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Formulation CAD – The tool of choice for Quality by Design

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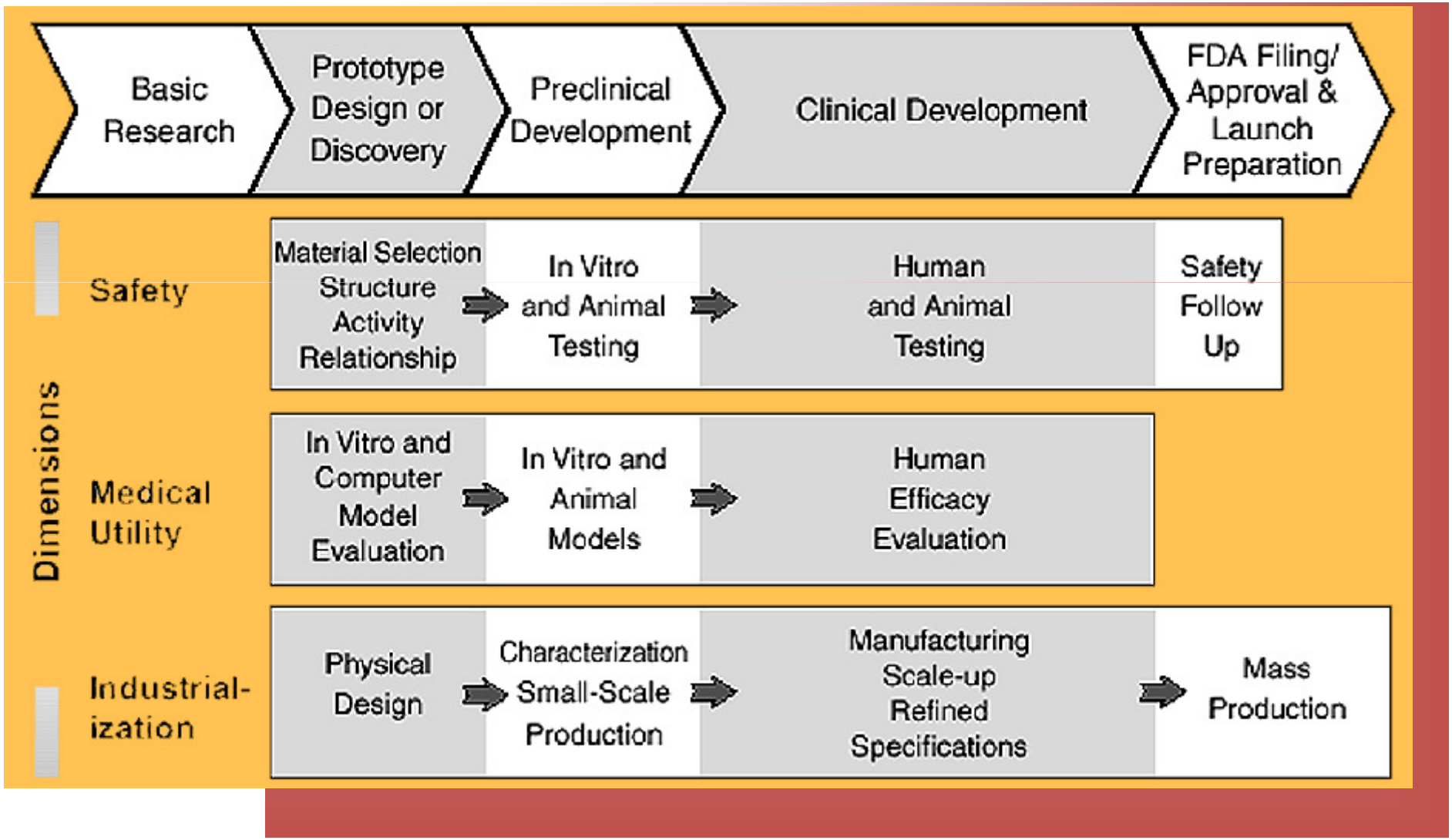
FDA Whitepaper March 2004
Three Dimensions of the Critical Path



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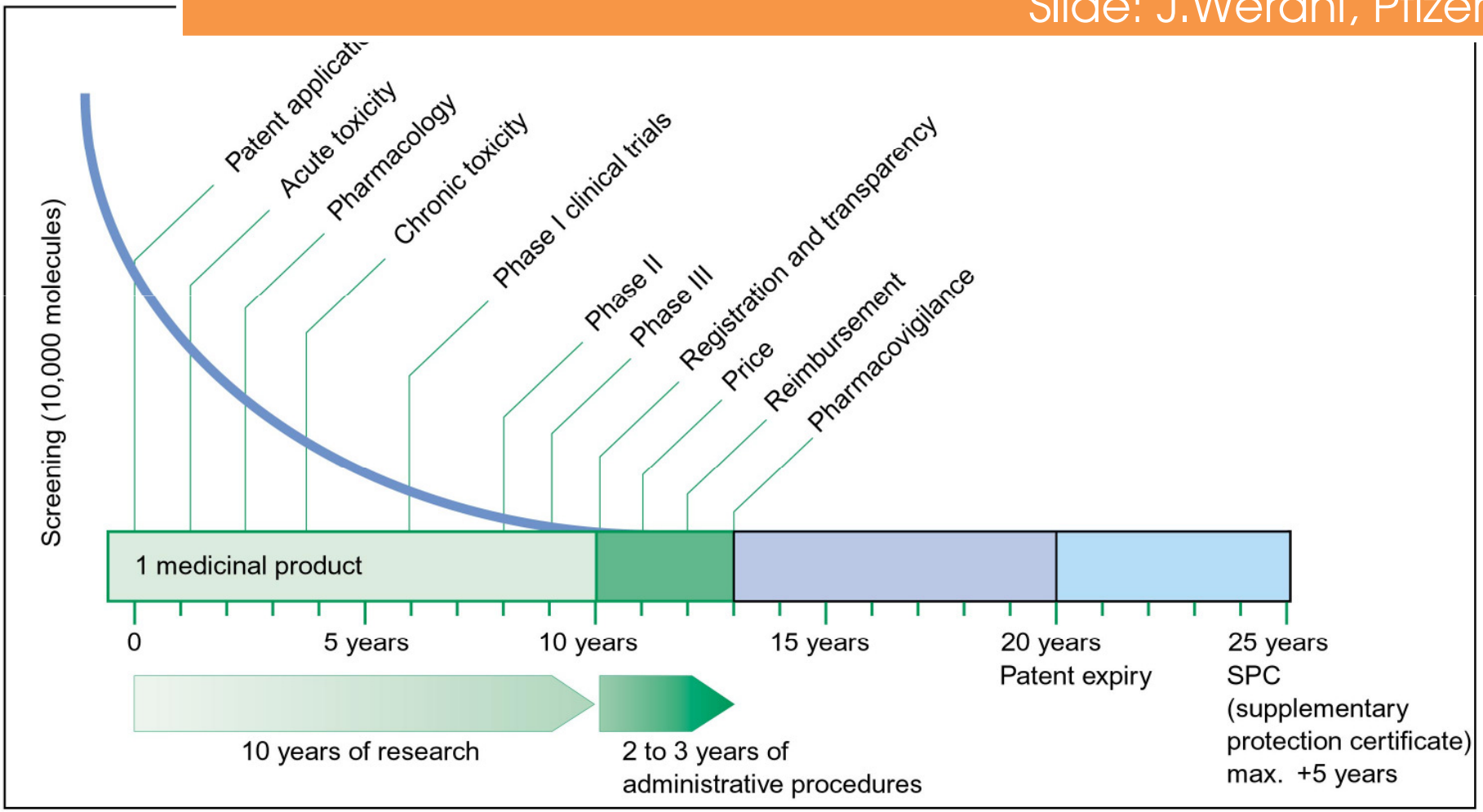
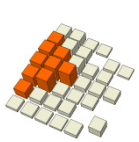
Research & Development Process
Slide: J.Werani, Pfizer





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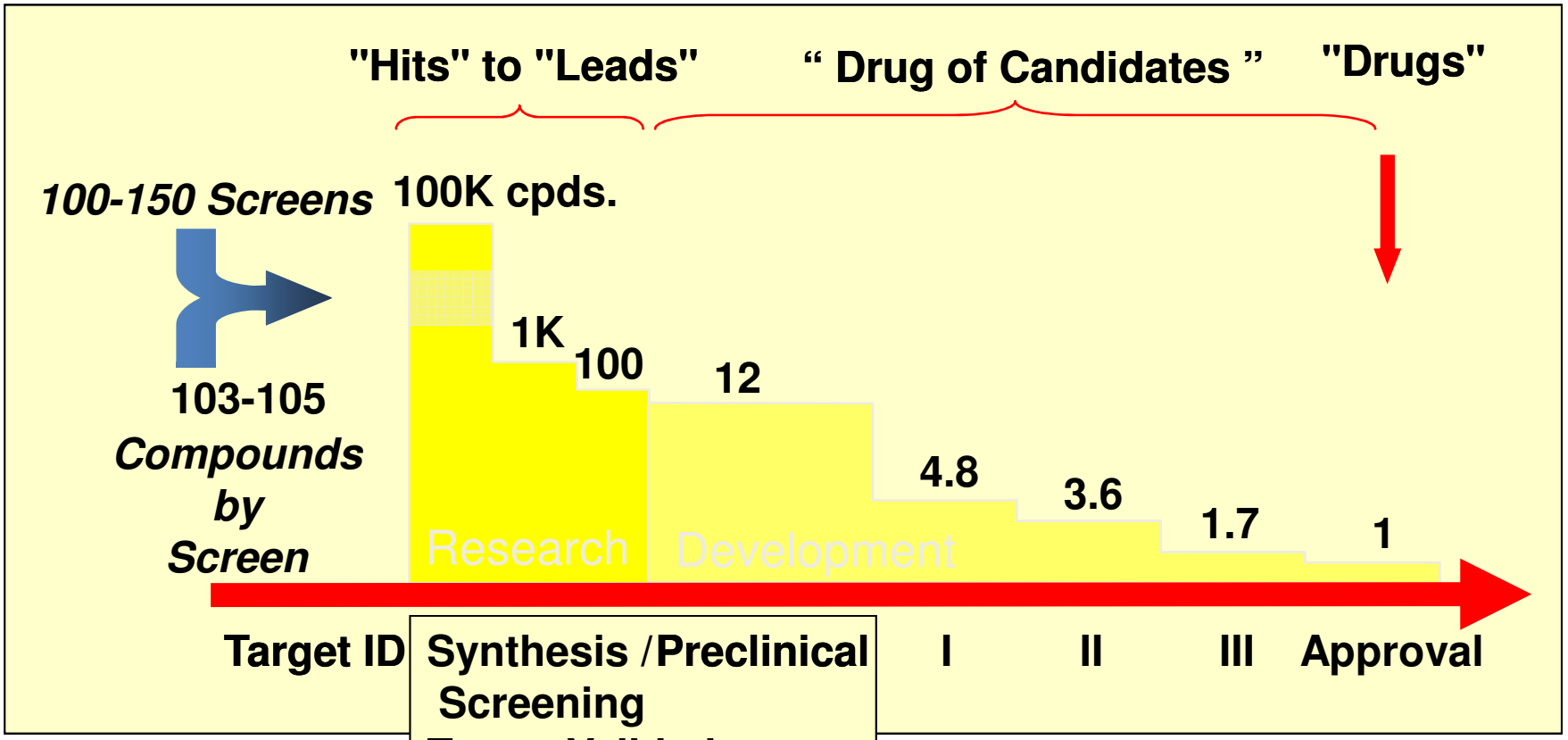
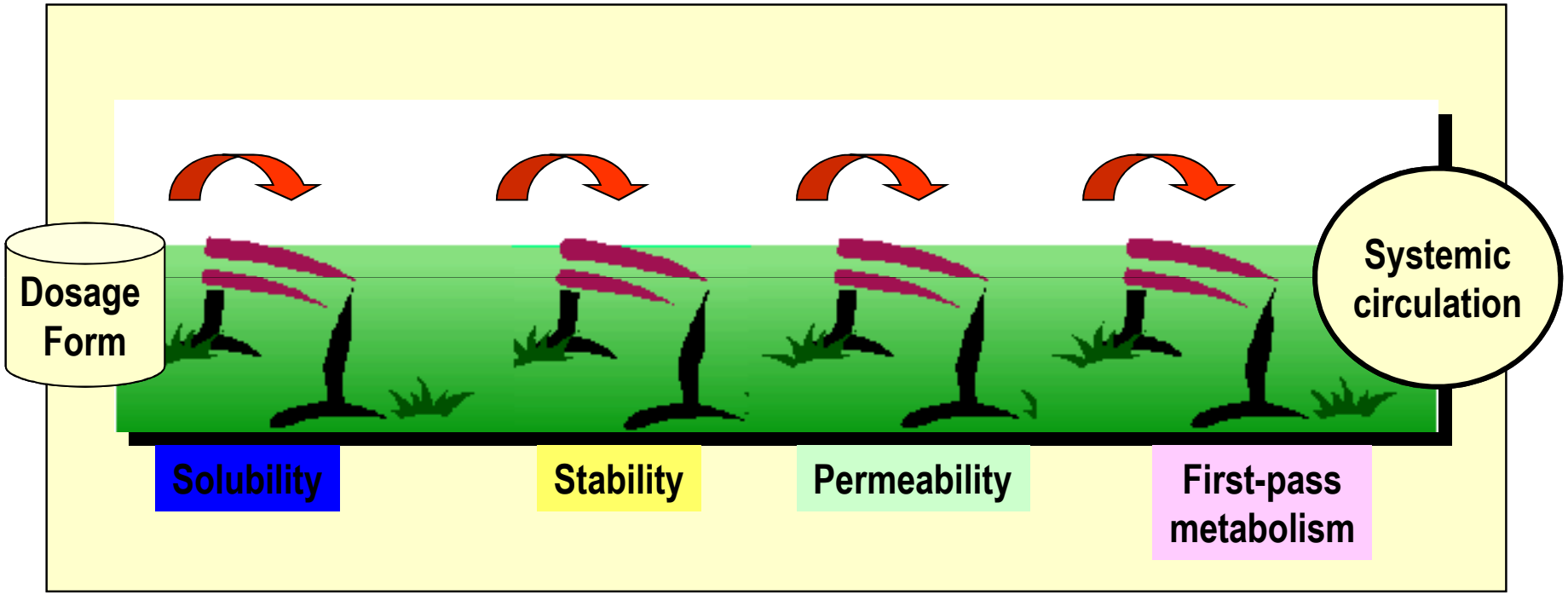
Drug substances in the pipeline
(Slide: A. Hussain, ex FDA)

