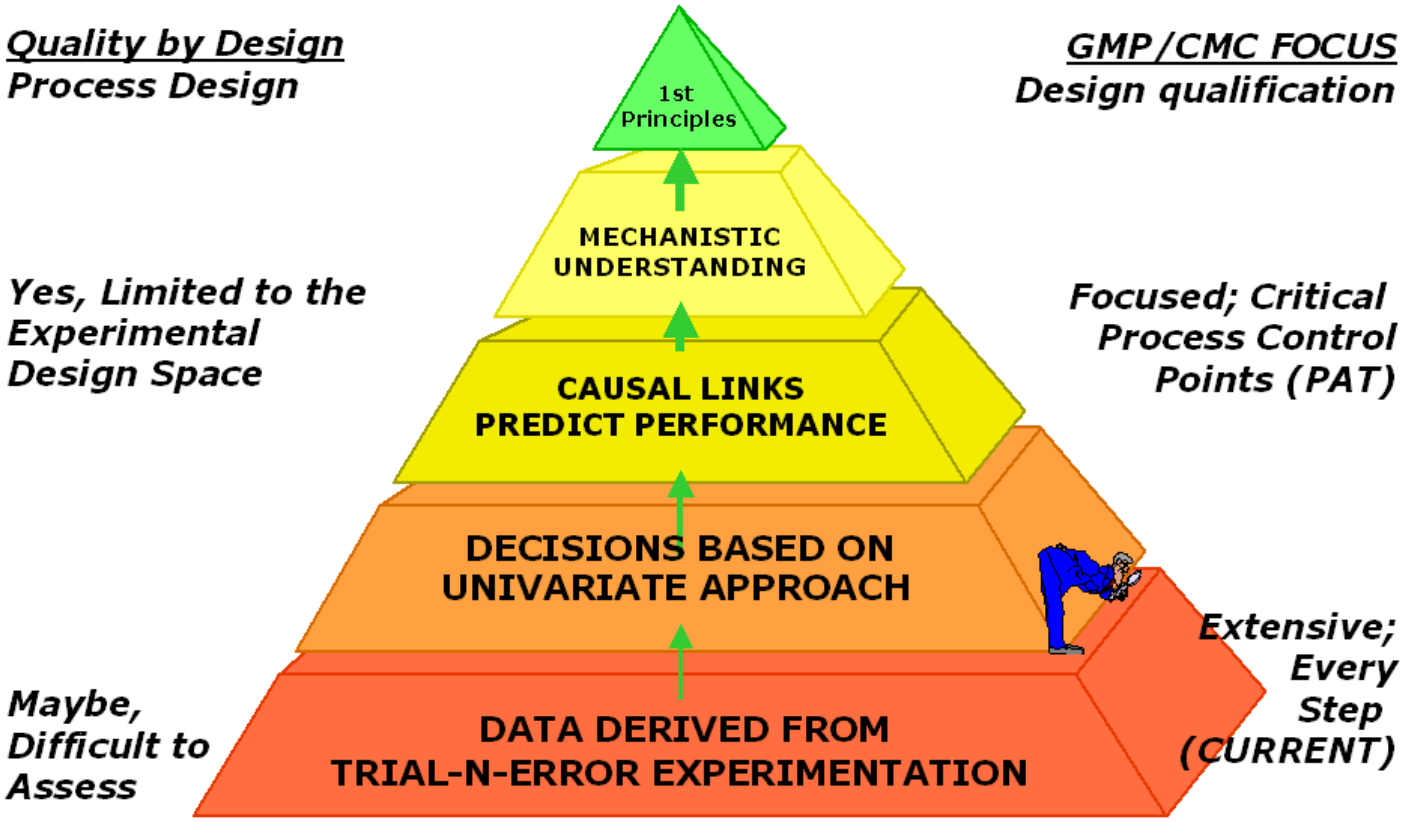
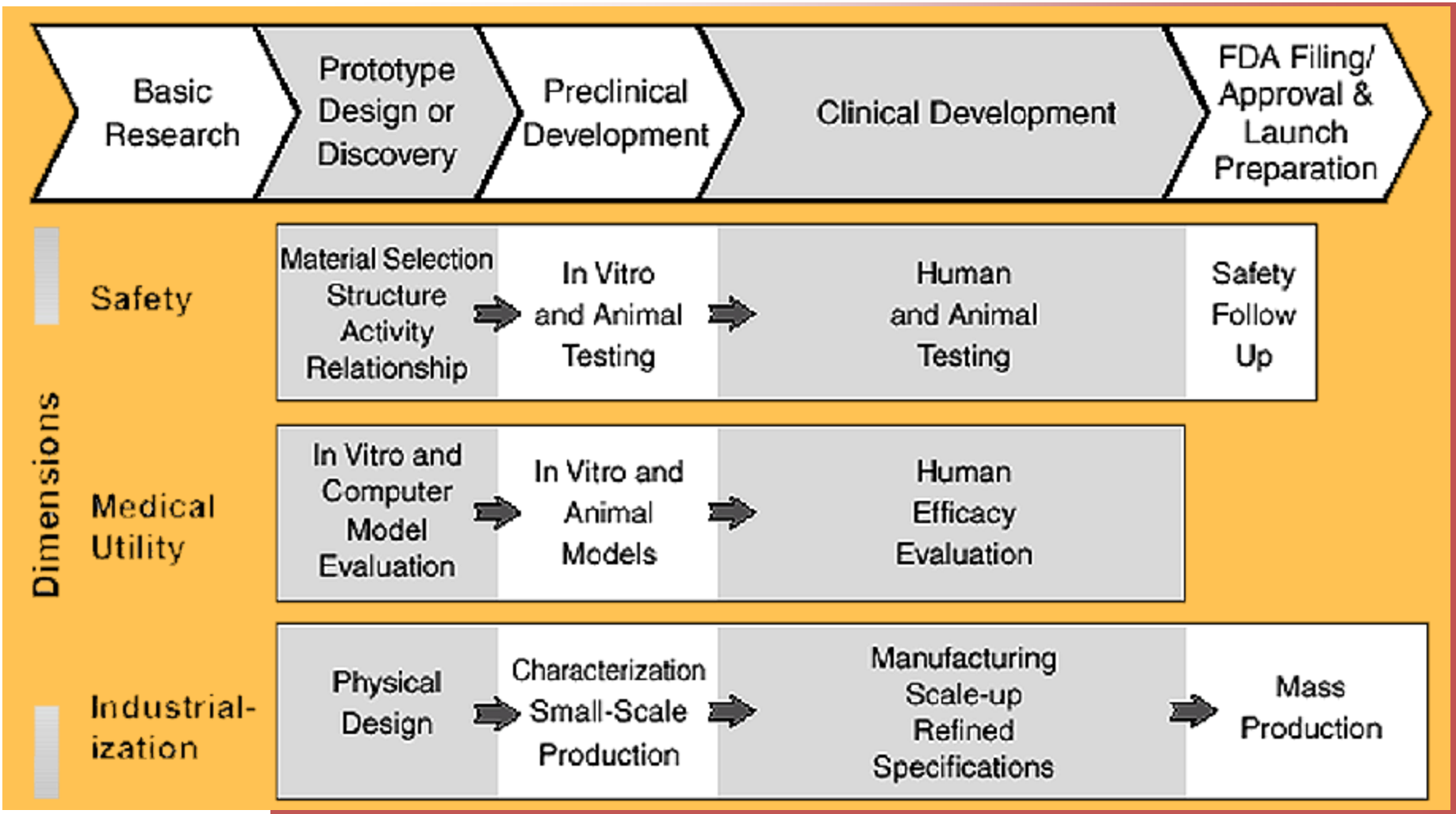
Subject: Ajaz Hussain Sent This Along: Thank you for all your contribution!
Date: Fri, 15 Apr 2005 13:31:50 -0400
From: Hussain, Ajaz S <HUSSAINA@cder.fda.gov>
To: 'Hans. Leuenberger (Hans.Leuenberger@unibas.ch)' <Hans.Leuenberger@unibas.ch>, 'Tony Moffat (TMoffat@rpsgb.org.uk)' <TMoffat@rpsgb.org.uk>, 'TOM Layloff (Tlayloff@msh.org)' <Tlayloff@msh.org>, "Kibbe (kibbe@wilkes.edu)' <kibbe@wilkes.edu>, 'Ken Morris (morris@pharmacy.purdue.edu)' <morris@pharmacy.purdue.edu>, 'ken@bensonassocs.co.uk' <ken@bensonassocs.co.uk>, 'Kelsey D. Cook (kcook@utk.edu)' <kcook@utk.edu>, 'Mel (mel@cpac.washington.edu)' <mel@cpac.washington.edu>

Team of the Year Award for FDA's PAT team:

Product and Process Quality Knowledge: Science-Risk Based cGMP's



FDA Whitepaper March 2004
Three Dimensions of the Critical Path



PAT (Process Analytical Technology) Initiative and Quality by Design (QbD)

- What means PAT, i.e. Process Analytical Technology?
- The basic idea: not to test – in the Quality but to build-in the Quality, i.e. "**Quality by Design**"!
- **PAT has been much better accepted by the responsible persons in Manufacturing than in the Development Departments**
- What is the reason?

PAT (Process Analytical Technology) Initiative and Quality by Design (QbD)

- The name of PAT with focus on **Analytical** is somehow unfortunate, which was soon realized by FDA

- Thus the first idea came up to instrument all processes by appropriate means such as NIR Technology, i.e. NIR Spectroscopy, NIR Imaging, Therahertz Spectroscopy and many more analytical techniques often based on Chemometrics using corresponding software packages.

- Thus the "in-line", "on-line" and "at-line"-measurements of the relevant properties has lead to the temptation to continue to "test-in" the quality!

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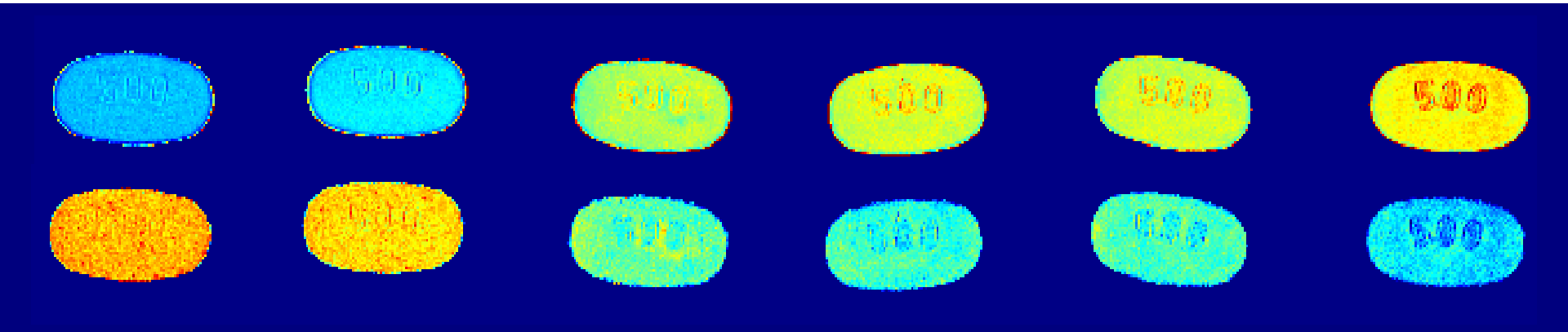
Near Infrared Spectroscopy/Imaging and Terahertz Pulsed Spectroscopy/Imaging for the Analysis of Solid Dosage Forms

