F-CAD:
In–silico Design of Solid Dosage Forms

Dr. Dr. h.c. mult. Hans Leuenberger

Prof. (em.) Pharmaceutical Technology of the University of Basel,

Institute for innovation in industrial pharmacy (www.ifiip.ch)

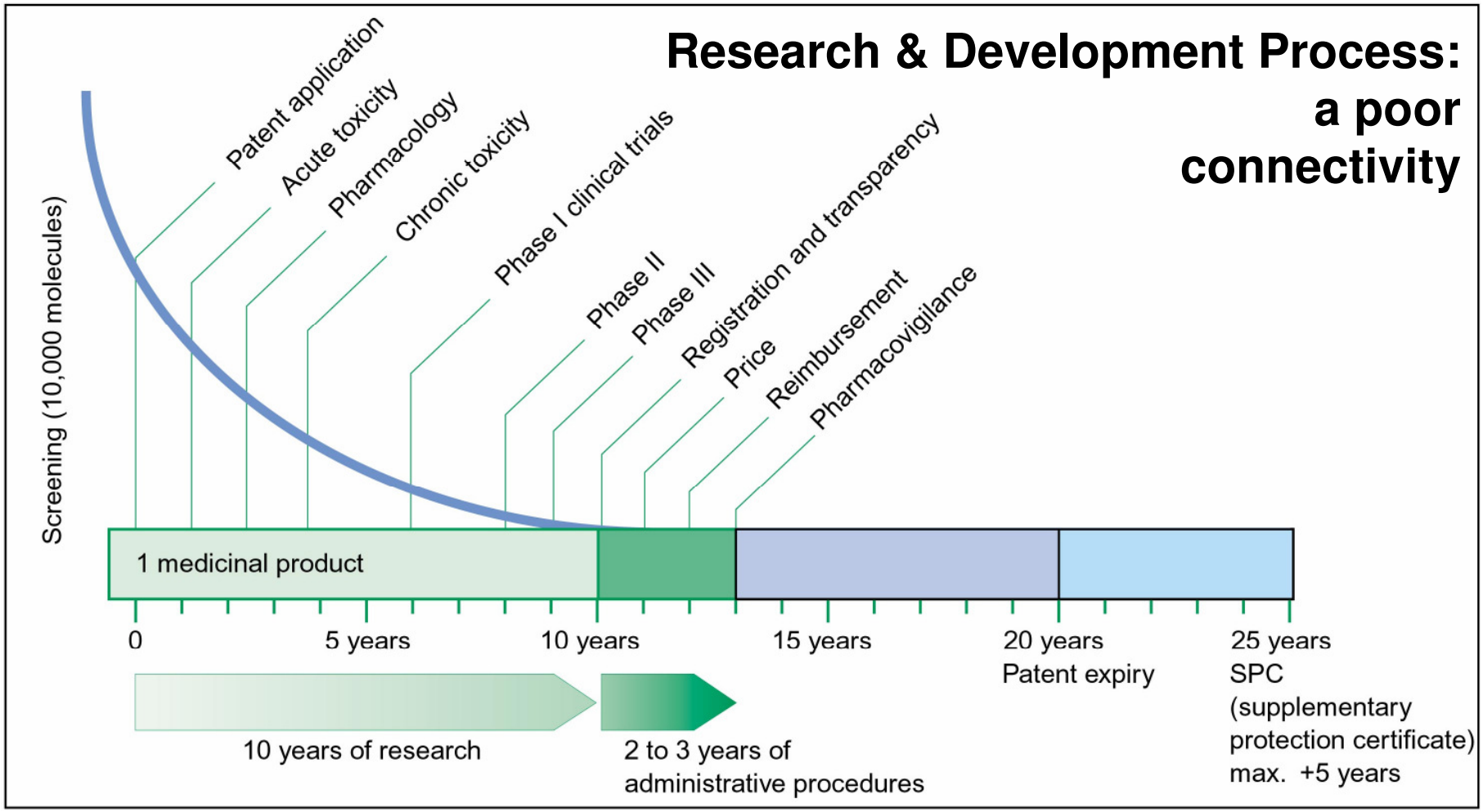
and

Dr. Maxim Puchkov