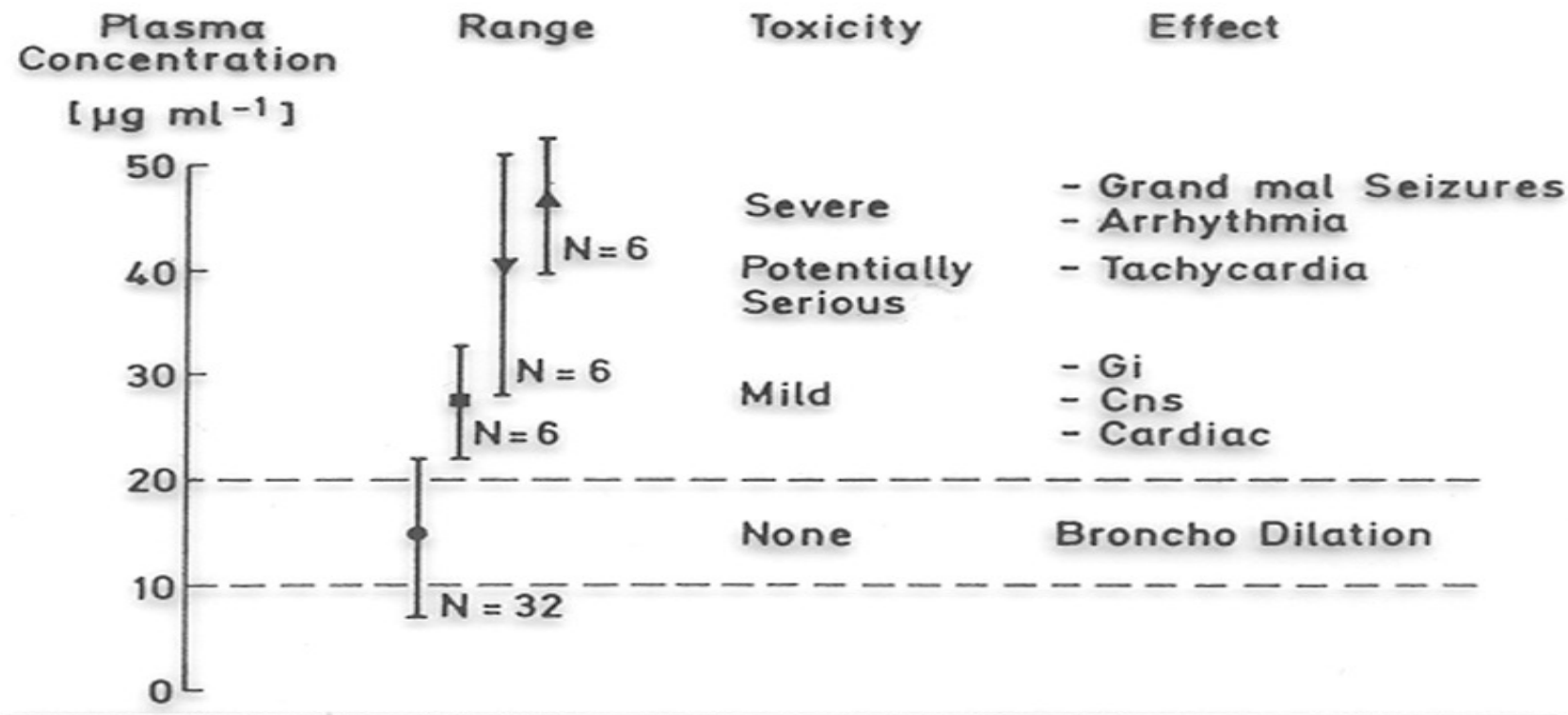


Estimated costs for a successful Introduction: 1 Billion USD

Major hurdles for a drug substance



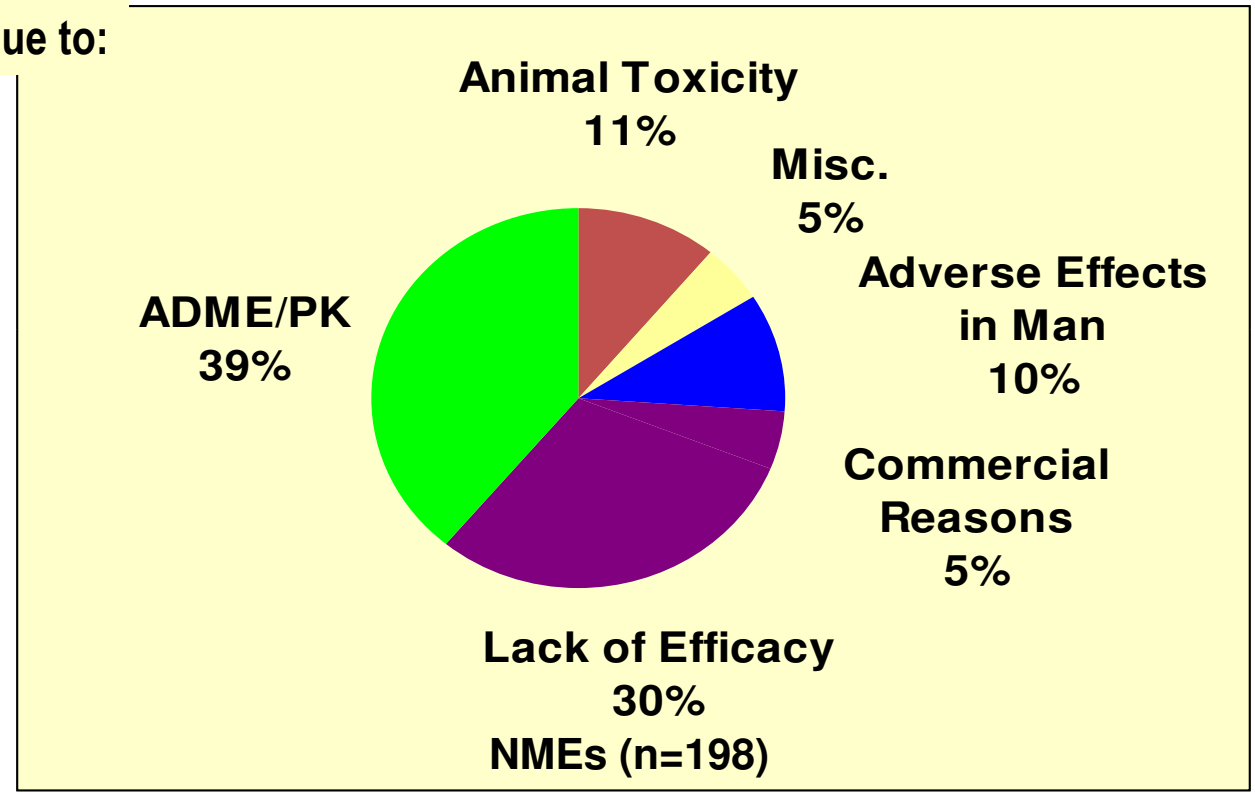
Systemic Circulation: E.g. Theophilline with therapeutic window



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

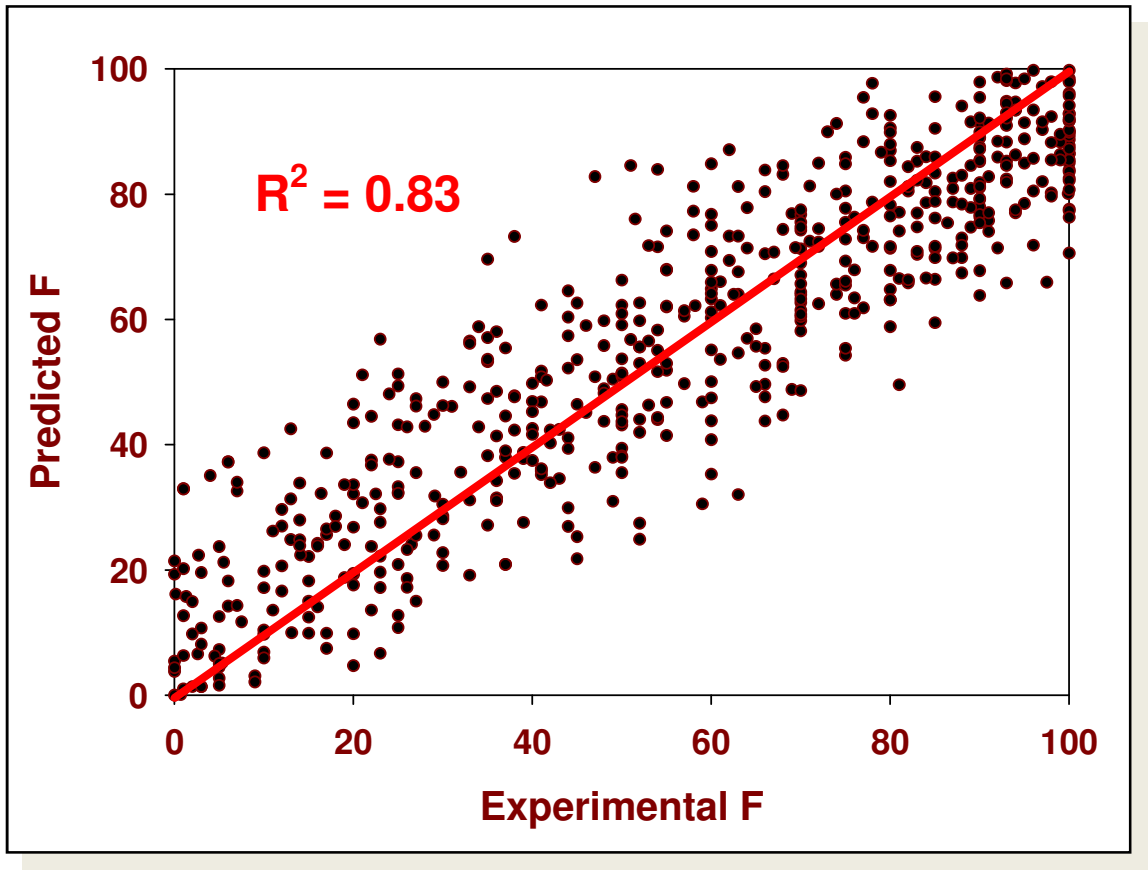
Failure of a project: Reasons

Failures due to:



Kennedy, T. (1997) drug Discovery Today, 2, 436-444.

Hurdle: Bioavailability of the drug substance



Yu, et al. Quantitative Structure Bioavailability Relation-hip (QSBR):
Pharm Res. 17:639-644 (2000)

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The Biopharmaceutical Classification System I

Class I - High Permeability, High Solubility

The drug substance is well absorbed, i.e.
the absorption rate constant
is much higher than excretion rate constant

Example: Metoprolol

Class II - High Permeability, Low Solubility

The bioavailability of such a drug substance depends on Its solubility in the gastro-intestinal tract.

Example: Glibenclamide

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The Biopharmaceutical Classification System II

Class III - Low Permeability, High Solubility

The absorption is unfortunately limited by the biological Membrane permeation rate. Thus the high solubility of the Drug substance is not helpful.

Example: Cimetidine

Class IV - Low Permeability, Low Solubility

Such drug substances have a poor bioavailability.
Worst case scenario:
The drug substance is not well absorbed over the intestinal mucosa and a high variability can be expected.

Example: Hydrochlorothiazide

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Goal: Robust Solid Dosage Form

Task: Development and production
of a **vehicle** that
delivers the drug substance savely and

precisely at the	**right time**
in the	**right quality**
in the	**right quantity**
to the	**right site** in the body.

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Classical Approach I

The final marketed dosage form - supposed To be a robust one - is ususally only defined in Clinical Phase II or Phase III ! For Dose Range Finding in Clinical Phase I Often preliminary hard gelatine capsule formulations are used, which can be problematic (see the 2 following slides !)

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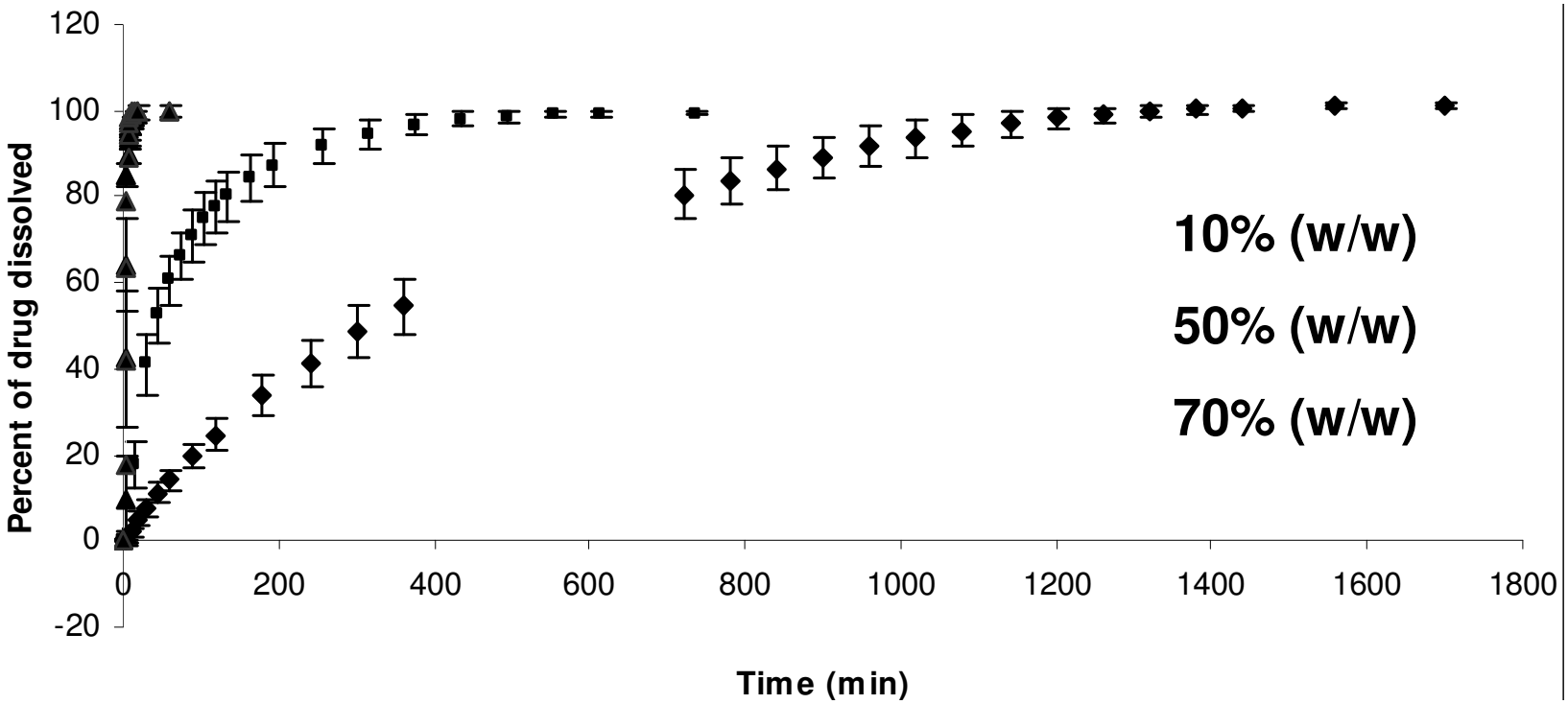
Drug A: Dissolution rate of capsule formulations

Capsule formulations were not robust being sensitive to the drug load (16, 79 and 109 mg, respectively 10% w/w, 50% w/w and 70% w/w.