Dissertation Lene Maurer, 2. Juni 2008



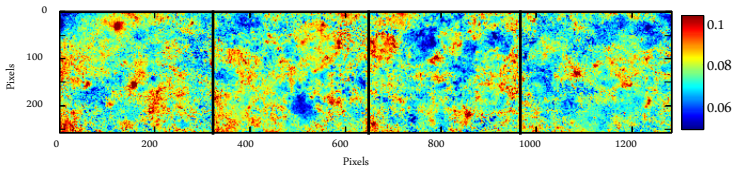
NIR Imaging

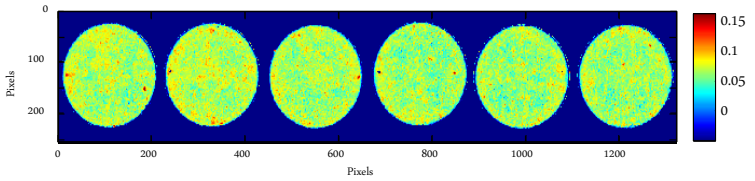
Wirkstoffverteilung in niedrigdosierten Tabletten

Tablettenschichten (abgefräst), B11

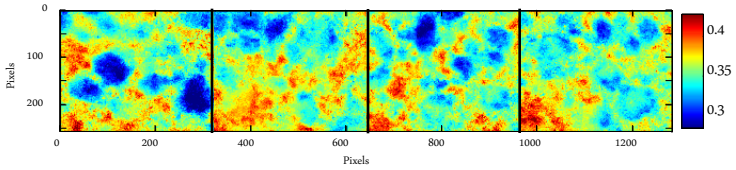
Tablettenflächen (abgefräst), B16-B21

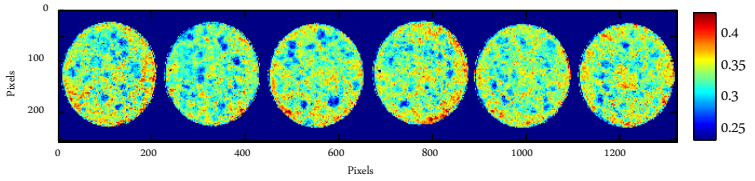
Wirkstoff



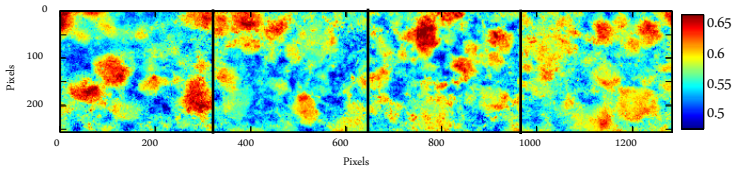


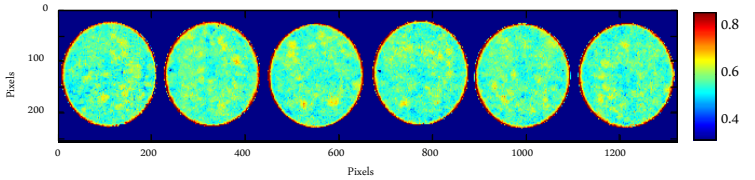
Hilfsstoff 1





Hilfsstoff 2





PLS-DA distribution maps

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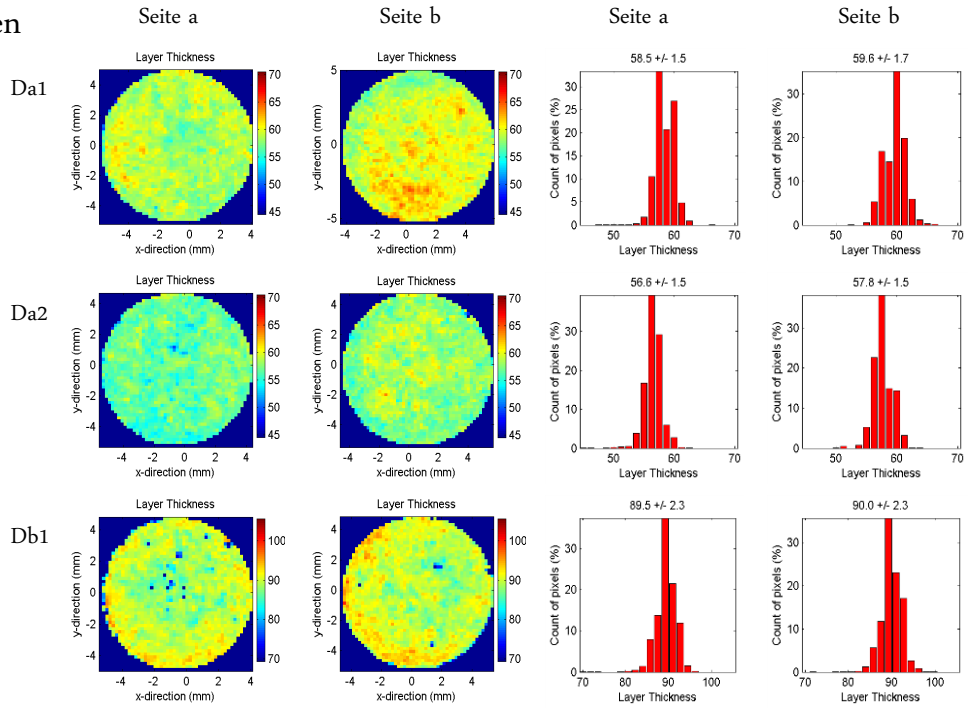
TPI Coated Tabs

Verschiedene Coatingdicken



PAT (Process Analytical Technology) Initiative and Quality by Design (QbD)

- However to "test-in" the quality was not the idea of FDA! On the over hand, it is important to monitor a process, which allows to analyse its behaviour!

- In the mean time many companies have instrumented in an excellent way their process equipment which will lead to a better process understanding and as a consequence to a higher quality.

- Thus If a process works in best conditions, it is possible to accept this result as to "build-in " the quality.

Advanced Powder Technol., Vol. 16, No. 1, pp. 3–25 (2005)

Also available online - www.vsppub.com

Invited review paper

Pharmaceutical powder technology — from art to science: the challenge of the FDA's Process Analytical Technology initiative

H. LEUENBERGER * and M. LANZ

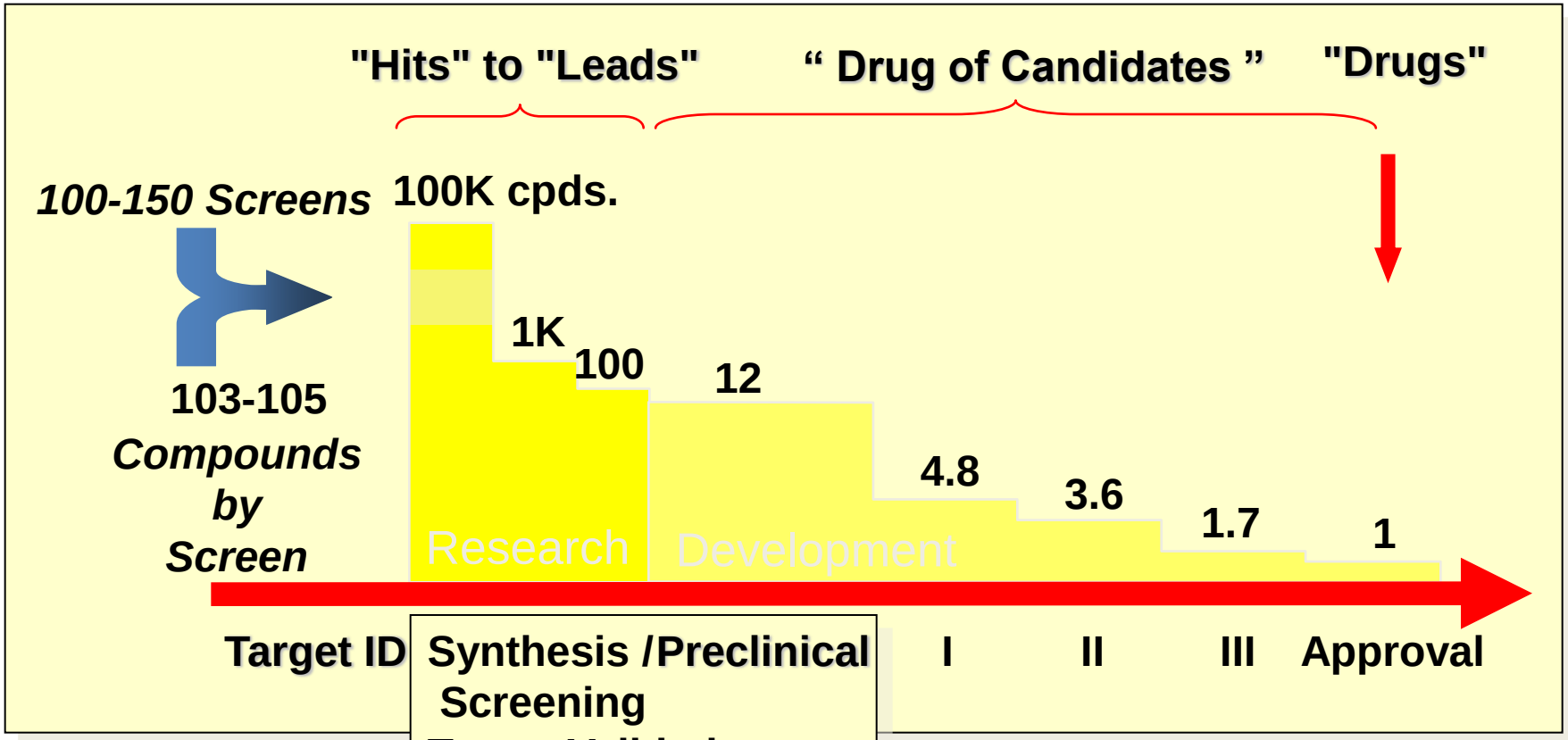
Institute of Pharmaceutical Technology, Pharmacenter of the University of Basel, Klingelbergstrasse 50, 4056 Basel, Switzerland

Quality by Design (QbD) is however the primary task of the Development Department!

- To achieve **QbD** it is essential that this happens in the **early phase of development**!
- The problem is that in the preclinical phase there maybe simultaneously 12 product candidates in the pipe-line and nobody knows, which of the twelve candidates will be successful!
- Which of the twelve candidates has which priority? Thus if all **12 are equal**, do we have **some** of them, which **are more equal**? How do we attribute the available human and money resources for these 12 candidates? How can we measure the performance of our development work/process?

Preclinical Phase:12 Drug Candidates !

Slide: A. Hussain, FDA



How to share the resources in case of 12 drug candidates?

- Due to the limited resources the following rule became popular: **the 20%/80% rule**
- This rule is a common practise in the pharmaceutical industry
- Thus **with 20% of time and effort** allocated to a project **80% of the goals** should be **achieved!**
- What about the **performance** ? How do we measure performance? Let us look at the **SIGMA CONCEPT!**

PAT (Process Analytical Technology) Initiative and Quality by Design (QbD) – Can we afford it ?