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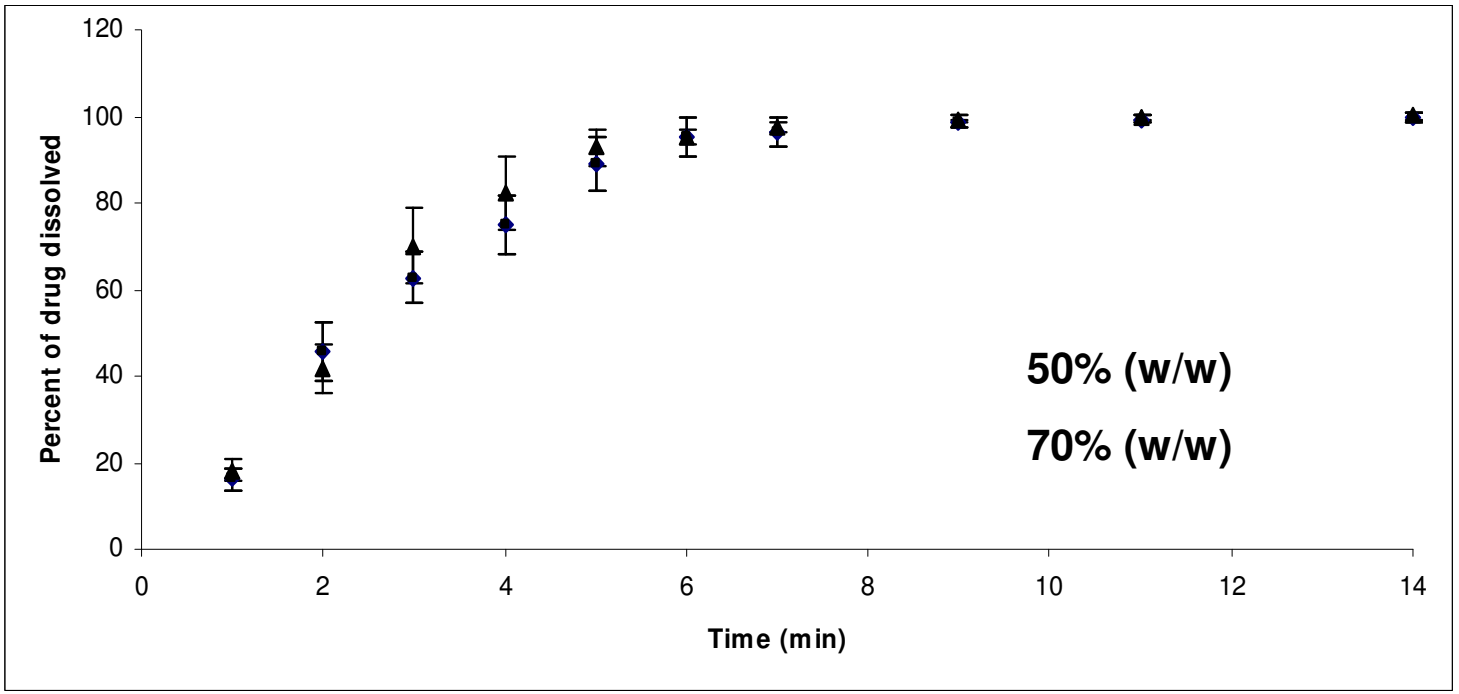
Drug A: Dissolution rate of tablet formulations

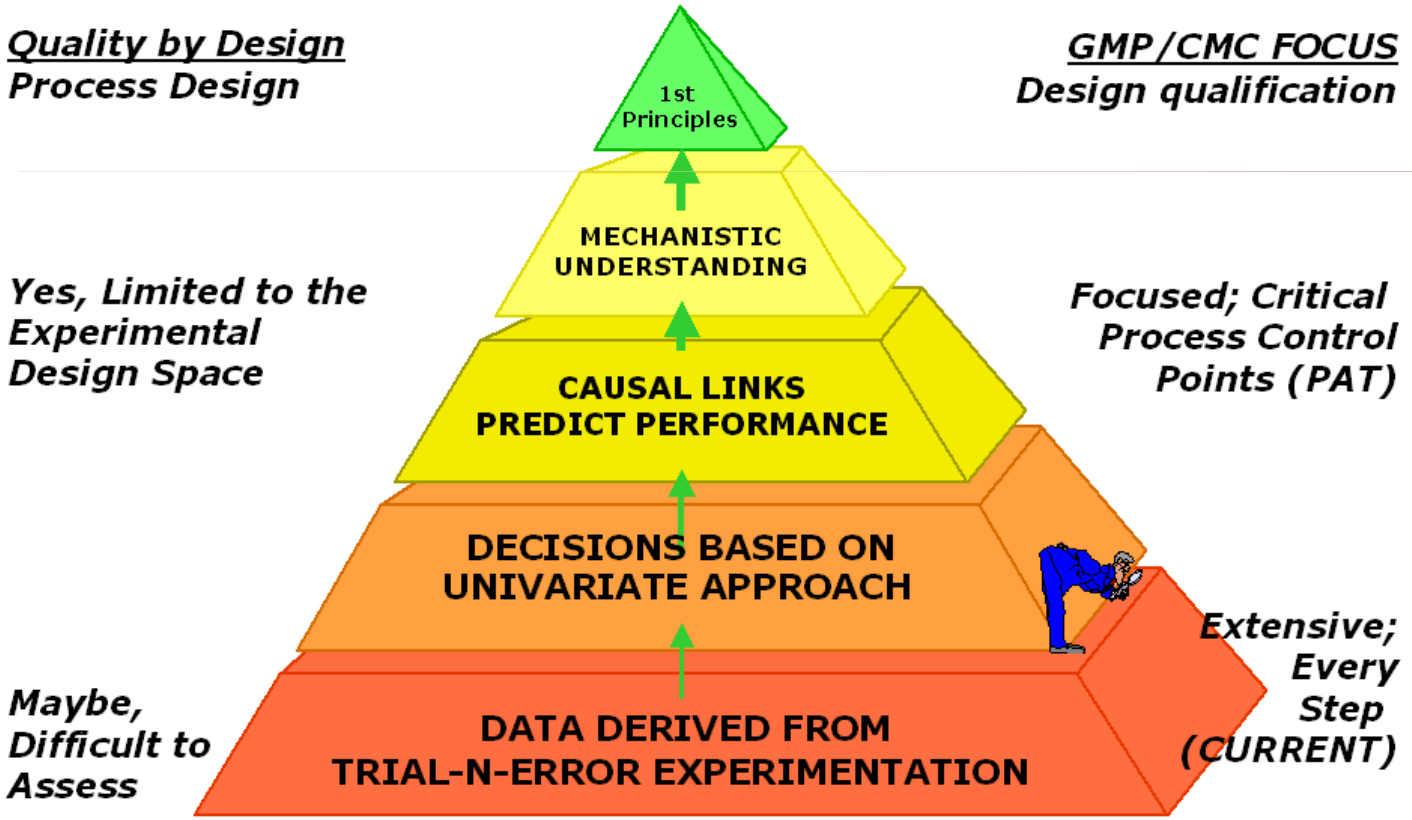
Tablet formulation have been robust and not sensitive to the drug

Load: 77mg, 109 mg drug substance, respectively 50% w/w, 70% w/w.

Reference: PhD Thesis Johannes von Orelli



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



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Alternatives to a classical hard gelatine capsule formulation for Dosage Range Finding in Clinical Phase I ?

Classical Hard Gelatine Capsule Formulations are usually based on a powder mix of the drug substance and suitable excipients such as Lactose, maize starch, magnesiumstearate etc

Suggestions/questions:

1) What would be the advantage to fill the hard gelatine capsules as a standard with more hydrophilic granules?
2) Would it be much better, i.e. The method of choice to use inert pellet Carriers such as „Cellets“ to be coated with a hydrophilic layer of the Drug substance?

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Classical Approach II

The reason to use a preliminary preclinical dosage form in Clinical Phase I is related to the fact, that it is impossible to develop and optimize simultaneously 12 robust formu-Lations for 12 drug substances.
In fact the famous 20% to 80% Rule has to be applied: Invest 20% of your resources to get 80% of your desired result!
Is this sufficient to get SIX SIGMA Quality?

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

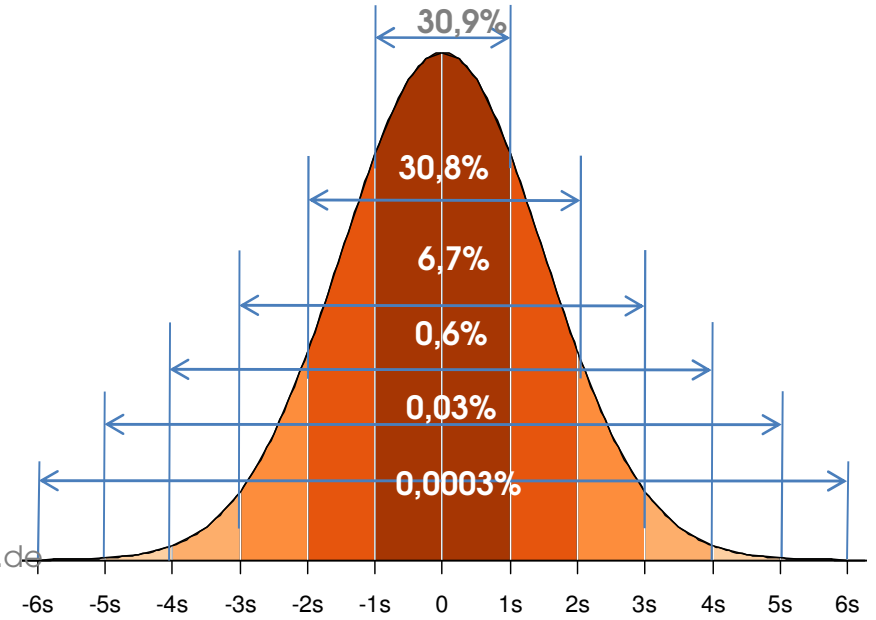
Performance of a process → Sigma value

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

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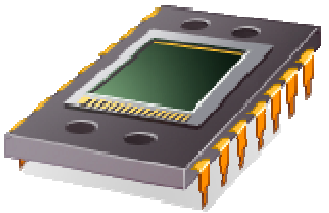
The SIGMA Concept

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:

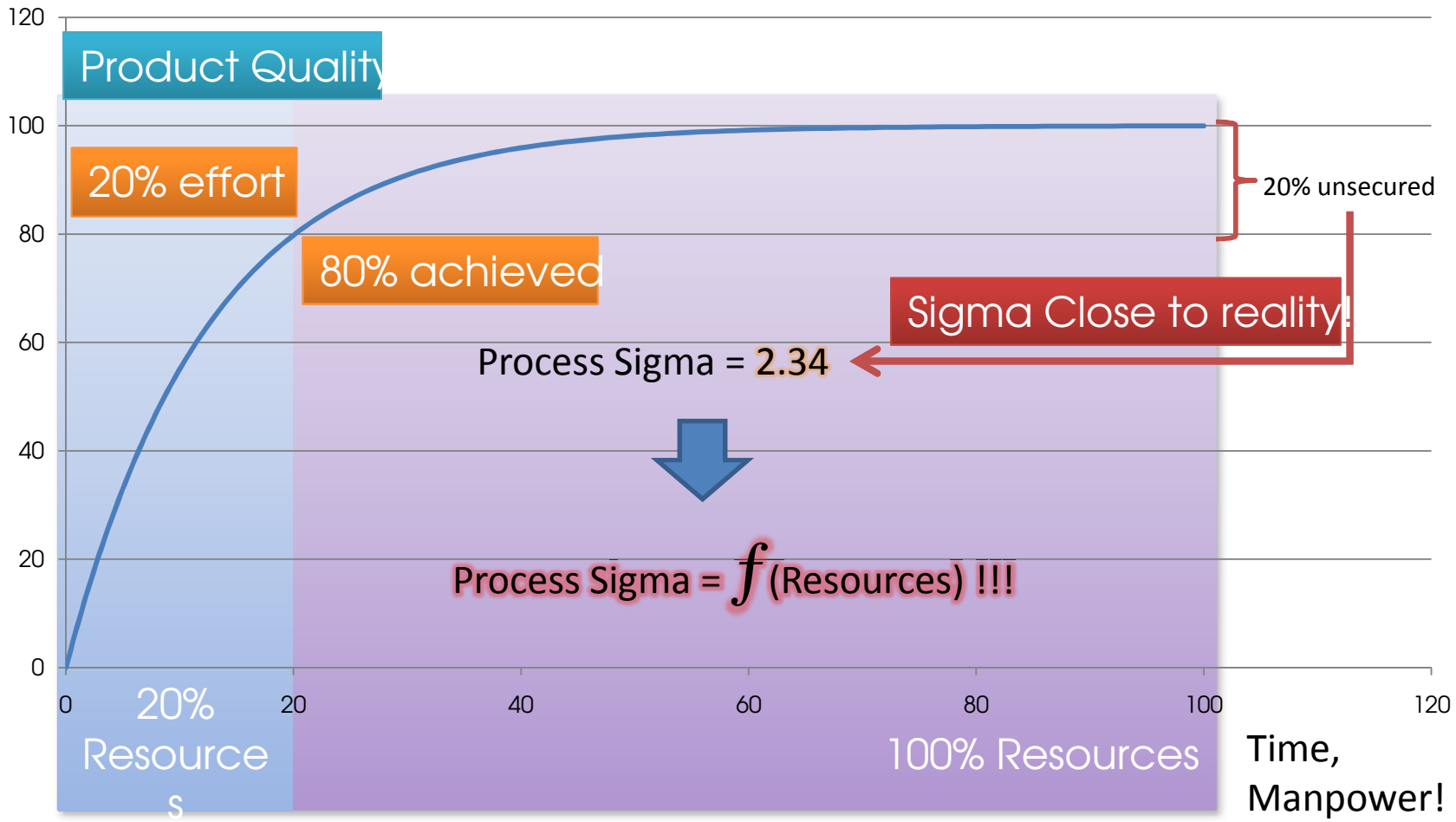
With 20% of time and effort dedicated to a project
80% of the goals can be achieved!