- Is it possible to reduce time to market and to enhance product quality?
- The Sigma Concept
- Goal: Six Sigma Performance

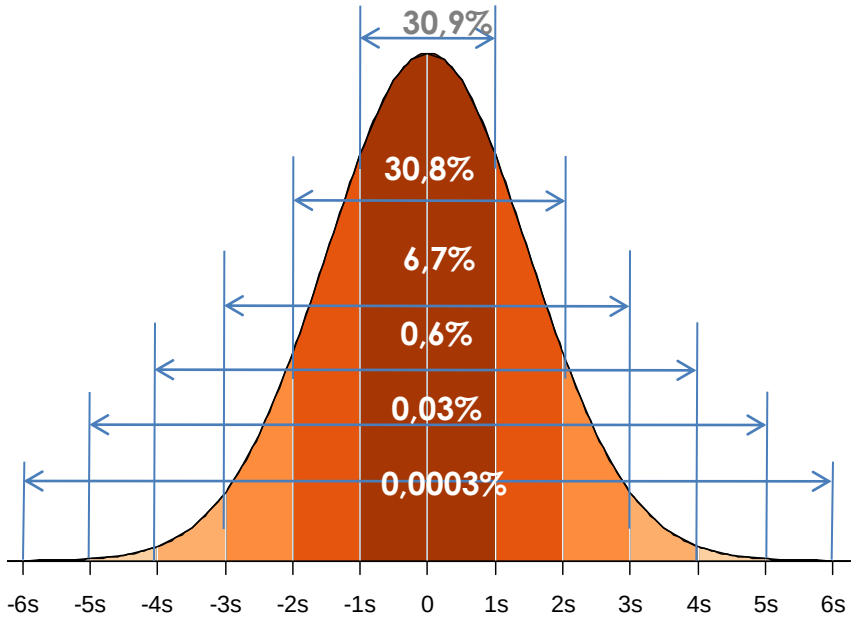
Performance of a process → Sigma value

Sigma	Yield, %	Defects, %	DPMO
1	30,9	69,1	690000
2	69,2	30,8	308000
3	93,3	6,7	66800
4	99,4	0,6	6210
5	99,97	0,03	320
6	99,9997	0,0003	3,4

Source: Kurt Haubner, www.sixsigma.de

Normal distribution - Gauss!

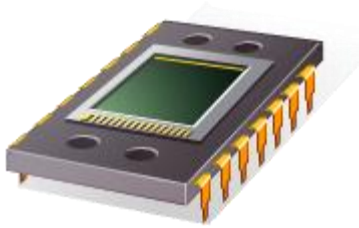
$$f(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{x^2}{2\sigma^2}}$$



Source: Jeremy Kemp, adapted

The SIGMA Concept

Champion: Chip industry



6 Sigma performance:

amount of defective samples = 3.4 DPMO

Performance

Pharmaceutical Industry ~ 2 Sigma

i.e. > 20% defectives in case of the **dynamical** Sigma Value, which has been adopted during the phases of early development, i.e. in thePreclinical Phase up to the decision point of defining the final marketed dosage form in the Clinical Phase I, II or even III?

i.e. ca. 4.5% defectives (snap-shot evaluation of the final dosage form (**static** Sigma Value!)

Common approach to keep costs under control

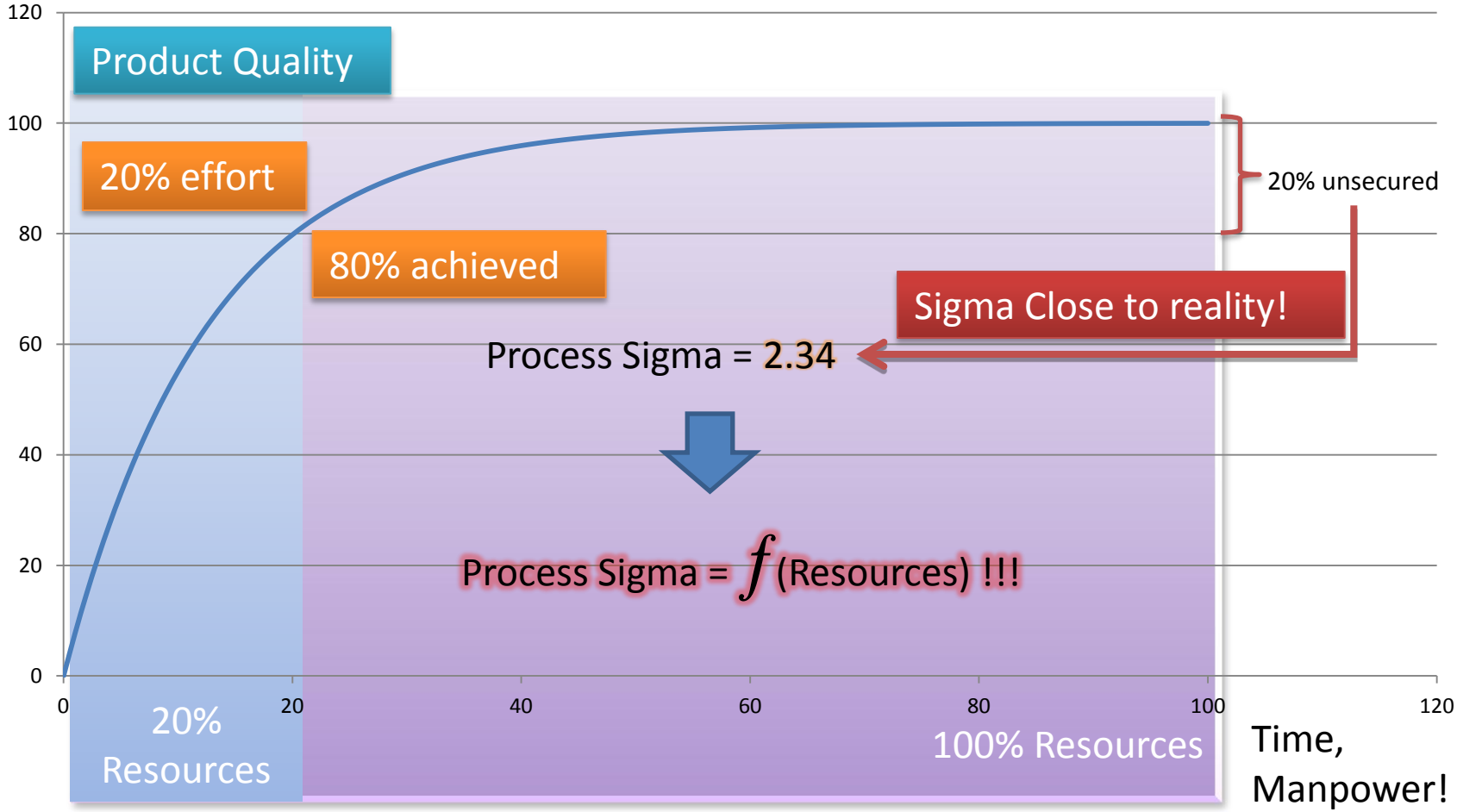
The 20% / 80% Rule:

With 20% of time and effort dedicated to a project
80% of the goals can be achieved!

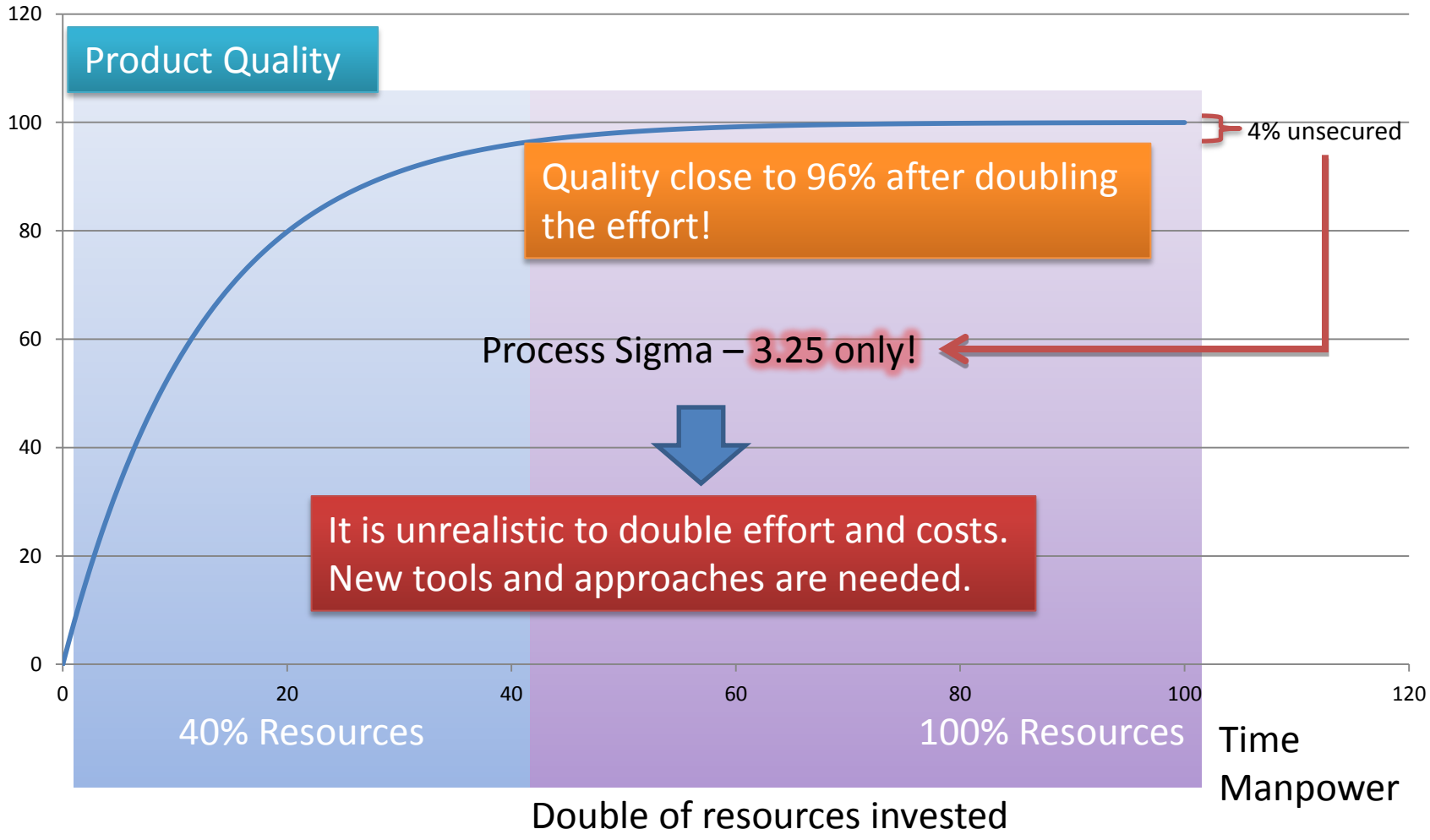
Is this approach adequate for an optimal Quality by Design?
Can we afford a 6 Sigma Quality? What is the Quality in case of the 20%/80 % Rule?

Let us make an estimate!