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?

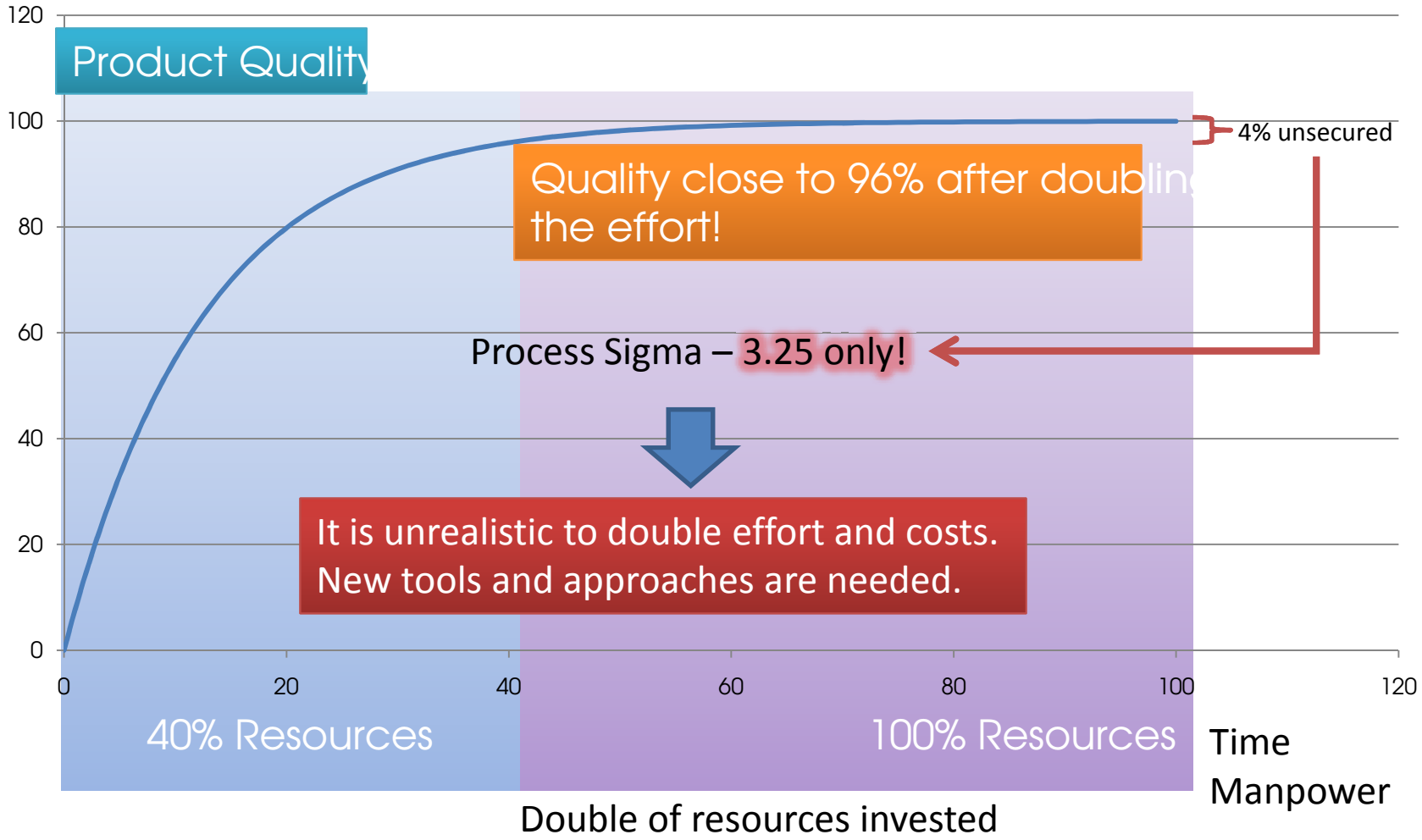
Let us make an estimate!

R.P.Scherer Workshop19.6.2008)

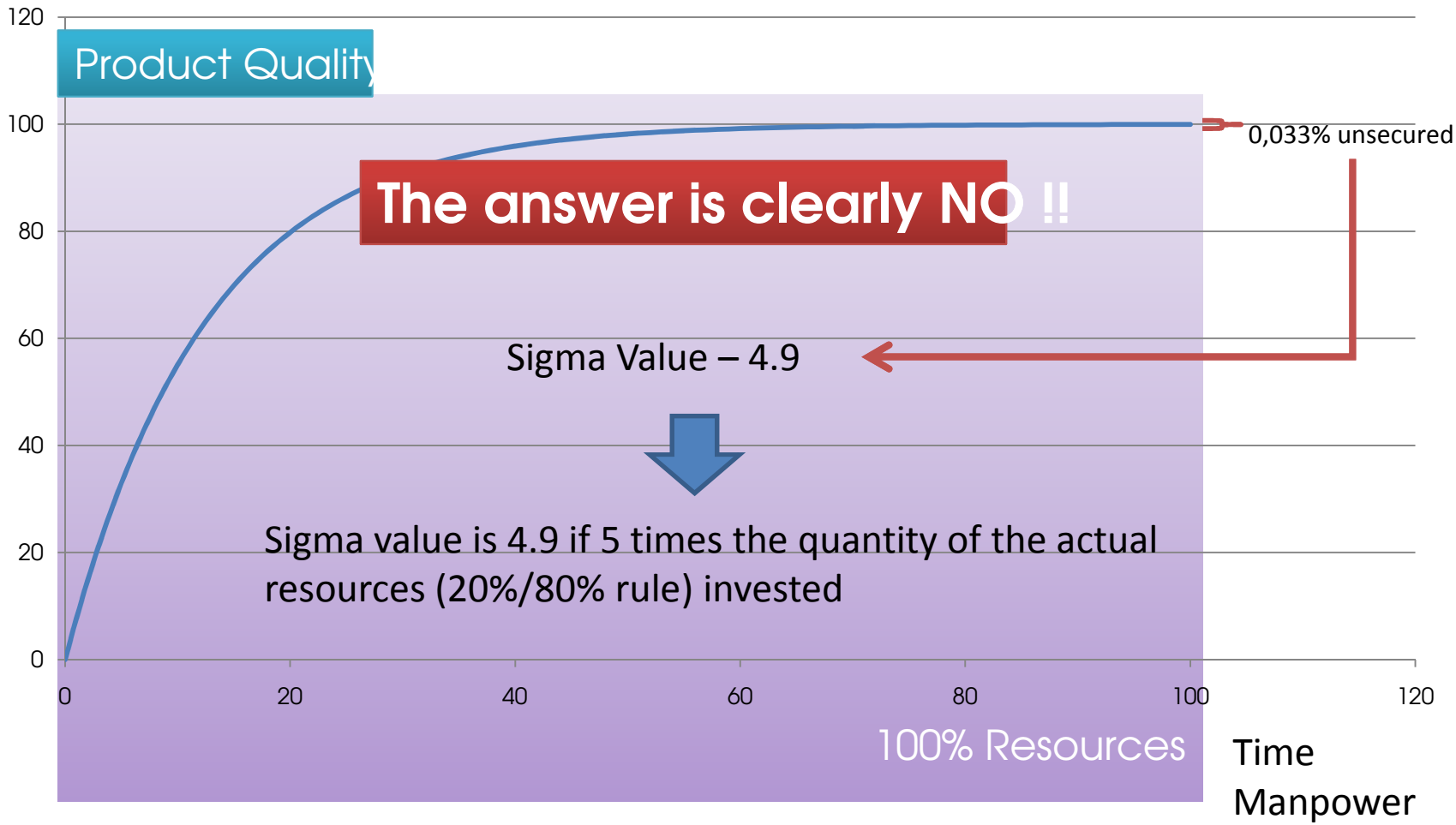
Sigma Value – function of resources



Can we afford to double effort and costs?!



Can Six Sigma be achieved with conventional tools?



New tools and approaches are needed!

- The previous slides showed clearly that the classical approach is not suitable to achieve SIX SIGMA Quality!
- Even if the 20%/ 80% rule is replaced by the 100%/ 100% rule, i.e. if the resources are increased by a factor **FIVE (!)** SIX SIGMA quality cannot be achieved!
- **Thus new tools and approches need to be explored!**
- **Proposal by PRICE WATERHOUSE COOPER PWC:**
- **E-Development: replace expensive lab and in-vivo experiments by „in-silico – experiments“!**

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!

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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.

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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?

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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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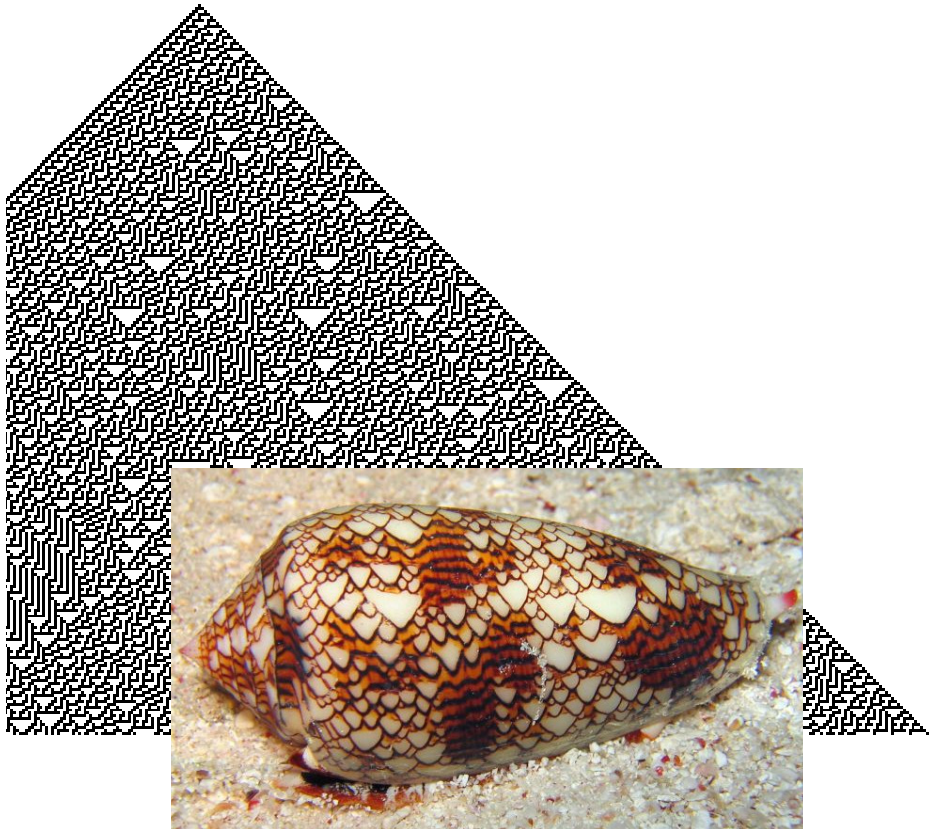
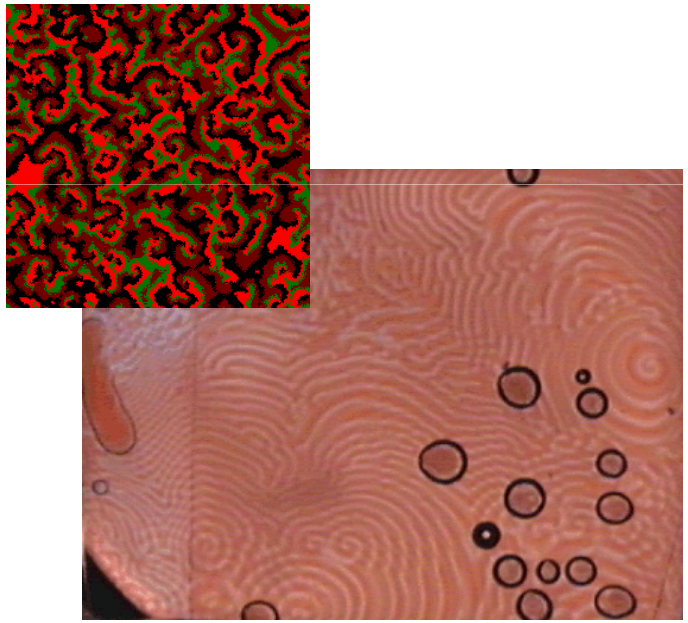
Cellular automata and modeling of natural phenomena



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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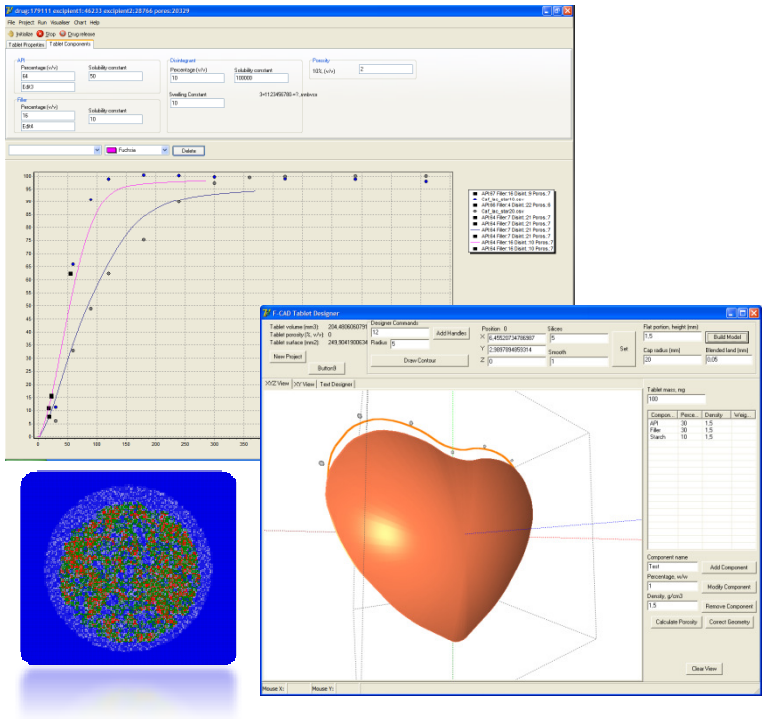
VES and F-CAD Screenshots



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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

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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.

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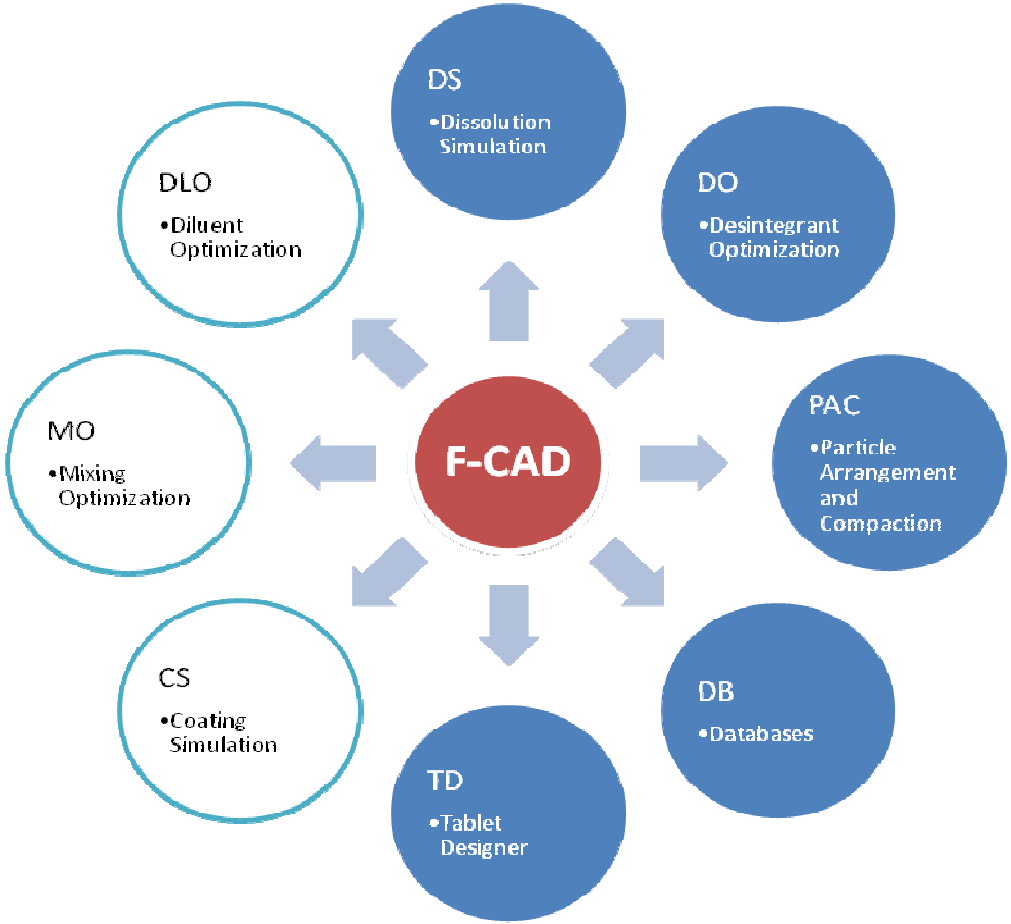
F-CAD Modules



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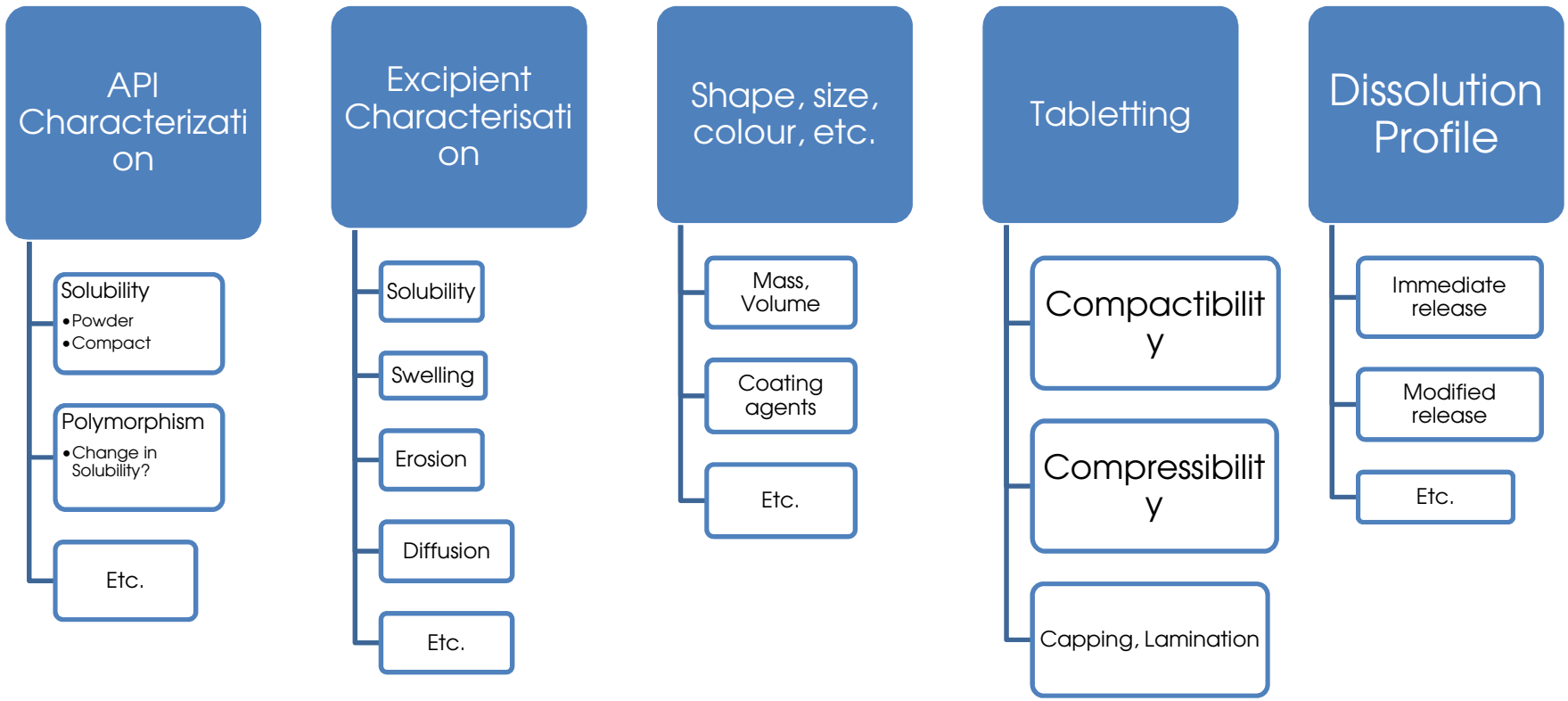
Formulation development with F-CAD



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F-CAD - QbD

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

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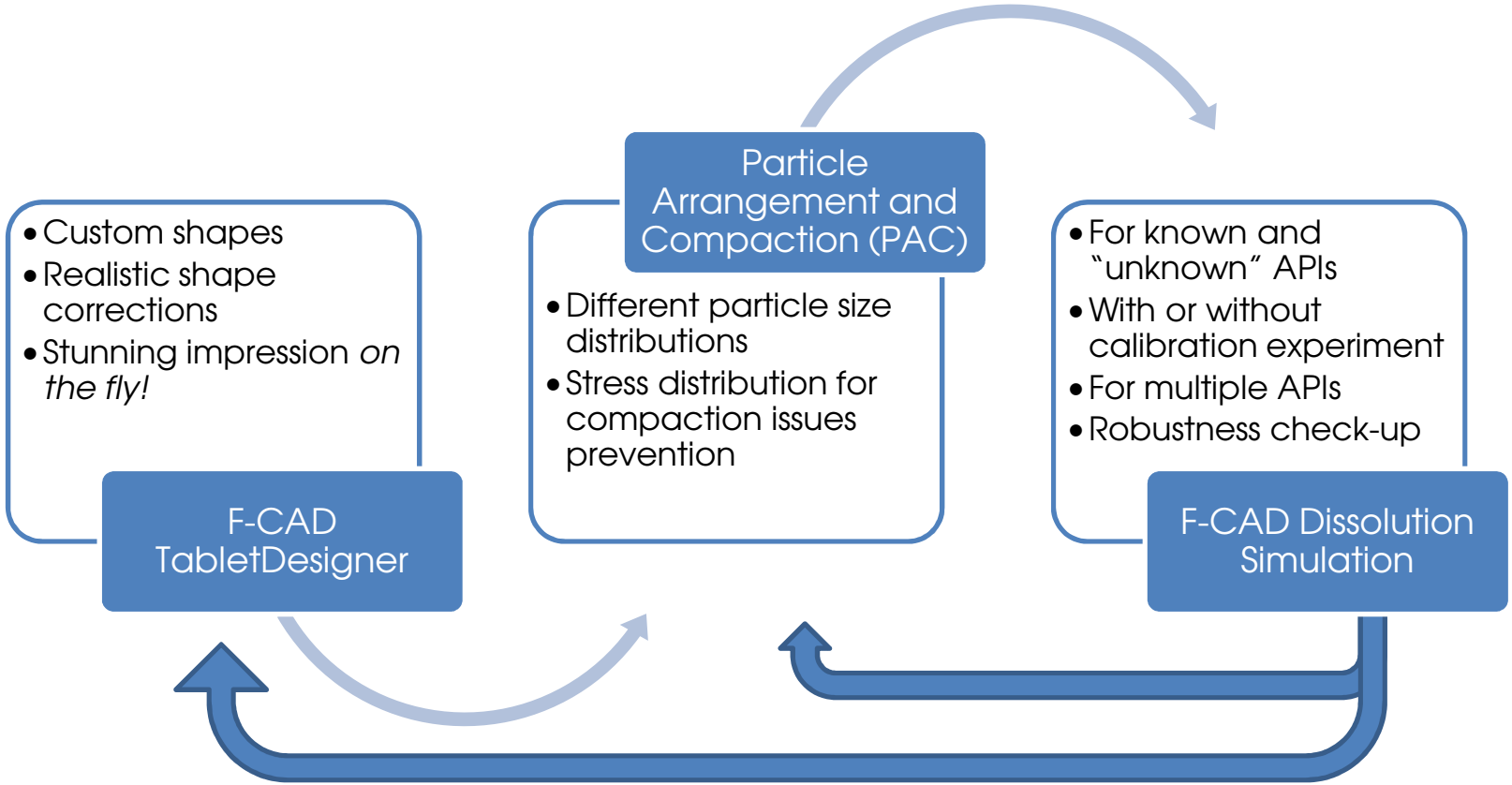
F-CAD modelling process



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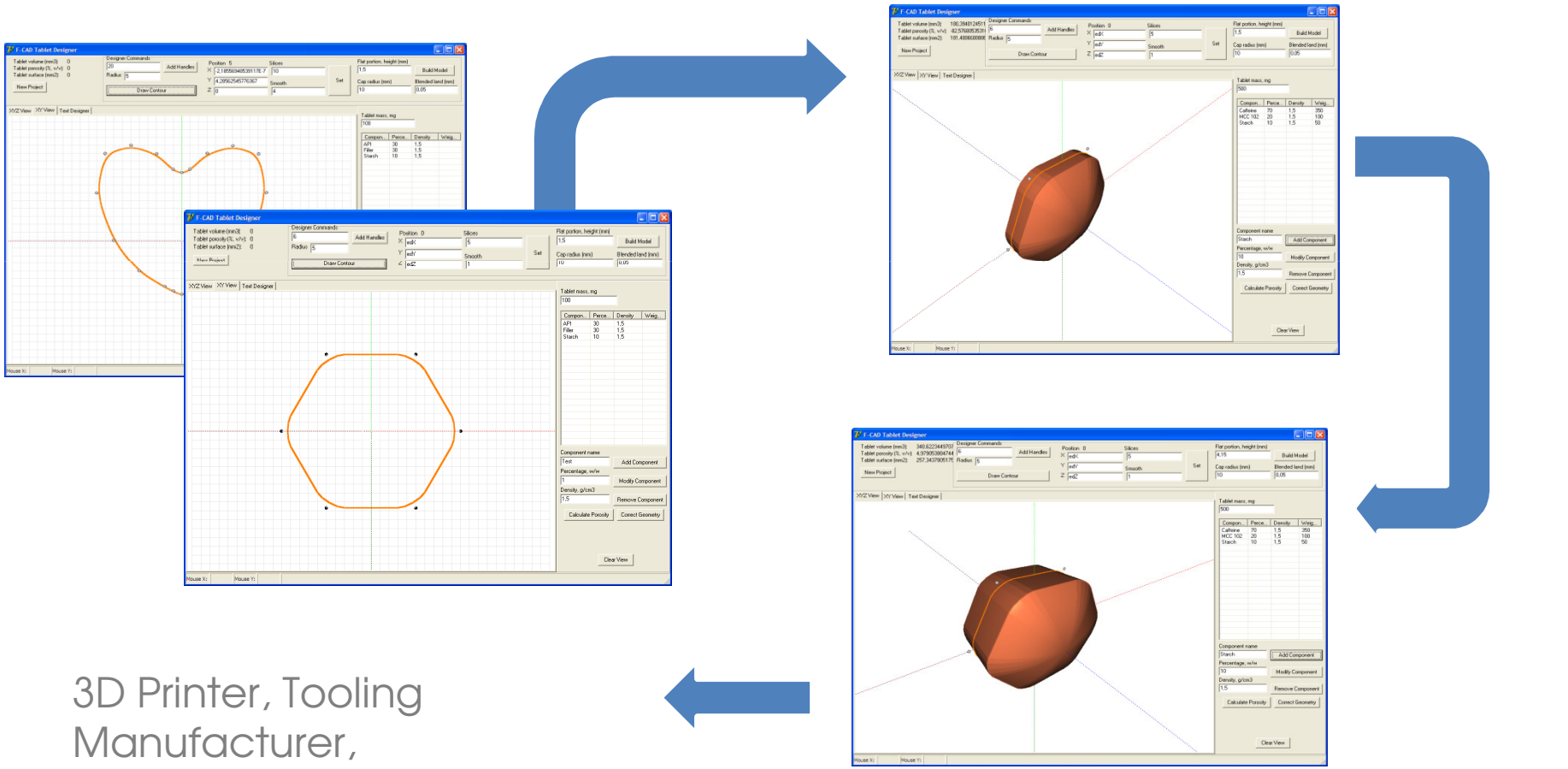
F-CAD Tablet Designer