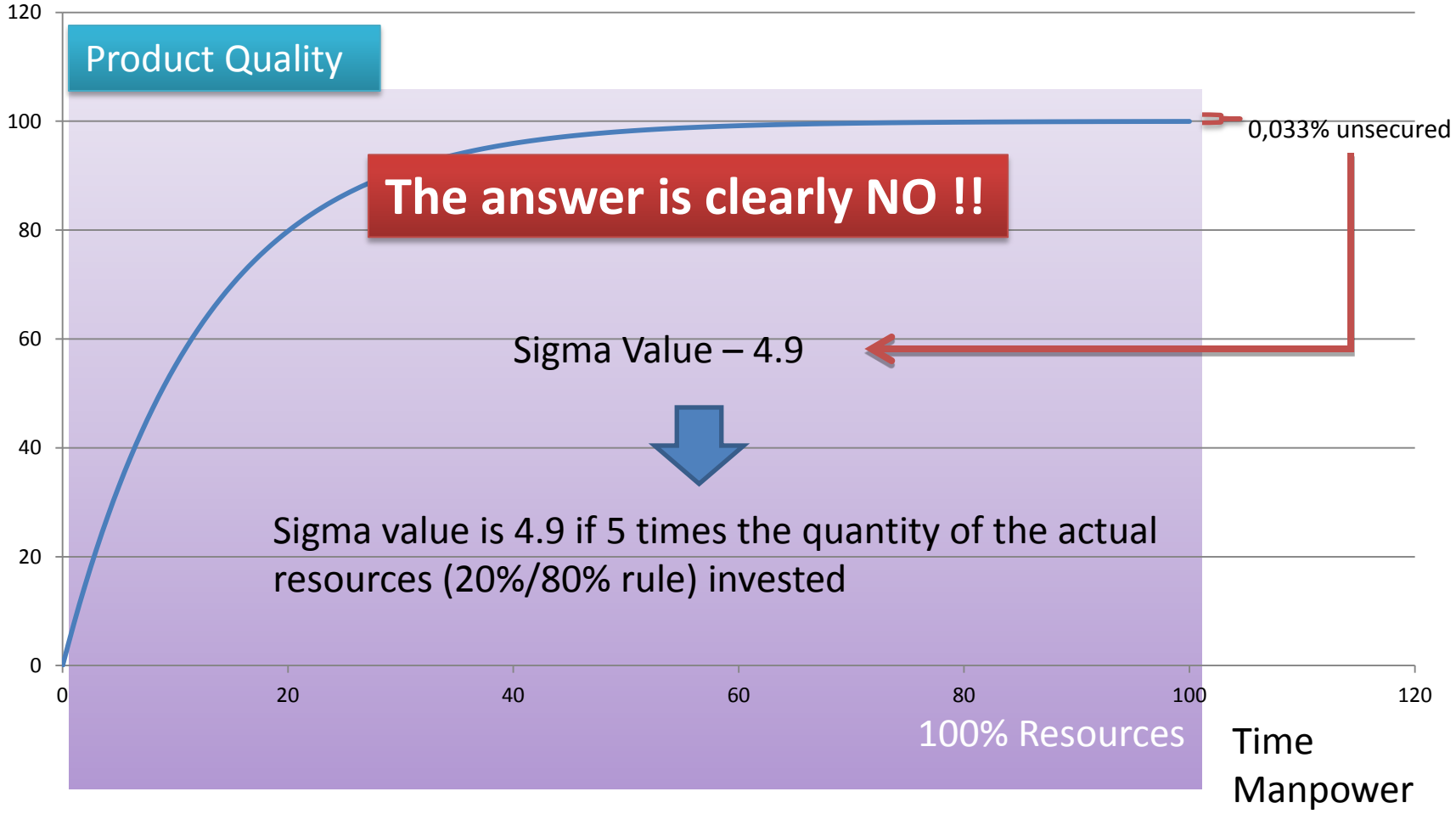
Sigma Value – function of resources



Can we afford to double effort and costs?!



Can Six Sigma be achieved with conventional tools?



PWC Pharma 2020: Vision e-Development

- SEE the study of Price Waterhouse Coopers :
- **PWC PHARMA 2020 – a Vision**

- **Is it possible to introduce special e-tools to facilitate the work of development?**
- **We think: YES**

- Is it possible to copy e.g. the concepts of the aircraft industry, using „in-silico“ Computer-aided design?
- Let us compare the aircraft building industry with the development of a solid dosage form!

Aircraft and drug formulation: similarities

- Development and production of a **vehicle** that
- **delivers the drug substance**
  - precisely at the **right time**
  - in the **right quality**
  - in the **right quantity**
  - to the **right site** in the body.

Designing aircraft: *in silico* approach

Boeing 777: 100% digitally designed using 3D solids technology

- The consequences were dramatic:
  - Elimination of > 3000 assembly interfaces, without any physical prototyping
  - 90% reduction in engineering change requests (6000 to 600)
  - **50% reduction in cycle time for engineering change request**
  - **90% reduction in material rework**
  - 50x improvement in assembly tolerances for fuselage.

How can we do that for pharma?

Source: http://www.cds.caltech.edu/conferences/1997/vecs/tutorial/Examples/Cases/777.htm

New tools and approaches are needed!

- Personally I know only one e-tool, which may fulfill this task:
- F-CAD, Formulation Computer-Aided Design by CINCAP, let us have a look:
- F-CAD is different from any existing e-tool such as
  - Expert System
  - Artificial Neural Network
  - Collection of existing formulations etc

New tools and approaches are needed!

- The Concept of F-CAD developed by CINCAP

- F-CAD is based on
  - Physical laws
  - Percolation Theory
  - Process Understanding
  - Particulate Formulation Design
  - And uses a sophisticated Algorithm taken from nature, i.e.
  - The Cellular Automata Approach
  - What are Cellular Automata?

What means a Cellular Automata Approach?

» What are Cellular Automata?

» Cellular Automata (C.A.) are simple mathematical idealizations of natural systems (Stephan Wolfram, Prof. Mathematics, Princeton University)

» In fact, C.A. can be considered as discrete idealizations of partial differential equations used to describe natural systems such as „Fick's Laws" in case of diffusional effects.

»Thus with relatively simple rules of C.A. can discribe complex textures in nature such as on a marine shell or the complex B.-Z. oscillating chemical reaction (see next slide).

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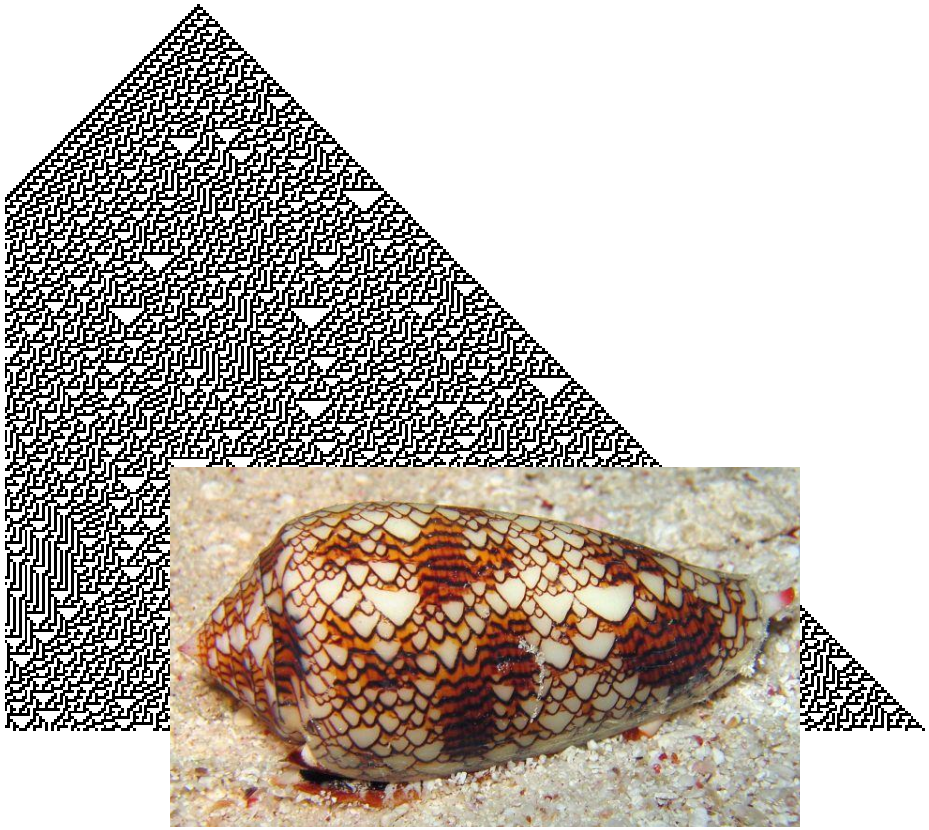
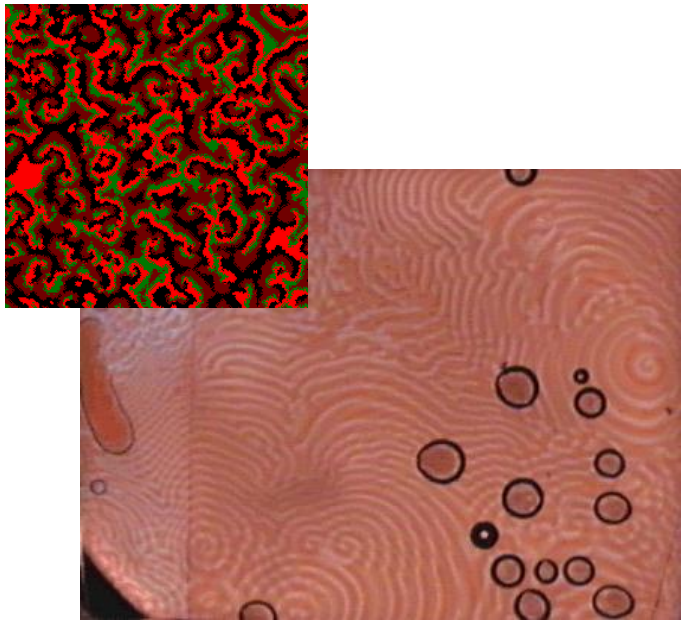
Cellular automata and modeling of natural phenomena



www.directopedia.org



Belousov-Zhabotinski Reaction

C.A.:What is in common with Percolation Theory?

The Concept of F-CAD:

F-CAD and its special tool C.A. need for the description of the tablet a (3D) Lattice like in case of Percolation Theory.

Percolation Thresholds p_c need to be known in 3D for developing a robust formulation. This can be calculated by C.A.

Thus it is necessary to define a 3D lattice and a very large number of particles (> 100 000 , better 1 000000) located on this lattice: i.e. Particles representing 1) the active substance, 2) the excipients involved, 3) the pores (particles representing void space!) of the tablet, 4) representing liquid droplets of water (in case of the drug dissolution process to be described)

What is needed to perform a C.A. calculation?

F-CAD needs:

A supercomputing facility
A special core algorithm to describe the process taking place locally at the site of the particle investigated:
i.e. At the site of the drug particle exhibiting a specific water Solubility
i.e. At the site of a excipient particle exhibiting a specific solubility (such as Lactose) or swellability (such as Maize Starch) etc
i.e. At the site of a pore, at the site of the surface of the tablet etc.

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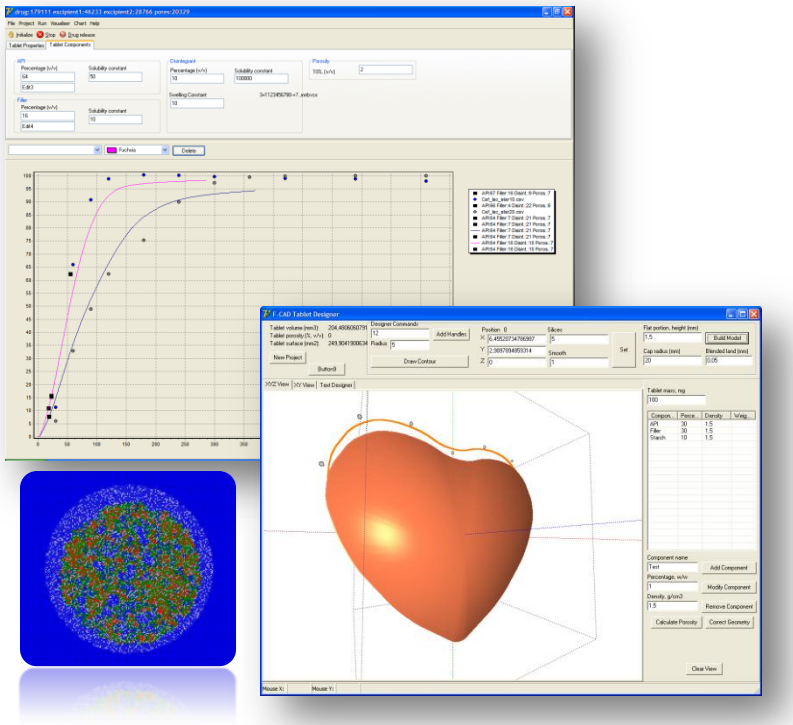
VES and F-CAD Screenshots



Orientation: Quality by Design (QbD)

Formulation R&D

- F-CAD
  - *In-Silico* formulation development
  - Risk assessment and mitigation
  - Cost reduction

F-CAD Robust Formulation!

Production

- Virtual Equipment Simulation (VES)
  - Continuous Education + Personalized Training
  - Minimum human error

VES Operator Training

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CINCAP F-CAD

F-CAD In-Brief

Benefits of F-CAD

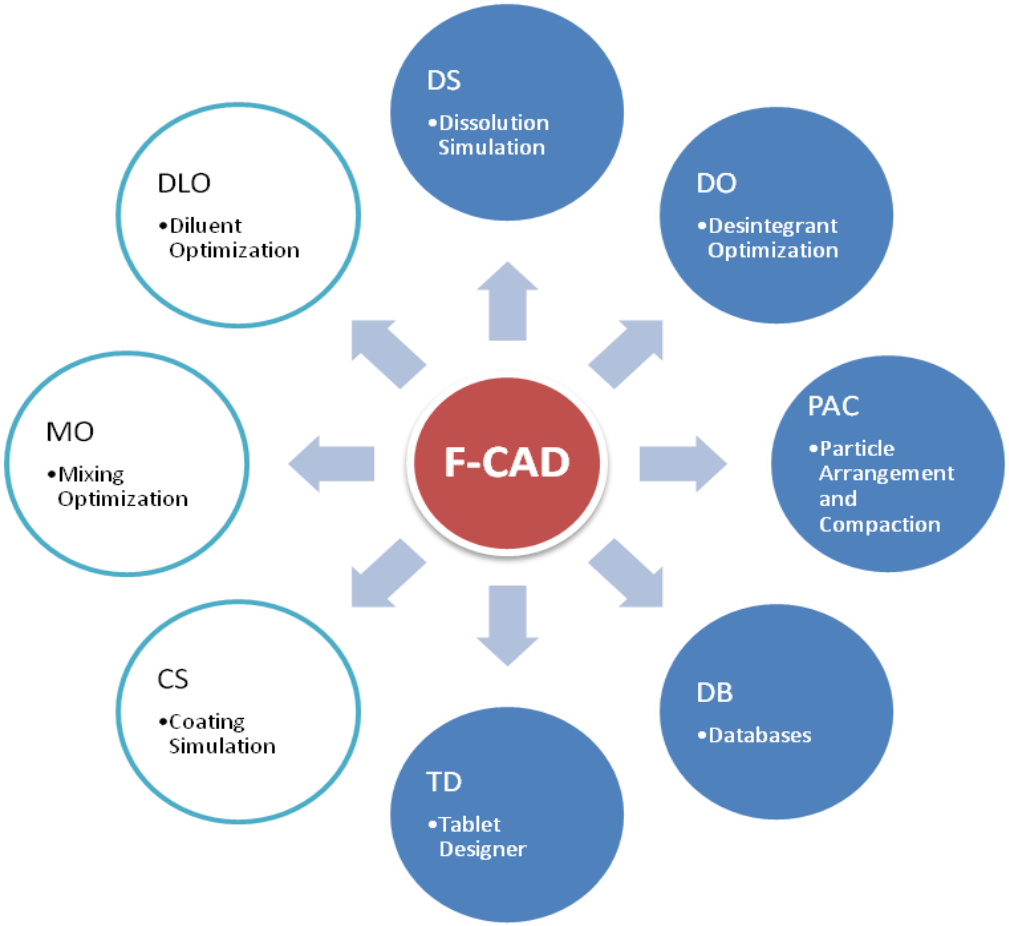
- Significant development **costs reduction**
- **Real connectivity** between marketing and pharma R&D and production depts.
- Higher end-product quality – **Quality By Design** (QbD)
- Knowledge and experience management
- Unified solution for
  - Immediate and controlled release formulations
  - Support for different unit operations (granulation, milling, etc.)
  - Tablet size and shape design

  ... and much more.

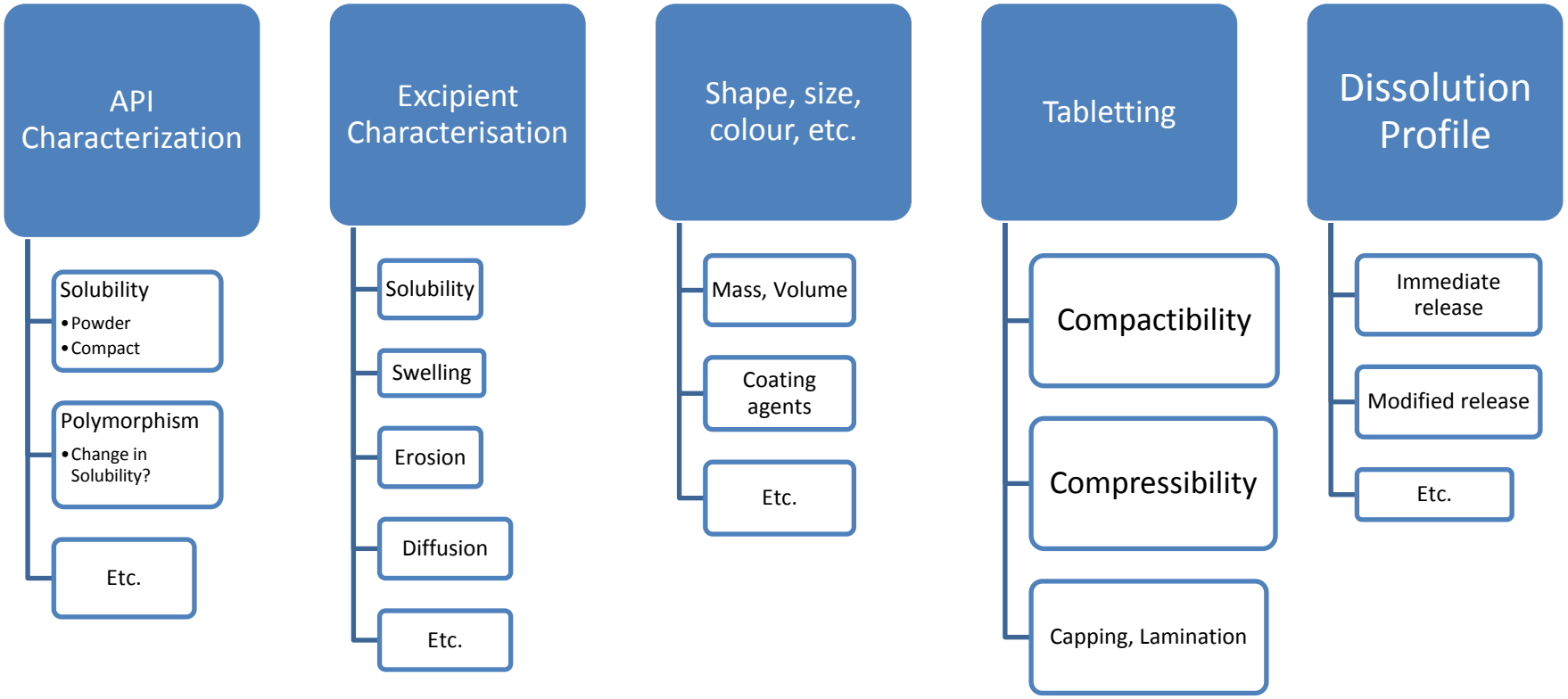
F-CAD Selected Features

- Formulation design with F-CAD starts with final-product desired properties, such as shape, dissolution rate, etc.
- F-CAD is tablet shape sensitive.
  - F-CAD can be used to find out differences in dissolution profiles for different shapes of tablets with identical composition.
- Different particles size distributions of components will result into different dissolution profiles
- Effect of compact porosity is taken into account along with hydrophilicity/hydrophobicity, including solubility and swellability of the components.
- Run-time visualization of tablet undergoing in-silico dissolution test.

F-CAD Modules



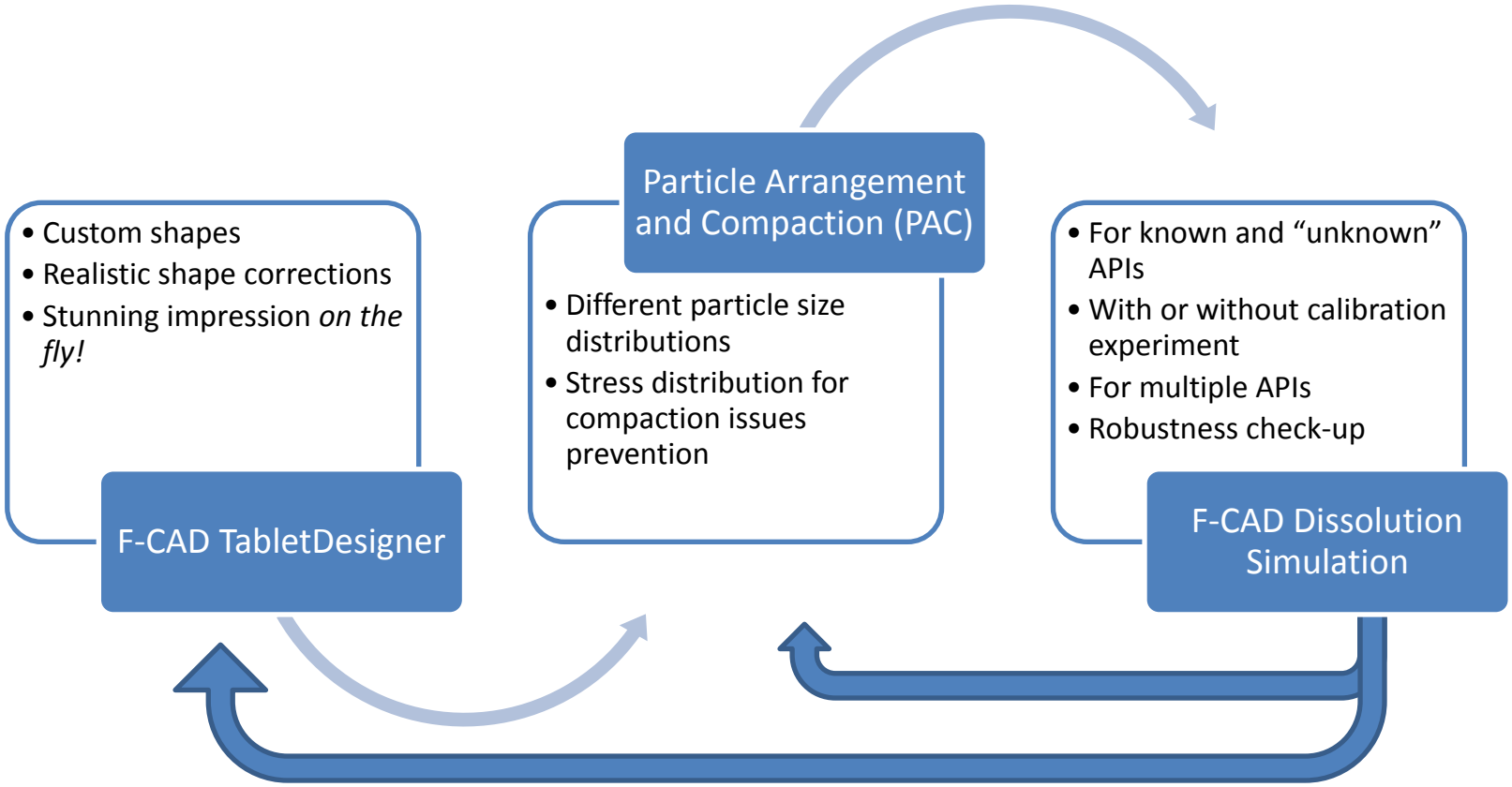
Formulation development with F-CAD



F-CAD - QbD

- Screening for robust formulation
- Setting up acceptance criteria for raw materials
- Analyse scale-up/scale-down issues and prevent problems