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

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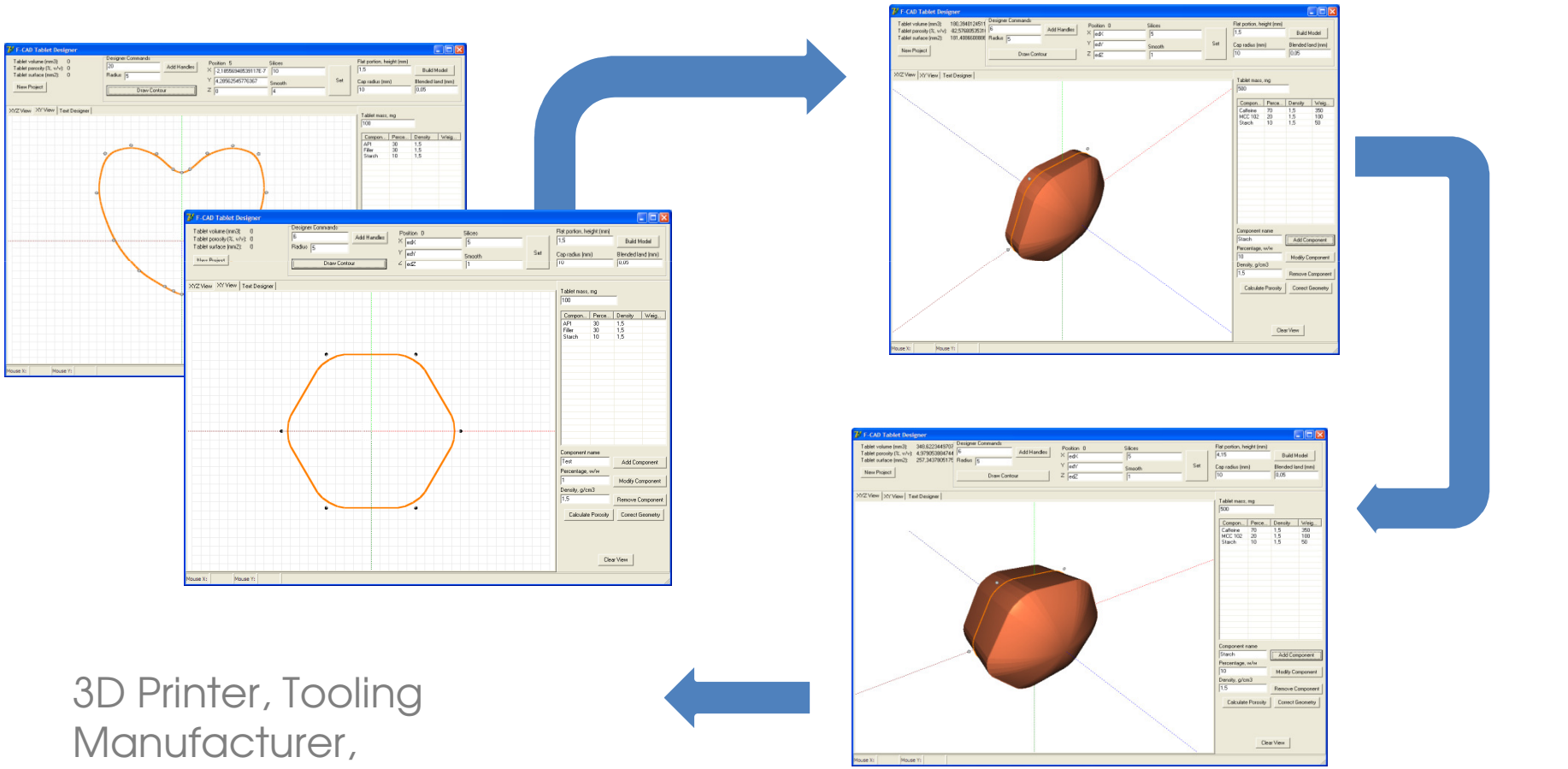
F-CAD Tablet Designer



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

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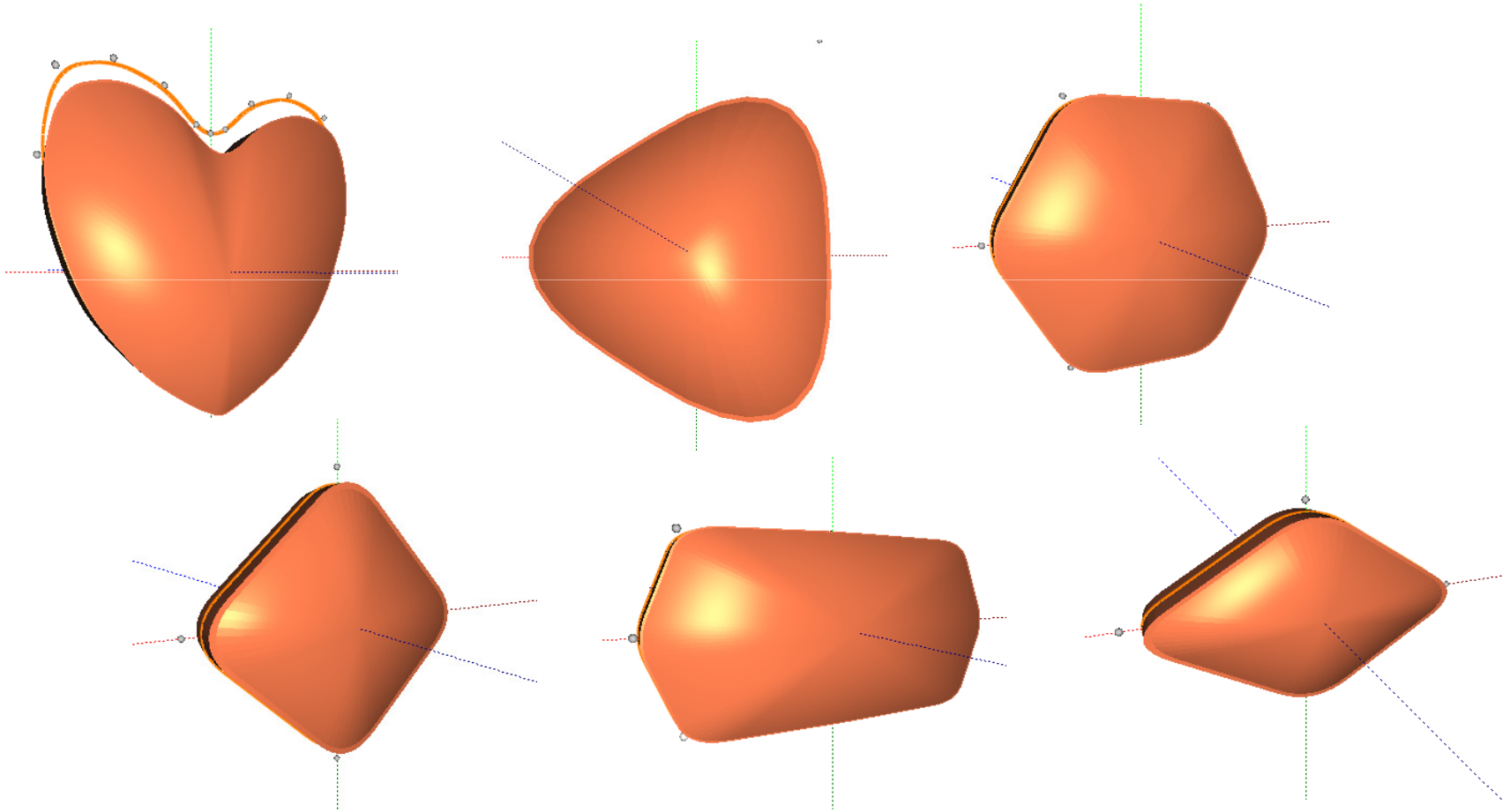
Custom Shapes with F-CAD Tablet Designer



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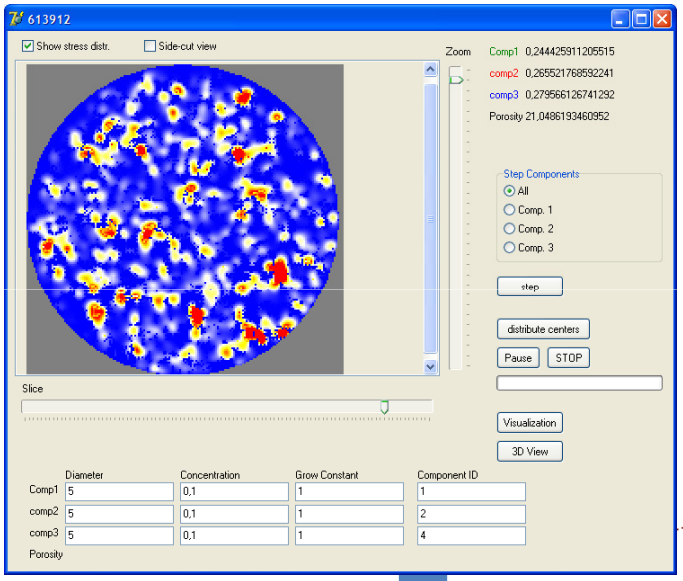
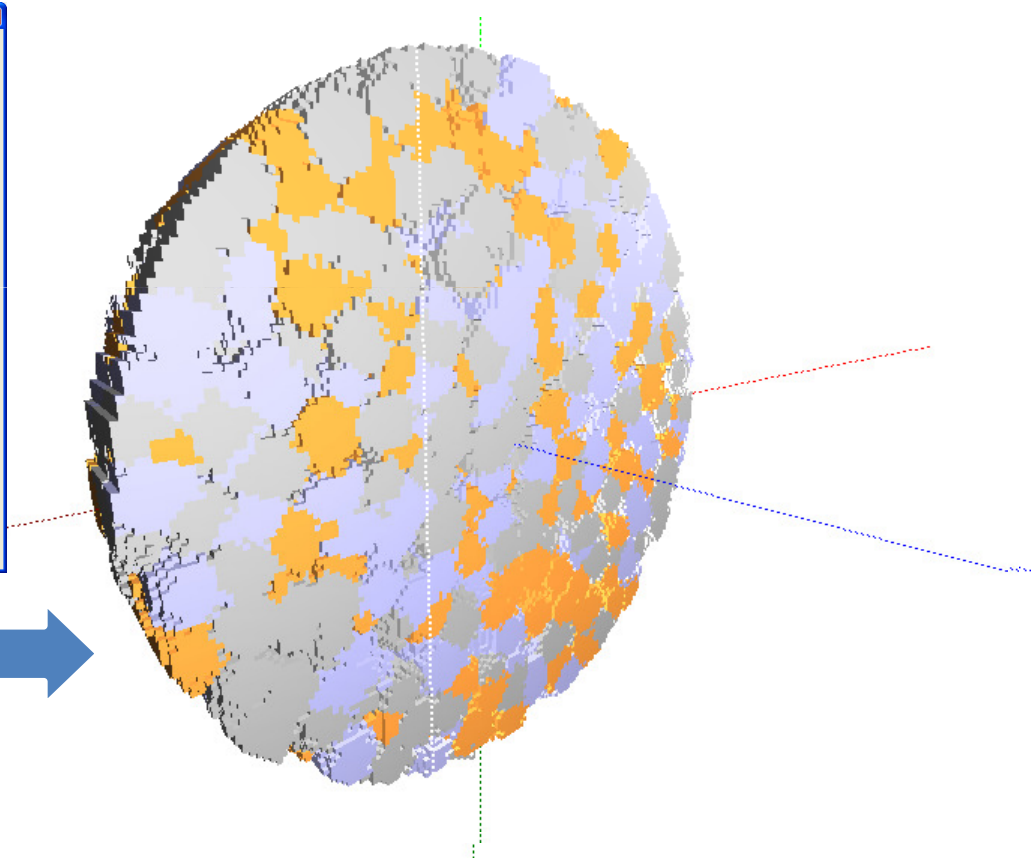
F-CAD PAC – Particle Arrangement and Compaction





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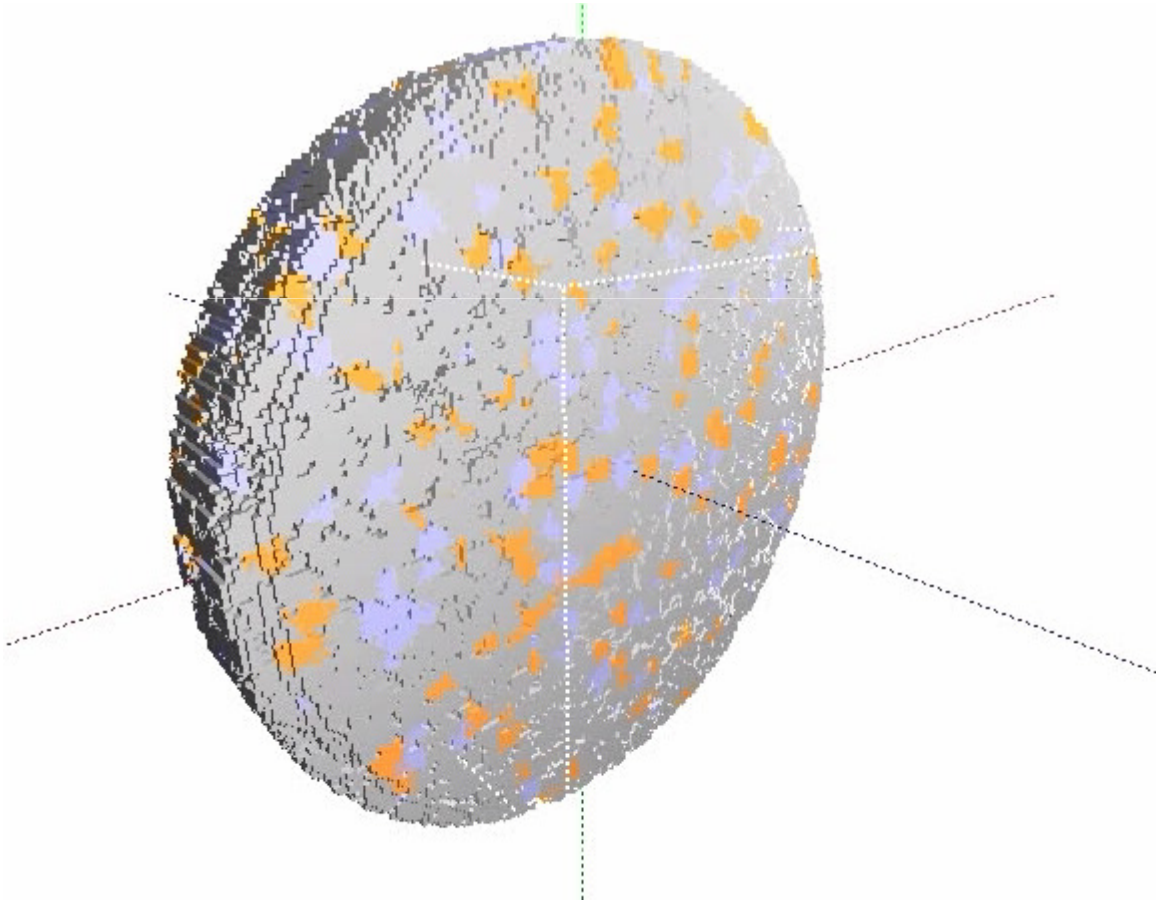
Resulting compact