F-CAD modelling process



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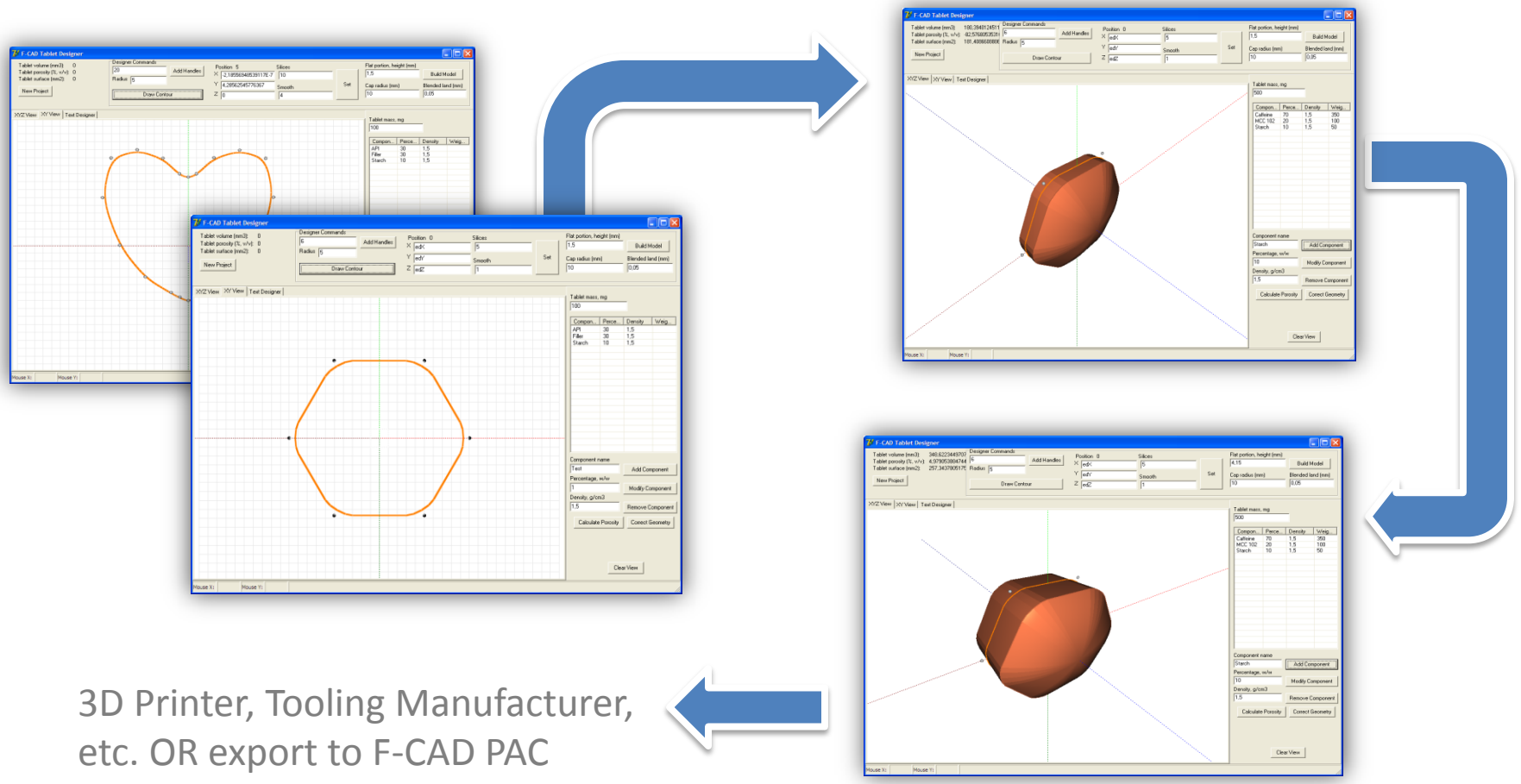
F-CAD Tablet Designer



3D Printer, Tooling Manufacturer,
etc. OR export to F-CAD PAC

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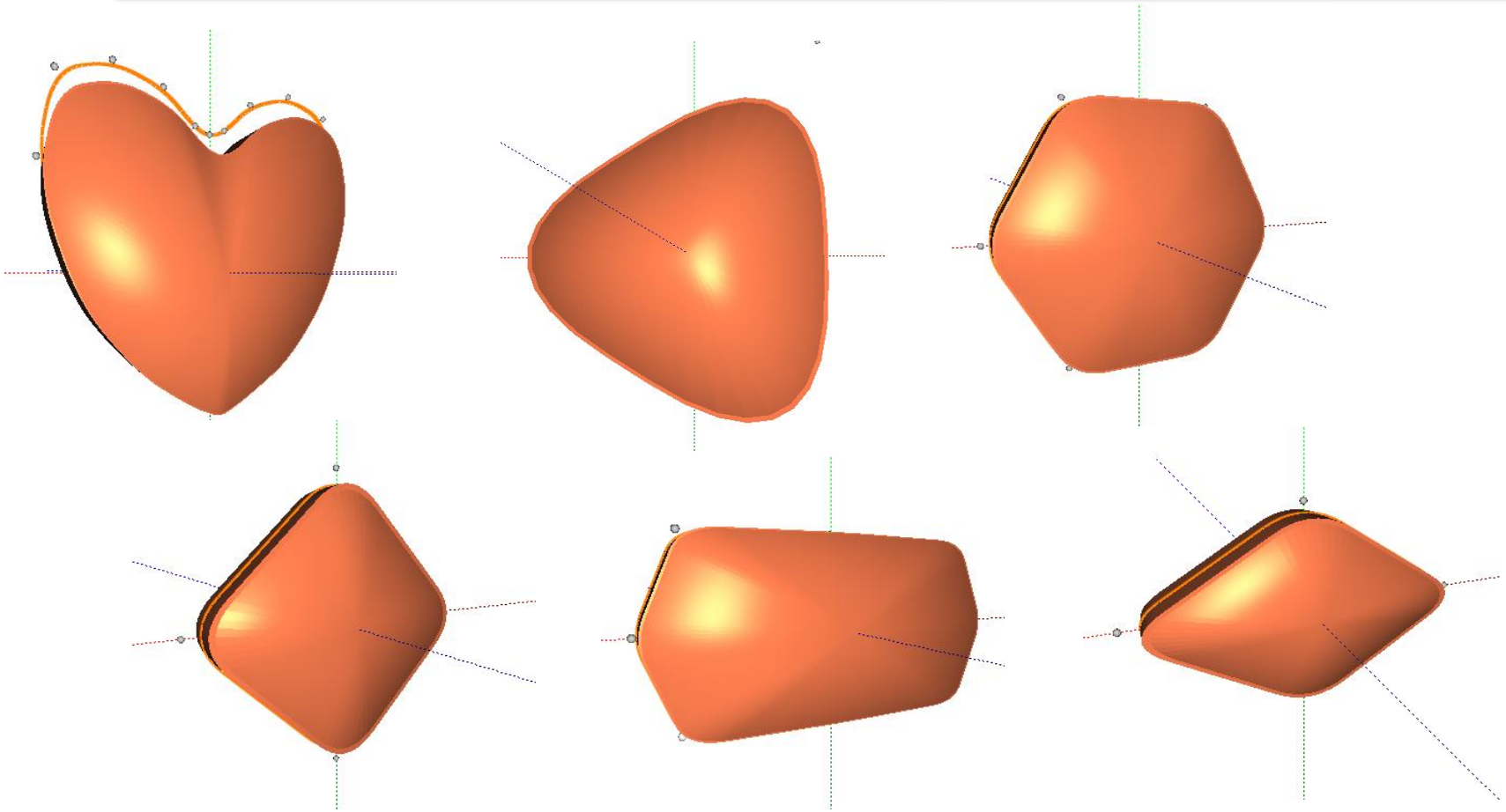
Custom Shapes with F-CAD Tablet Designer



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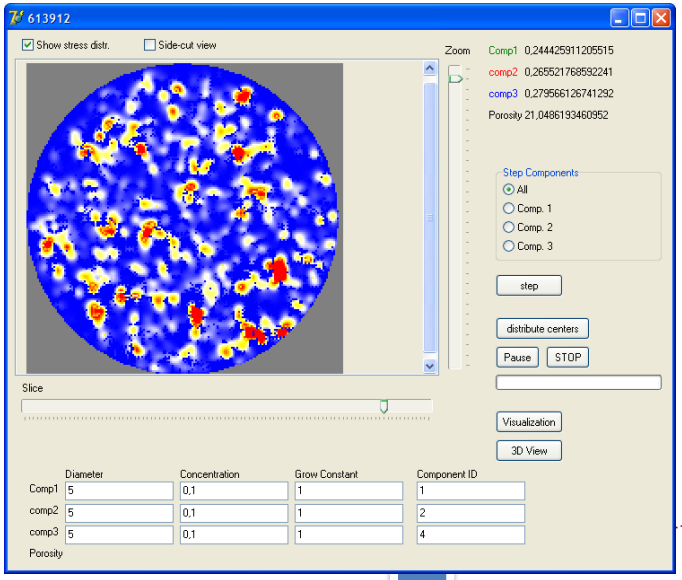
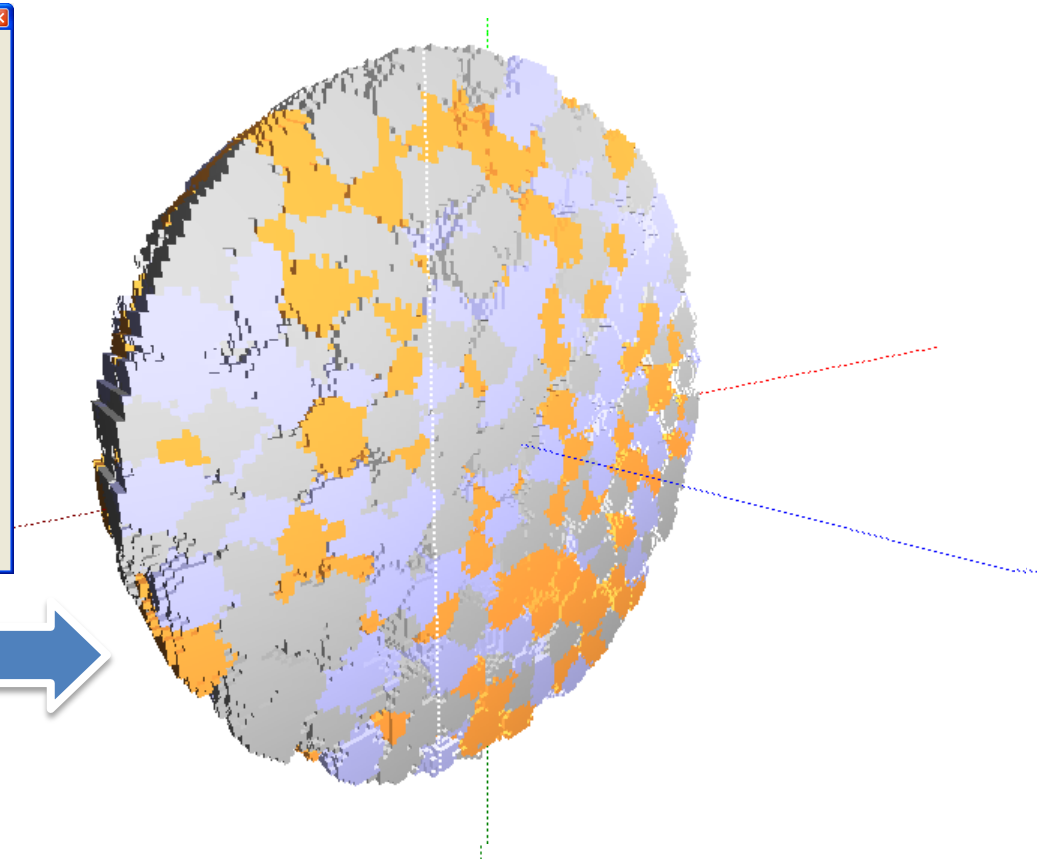
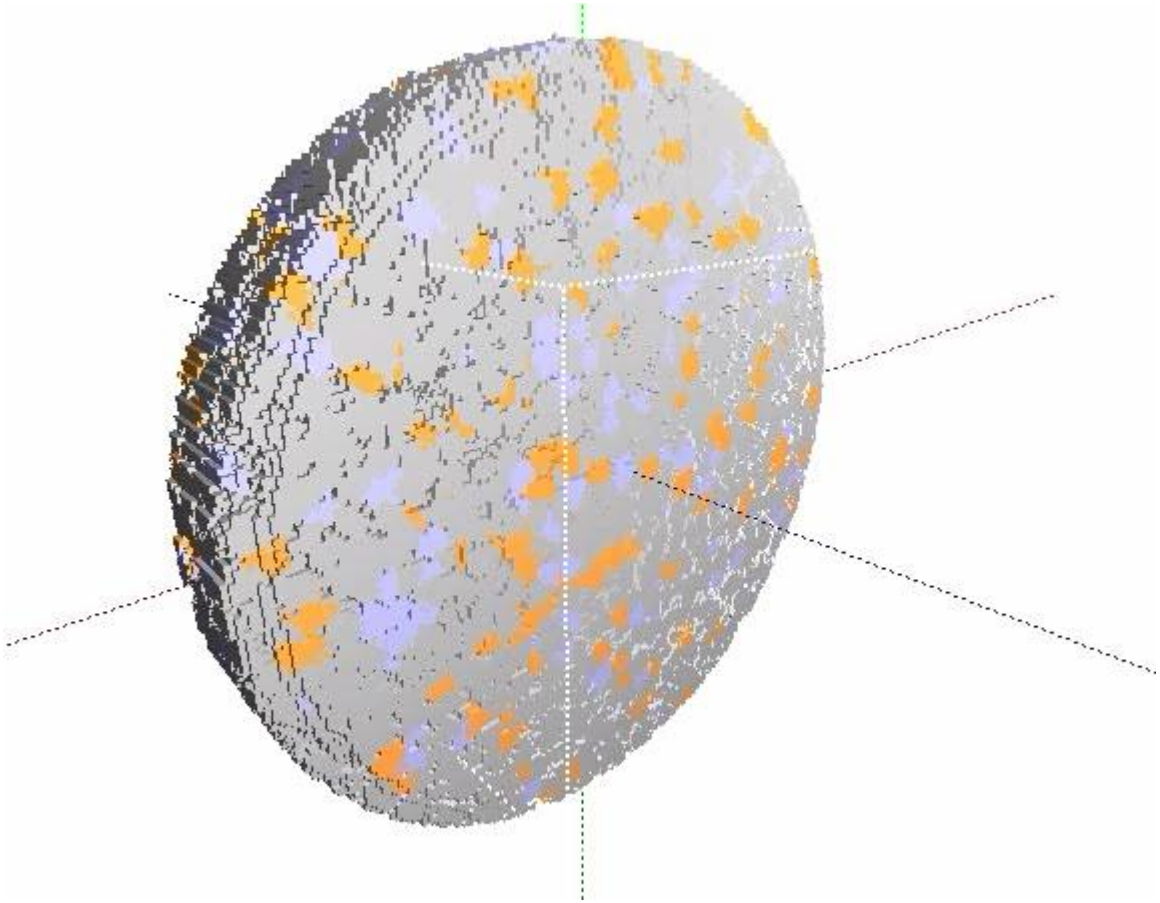
F-CAD PAC – Particle Arrangement and Compaction