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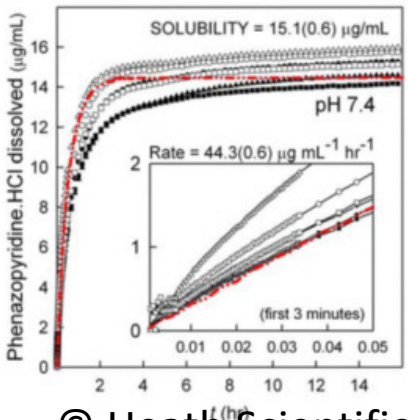
F-CAD DS – *in silico* Profiles



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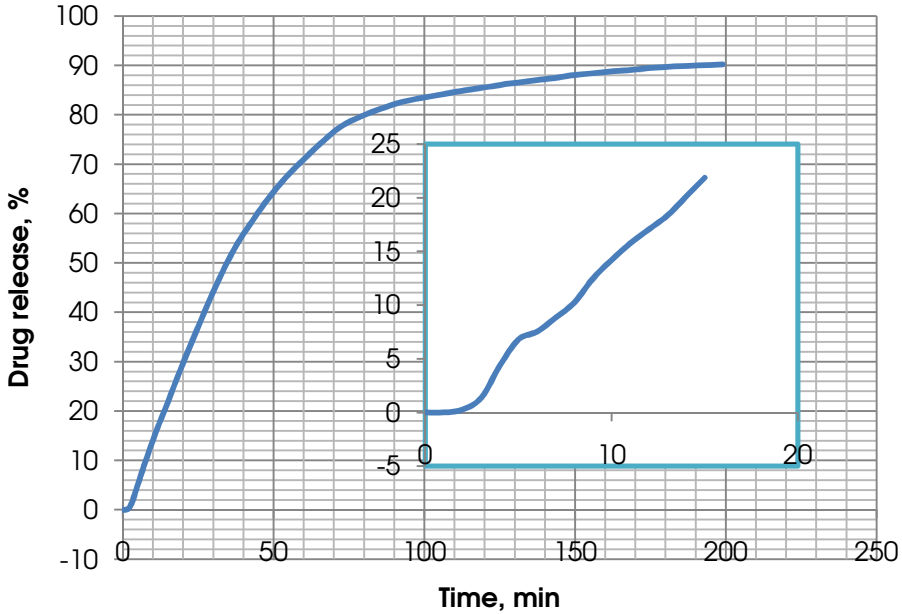

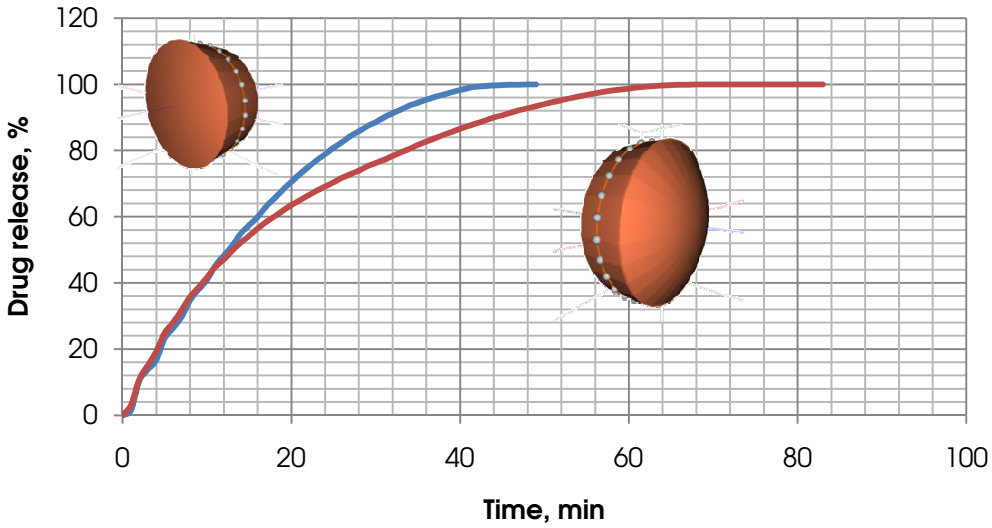

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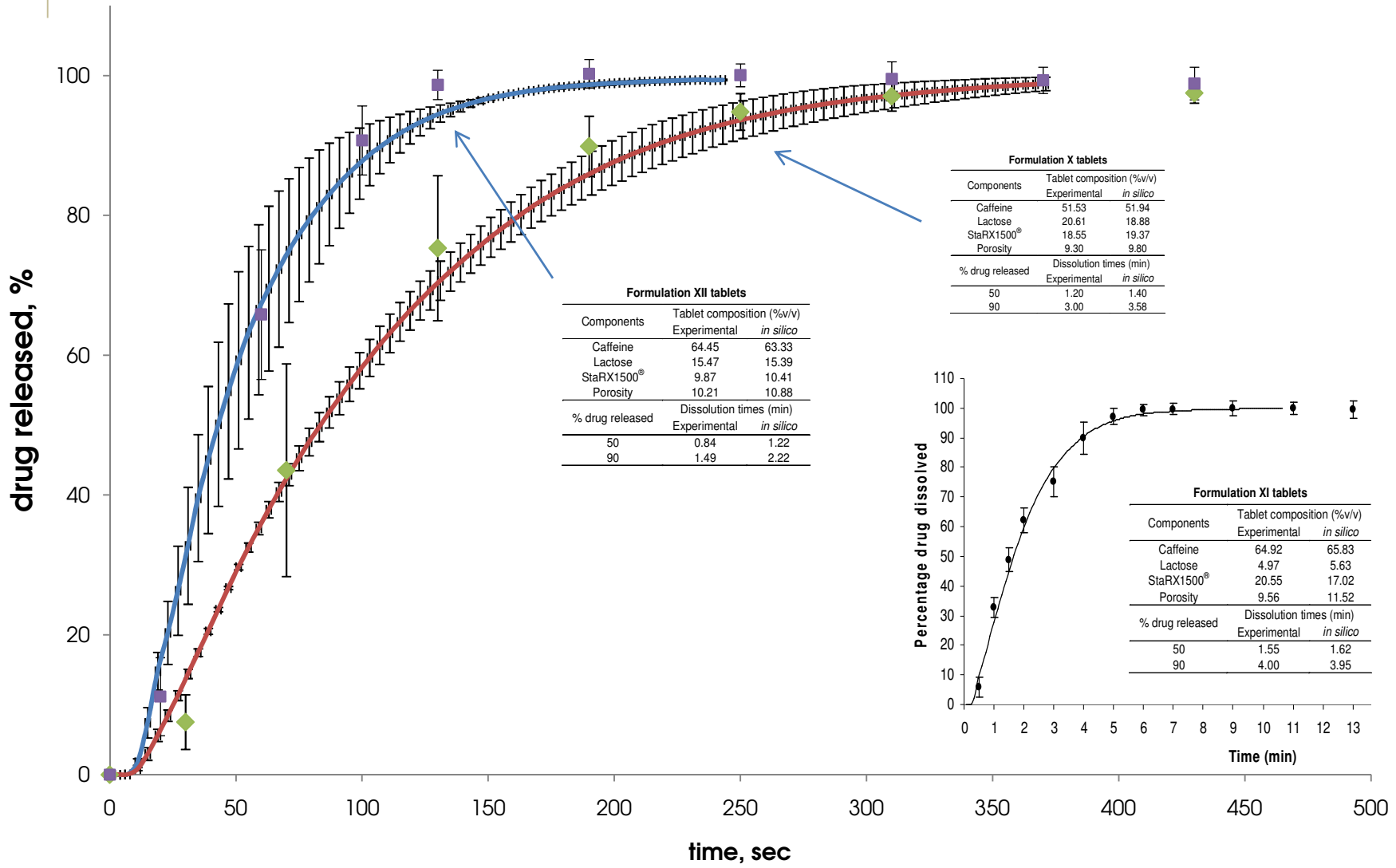
Experimental vs. in silico dissolution profiles of different formulations with caffeine



Formulation 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."

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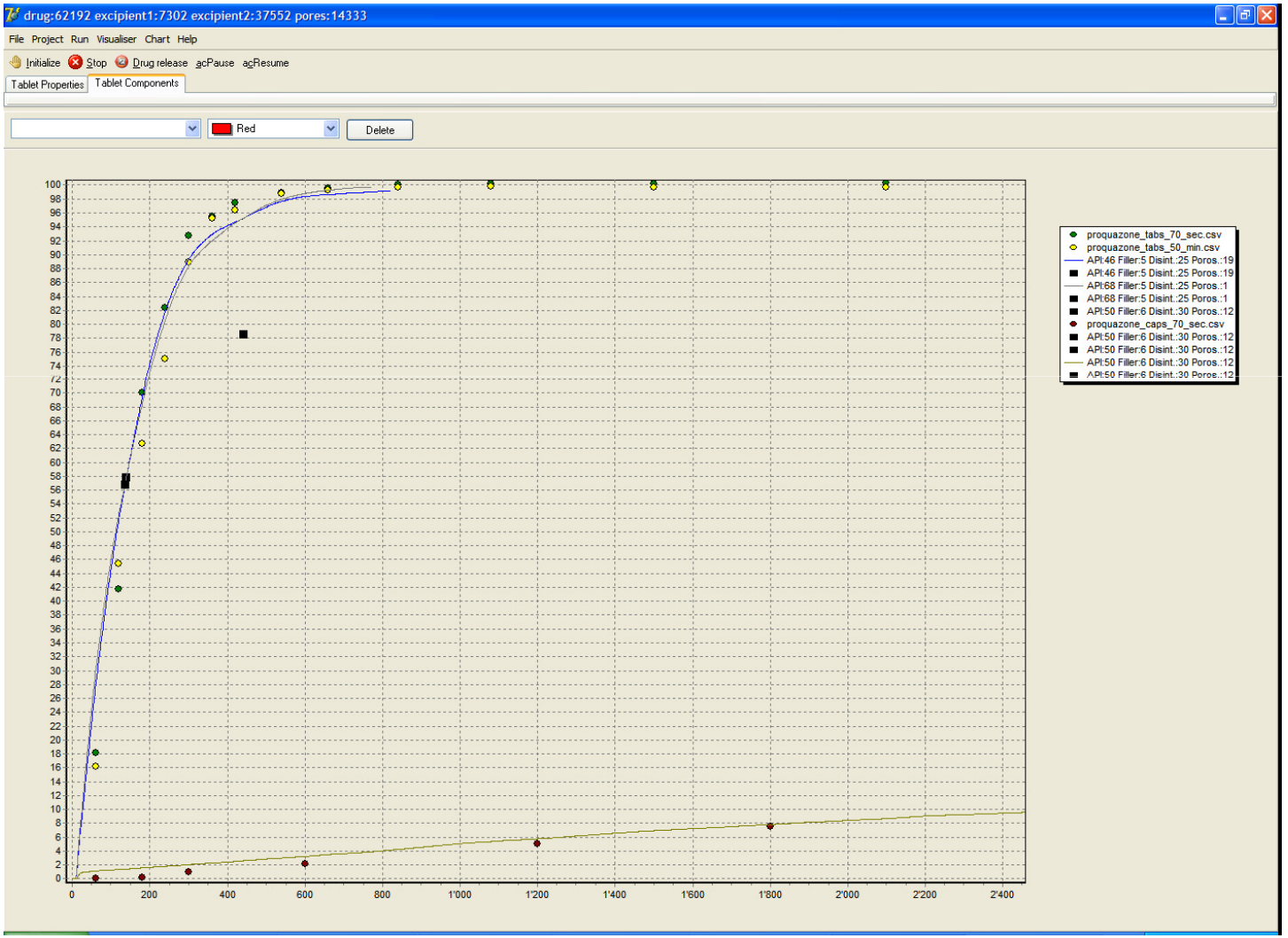
Capsule/Tablet simulation



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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)

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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

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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.