Resulting compact



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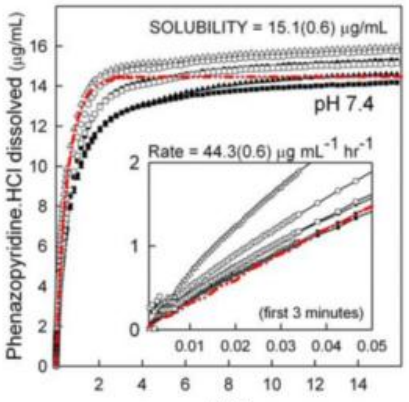
F-CAD DS – *in silico* Profiles



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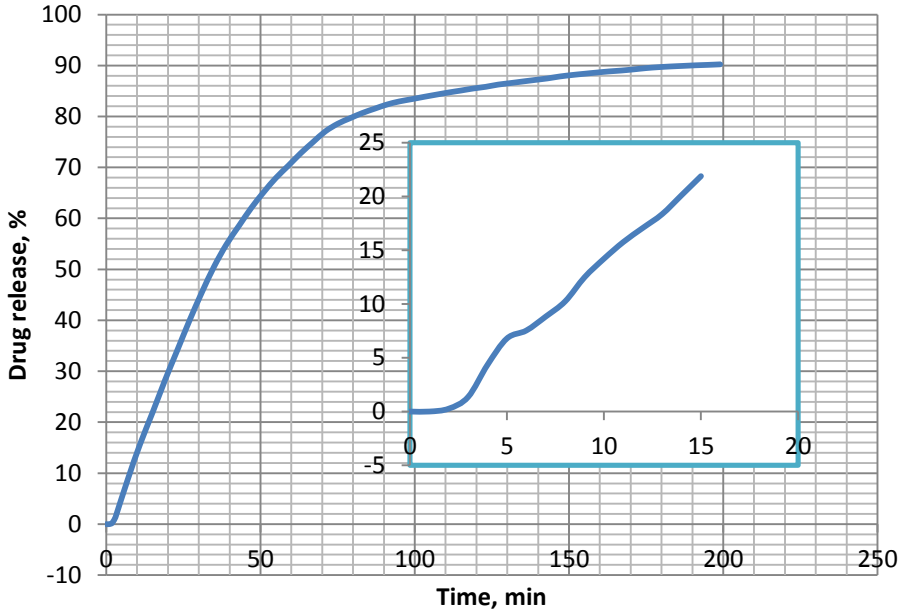

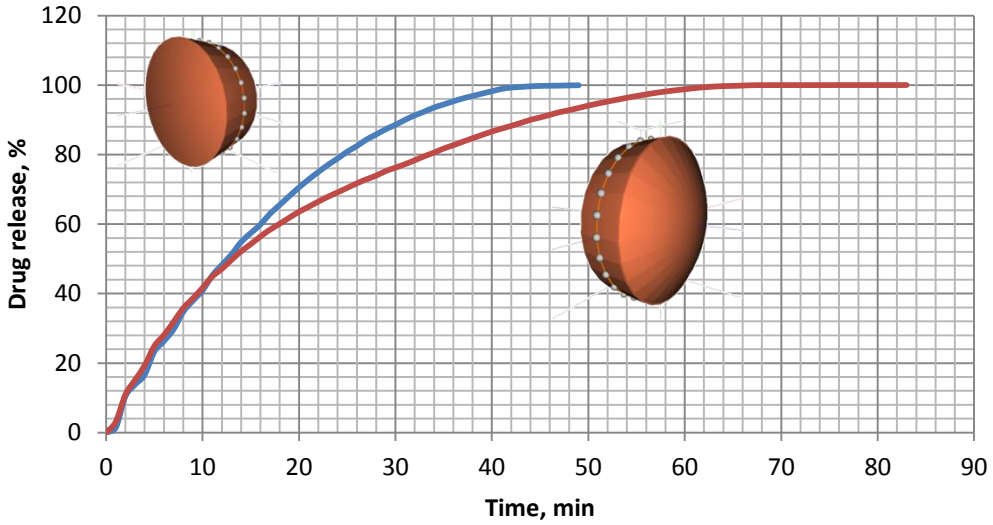

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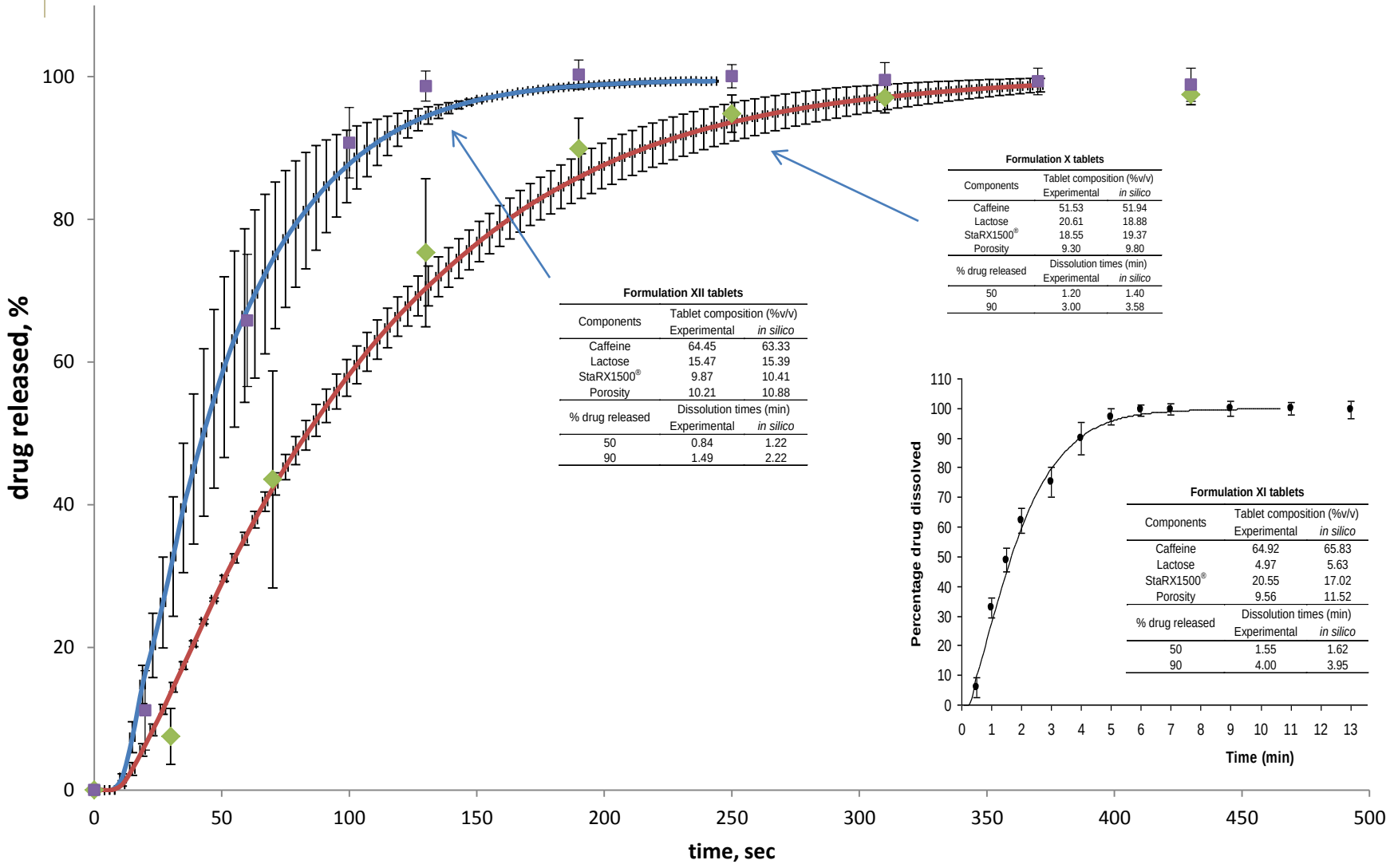
Experimental vs. in silico dissolution profiles of different formulations with caffeine



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 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 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."

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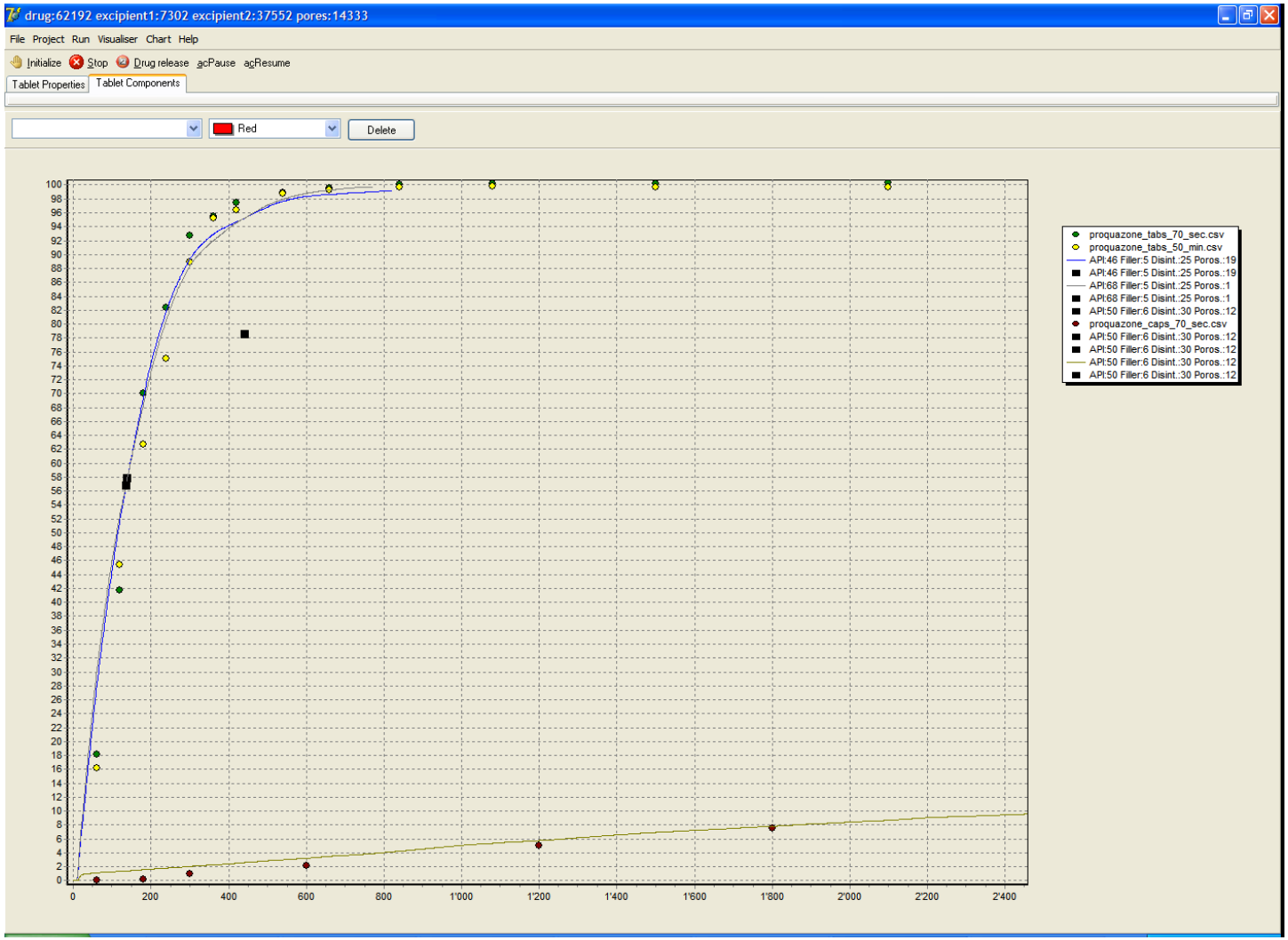
Switzerland

Capsule/Tablet simulation



One for All

- F-CAD Core Algorithm
  - PAC
    - Calculation of stress distribution
    - Multi-layered tablets
  - DS
    - Extended release
    - Immediate release
    - Combination drugs
  - Coating (under development)
    - Bridging
    - Peeling
    - Roughness
  - Flowability in hoppers, feeders of arbitrary geometries (under development)

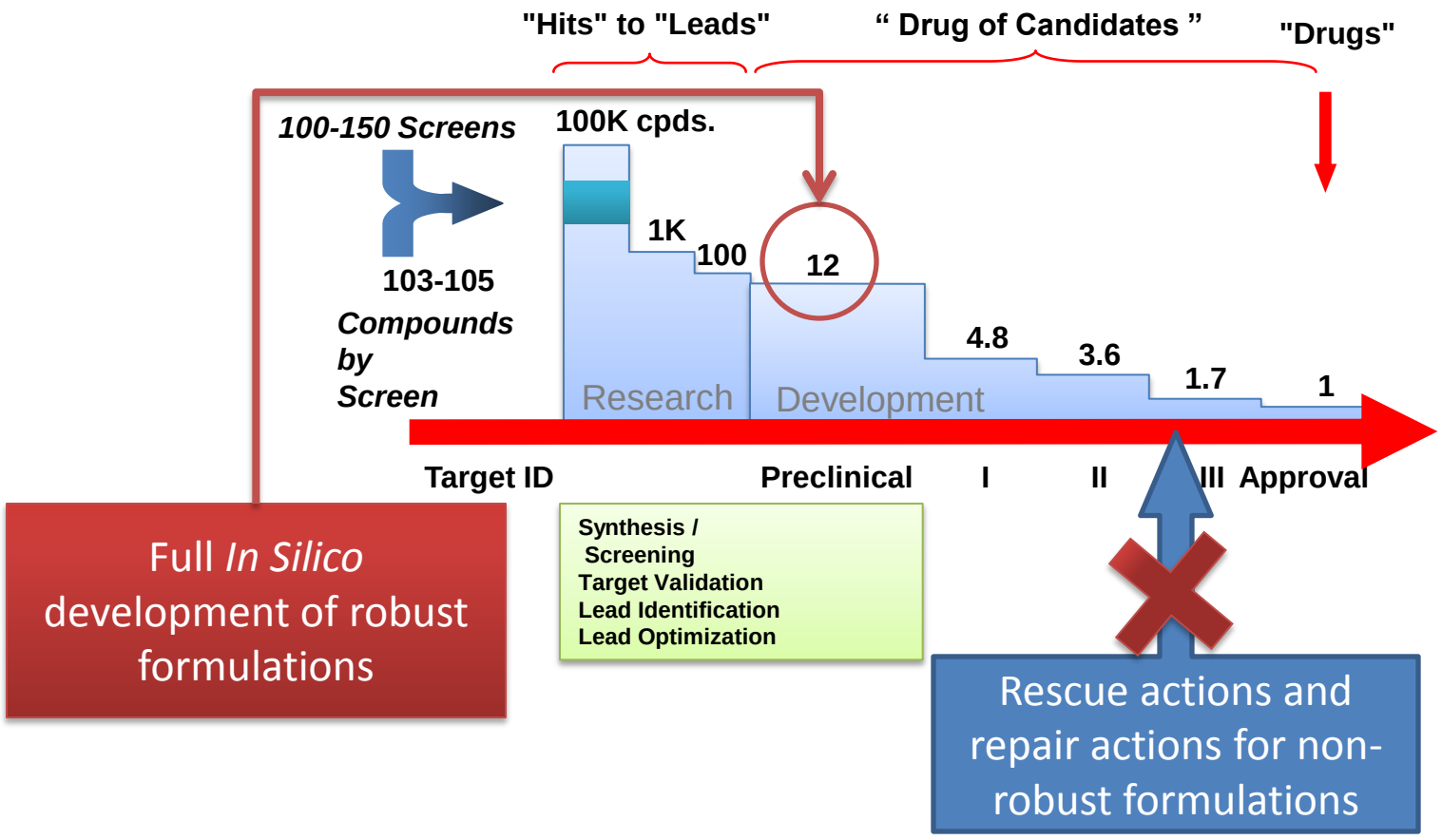
F-CAD Realms

- Marketing
  - Shape, colour, size design
- R&D Support
  - In-silico robust formulation design
- Manufacturing Support
  - In-silico Scale-up and Launch Support
- Finance
  - Cost assessment
- Risk management
  - Risk assessment and mitigation

Computing formulation quality

- If we use computation do we still need experimental trials?
  - Yes. However, not for screening but confirmation
- If it is so good, can I substitute human scientists with it?
  - No. However, free your scientists from innovation hurdles induced by costly, time-consuming lab tests
- I have my know-how (technology, physical and chemical effect, etc.), can I integrate them into computational algorithms without going deep into mathematical or computational science?
  - You can and you have to! You can naturally use and enter all your available know-how(s), previously obtained experimental data to boost up versatility of your computed models.

Slide: A. Hussain, FDA



Summary: Goals of F-CAD

- Superior quality of formulations than with existing approach
- Possibility to quantify the robustness of the formulation
- Possibility to define specifications based on science
- Reduction of time to market
- Boosting formulation and process technology understanding
- Computer aided design of formulations similar to aircraft design
- Savings comparable to the savings of the aircraft industry

F – CAD is a tool to replace lab experiments

- **Physical process** - a sustained phenomenon or one marked by gradual changes through a series of states
- **Computation** is a process following a well-defined model that is understood and can be expressed in an algorithm, protocol, network topology, etc.
- Physical process + Computation = **Result!**

For EVERY time-step!

- **The F-CAD experiments are close to reality, but can be done with much lower costs and much much faster. Thus hundreds of formulations can be studied in a short time to find the best option!**

F – CAD : examples of estimates for cost savings

- **Example I: Feasibility study** – concerning the development of a generic formulation
- **Costs of lab experiments** depend on the specific medicinal product to be copied or slightly modified such as an immediate release or sustained release formulation. Thus according to a rough estimate costs between **100 000 and 200 000 Euros** can be expected.
- **Costs of in silico experiments:** between **10 000 and 20 000 Euros, thus savings of up to 90%**
-

Savings for each lab work possible !

F – CAD : examples of estimates for cost savings

- **Example II: High quality formulations "ready" for market already in the preclinical phase** – concerning the development of a new medicinal product or formulation
- **Costs of lab experiments** to develop a first workable formulation based on existing know-how and knowledge with a small amount of the new, at this stage extremely expensive drug substance: **100 000 and 200 000 Euros**, neglecting costs of the drug substance (conservative estimate).
- **Costs for 12 drugs** in the pipe-line **with 2 strengths** of API: between **2 400 000 and 4 800 000 Euros**, neglecting costs for the API at this early stage!
- **Costs of in silico experiments:** between **240 000 and 480 000 Euros, thus savings of up to 90%!**

F – CAD applications for

- Marketing
  - Shape, colour, size design
- R&D Support
  - In-silico robust formulation design
- Manufacturing Support
  - In-silico Scale-up and Launch Support
- Finance
  - Cost assessment
- Risk management
  - Risk assessment and mitigation

How will the Quality by Design Initiative Affect Formulation Development and Manufacturing?

CONCLUSIONS

- **MANUFACTURING**
  - More at-line, on-line and in-line IN – PROCESS TESTING
  - GOAL: Parametric release of the batches
- **PHARMA R&D**
  - New tools are necessary to achieve a SIX SIGMA PERFORMANCE
  - I am convinced that e-DEVELEOPMENT will have a future
  - In order to save money and to increase the quality of the formulations and processes

F-CAD may become State of the Art

Thank you for your attention!

Audience Q&A

About CINCAP

- The Center for Innovations in Computer-Aided Pharmaceutics, CINCAP GmbH is a start-up enterprise mainly focusing on the novel, science-based software products to assist in design, development and production of modern pharmaceutical products.

- CINCAP main activities include:
  - Development of the computer-aided formulation design software and technologies, along with scientific research in pharmaceutical process technology, process optimization and modeling. The corresponding software product of CINCAP is **F-CAD.**
  - Research and development of reliable process simulators of existing pharmaceutical machinery for different unit operations. This concept and technology is also known as **Virtual Equipment Simulators (VES).**
  - Additional services rendered at CINCAP include design and development of computationally intensive software for process simulation; pharmaceutical, medical, and biological fields of science and technology.

- CINCAP GmbH is incorporated in Switzerland (BL) as Limited Liability Company.
- Founders: Prof. Hans Leuenberger, Dr. Maxim Puchkov