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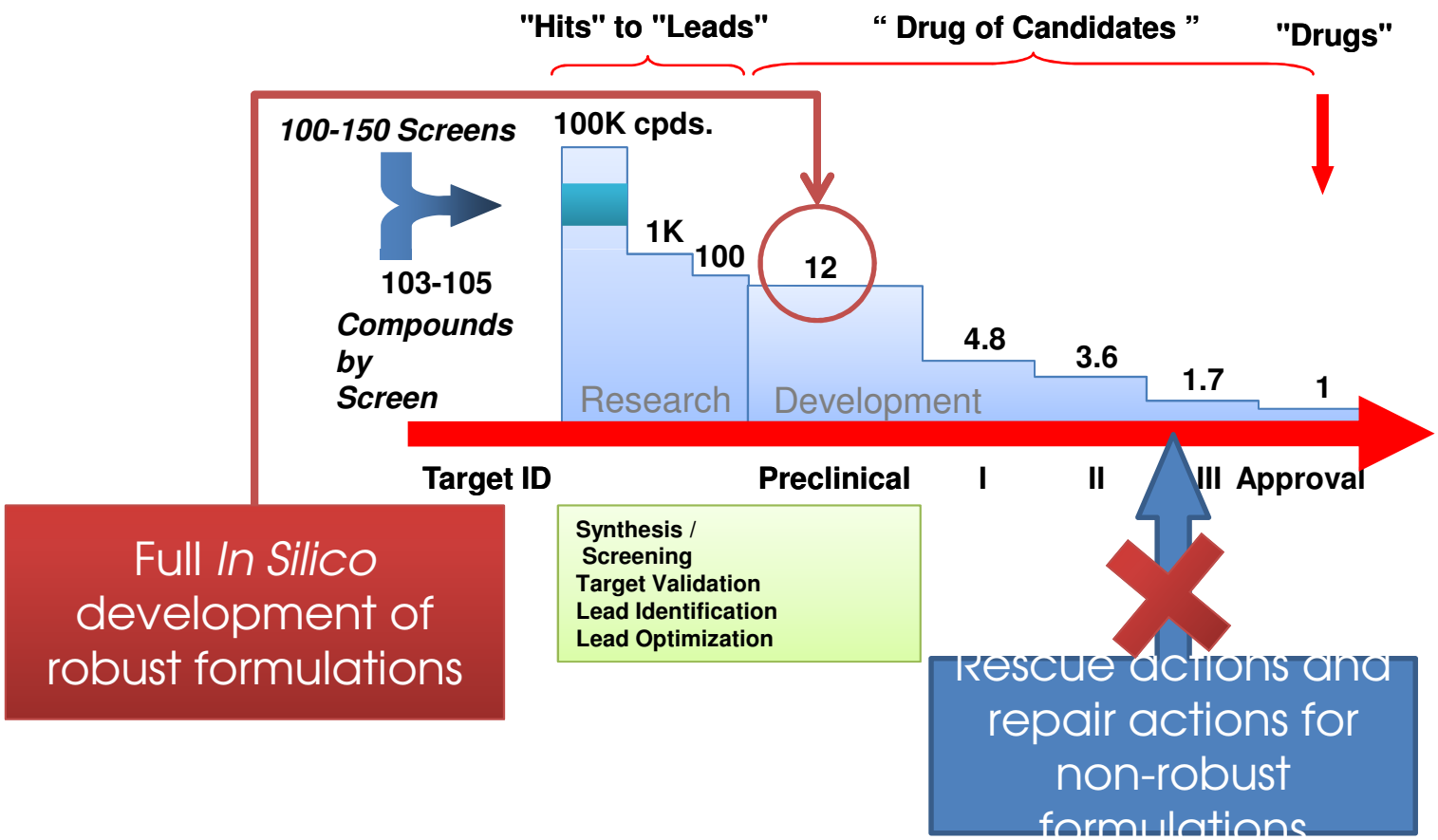
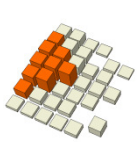
Slide: A. Hussain, FDA





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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

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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!**

- **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!**

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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 !

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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%!**

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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

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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

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Thank you for your attention!

Audience Q&A

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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

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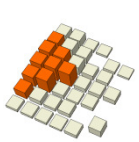

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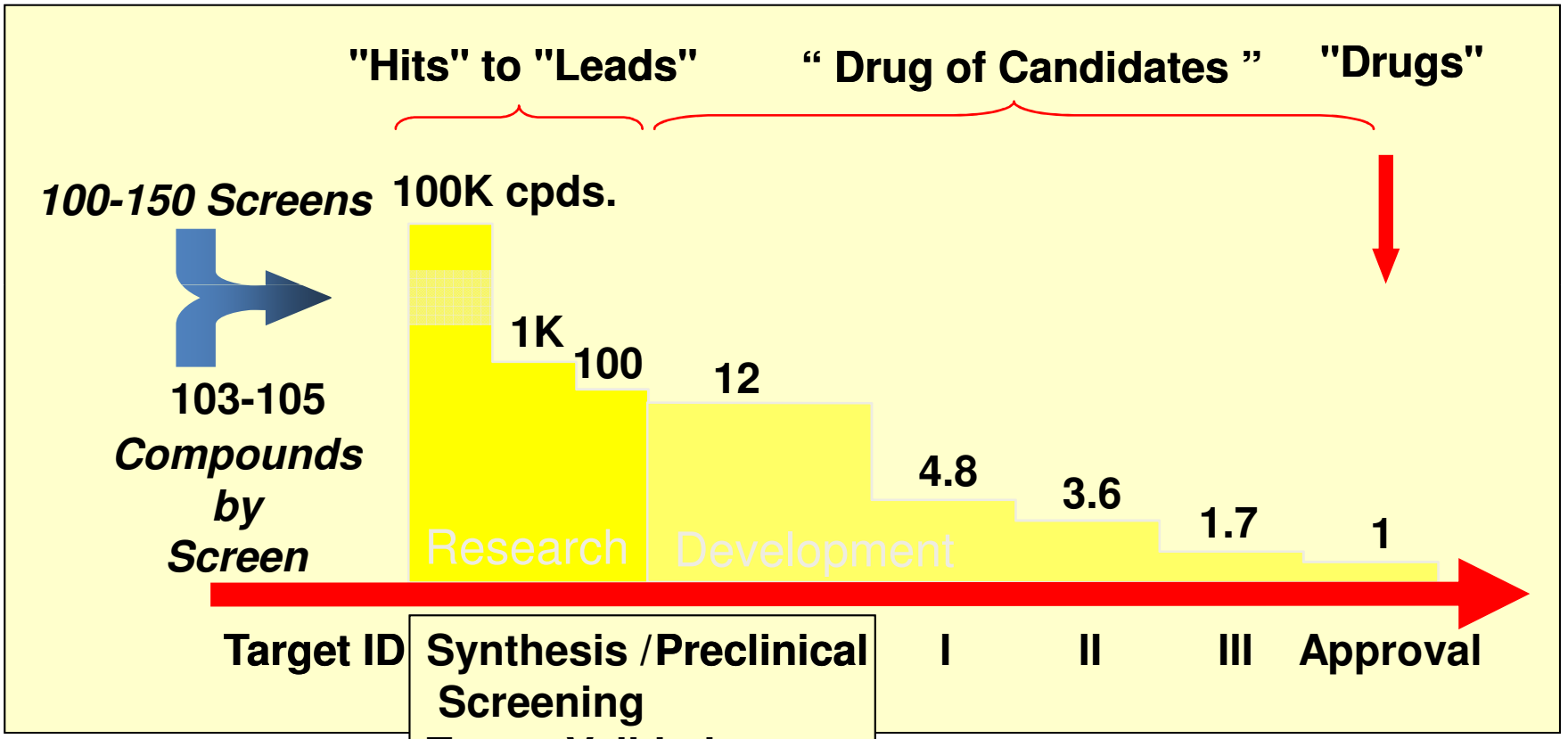
Design of a robust solid dosage form in the preclinical phase – a mission impossible?



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Goal: Robust Solid Dosage Form

Task: Development and production
of a **vehicle** that
delivers the drug substance savely and

precisely at the	**right time**
in the	**right quality**
in the	**right quantity**
to the	**right site** in the body.

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The Goal is similar to the task of designing an aircraft:

Task: Development and manufacturing of an aircraft that
delivers the passengers safely and precisely

at the	**right time**
in the	**right quality**
in the	**right quantity**
to the	**right site (destination).**

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Boeing 777 and Airbus 380 were fully designed in-silico

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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

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Designing a solid dosage form: *in silico* approach I?

Tablet: 100% digitally designed using 3D solids technology?

Prerequisites and primary requirements:

How can we do that for pharma?

Best possible knowledge of the ***Physico-Chemical*** and ***Biopharmaceutical Properties*** of the drug substance and of the excipients such as
Drug/Excipient Compatibility
Issue of Polymorphism etc.

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Designing a solid dosage form: *in silico* approach II?

How can we do that for pharma?

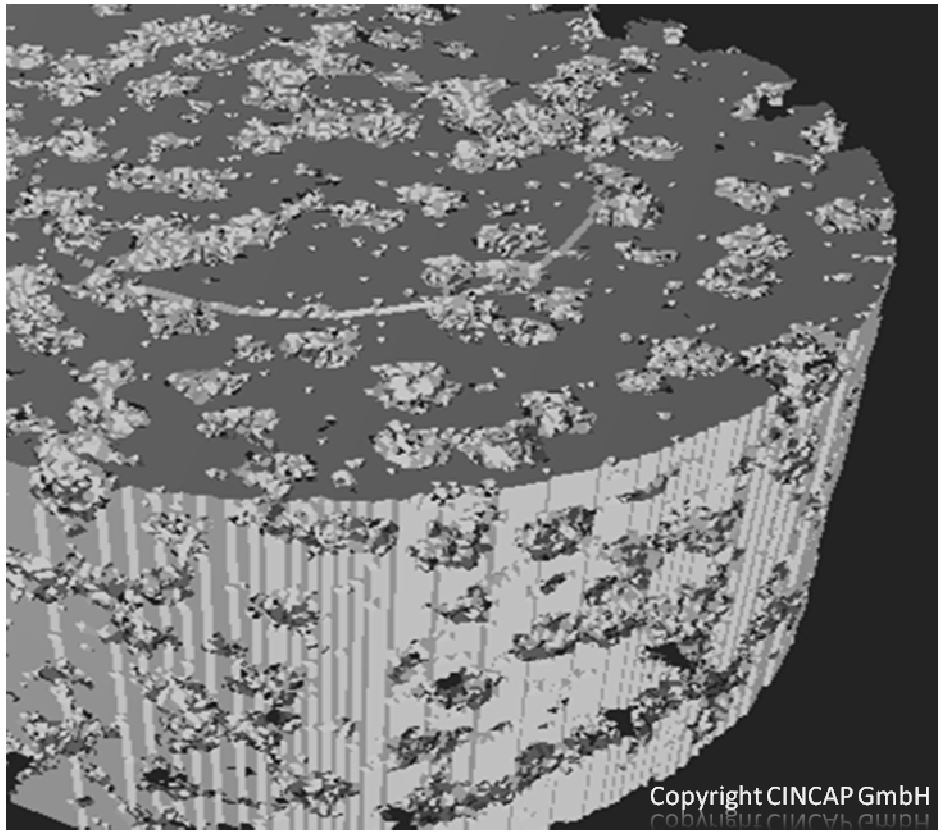
Tablet: 100% digitally designed using 3D solids technology?

Prerequisites and primary requirements:

1)Availability of a corresponding *software* to design the solid dosage form, taking into account *percolation theory, physico-chemical and mechanical* properties of the substances Involved etc. and

2) Availability of the corresponding hardware (supercomputer).

Leached Matrix Controlled Release Tablet: Real – left (PhD Thesis J.D. Bonny) Computer Generated System - right



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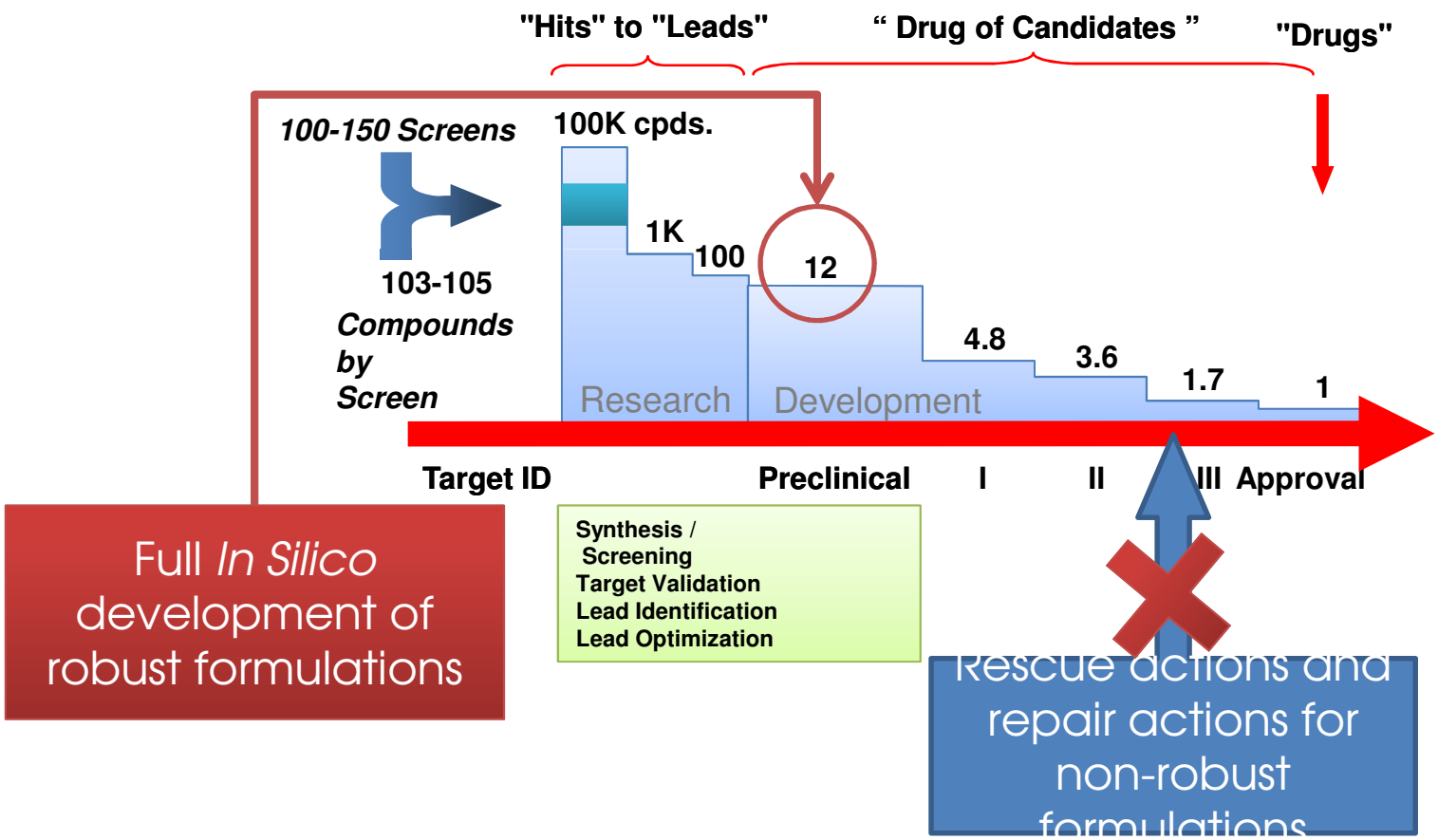

PWC Pharma 2020: Vision e-Development

- 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!

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Applications of in-silico design in various fields:

Computer simulations can be used

1. to interprete experimentally measured data by providing the underlying physical models.

2. to provoke experiments, that may confirm unexpected theoretical predictions.

3. to replace e.g. biological experiments in case that the accuracy of the in-silico experiment is better than that of an experiment in a lab environment.

4. to establish intellectual property rights by providing results for systems that have not yet been performed experimentally.

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Thank you for your attention!

Audience Q&A