CINCAP GmbH (www.cincap.ch) CH - 4148 Pfeffingen, Switzerland

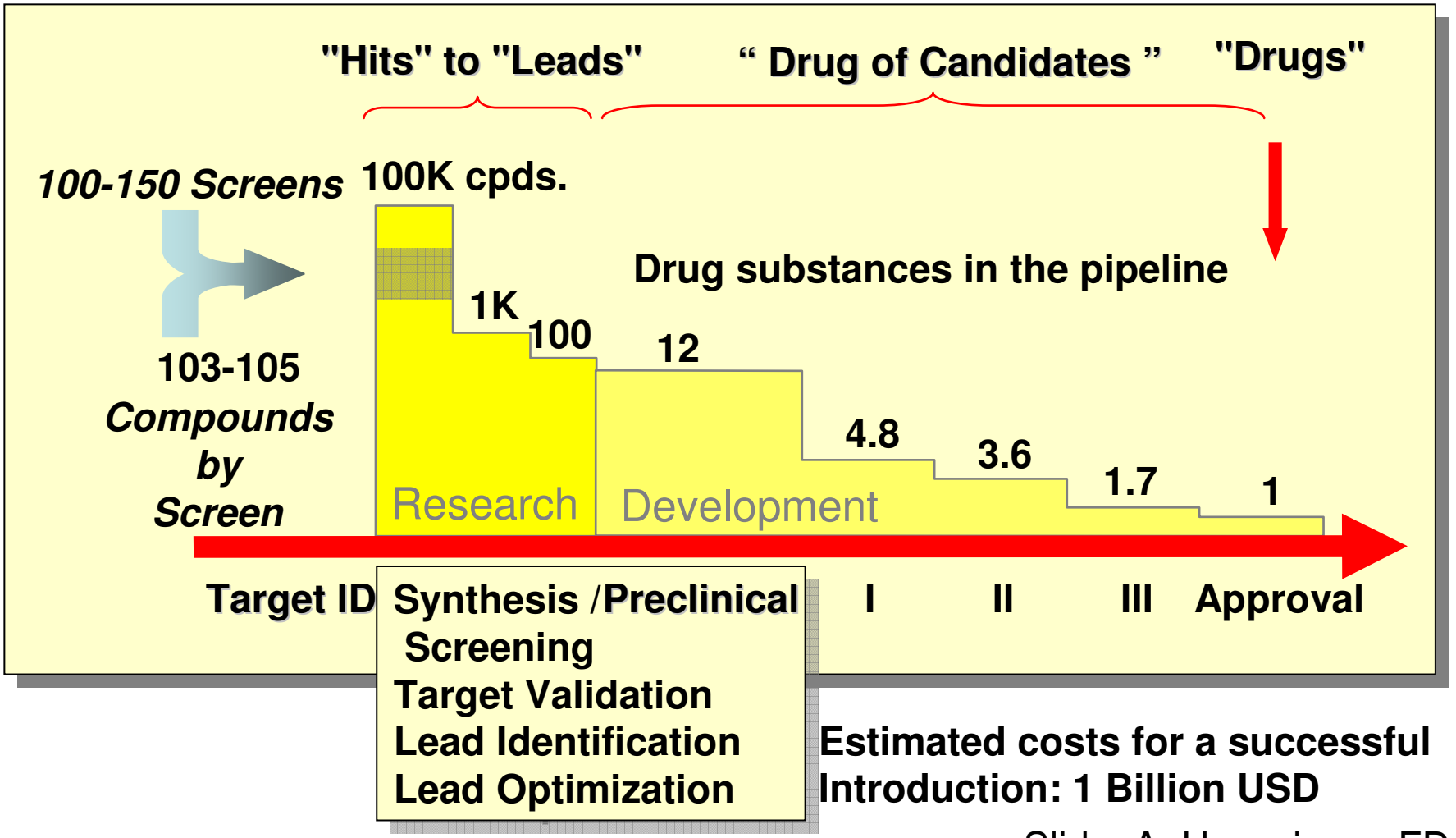
© European Compliance Academy (ECA)

Research & Development Process: a poor connectivity



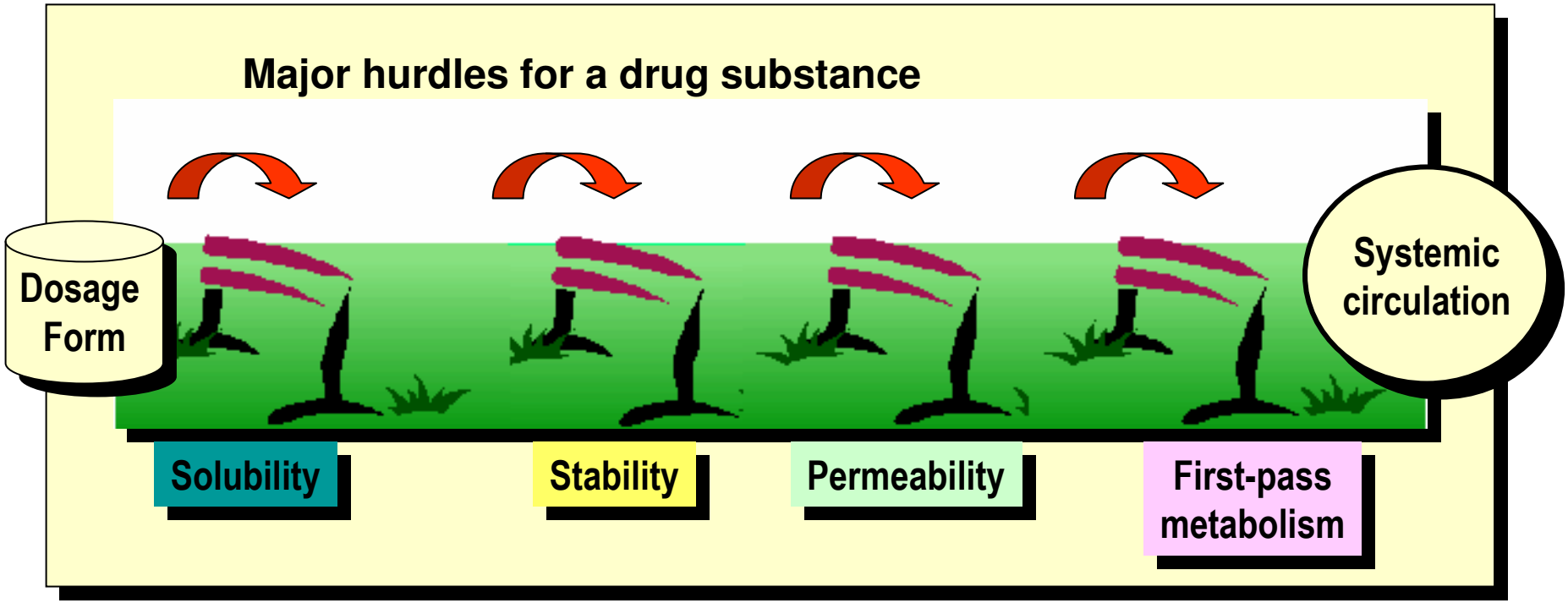
Slide: J. Werani, Pfizer

© European Compliance Academy (ECA)



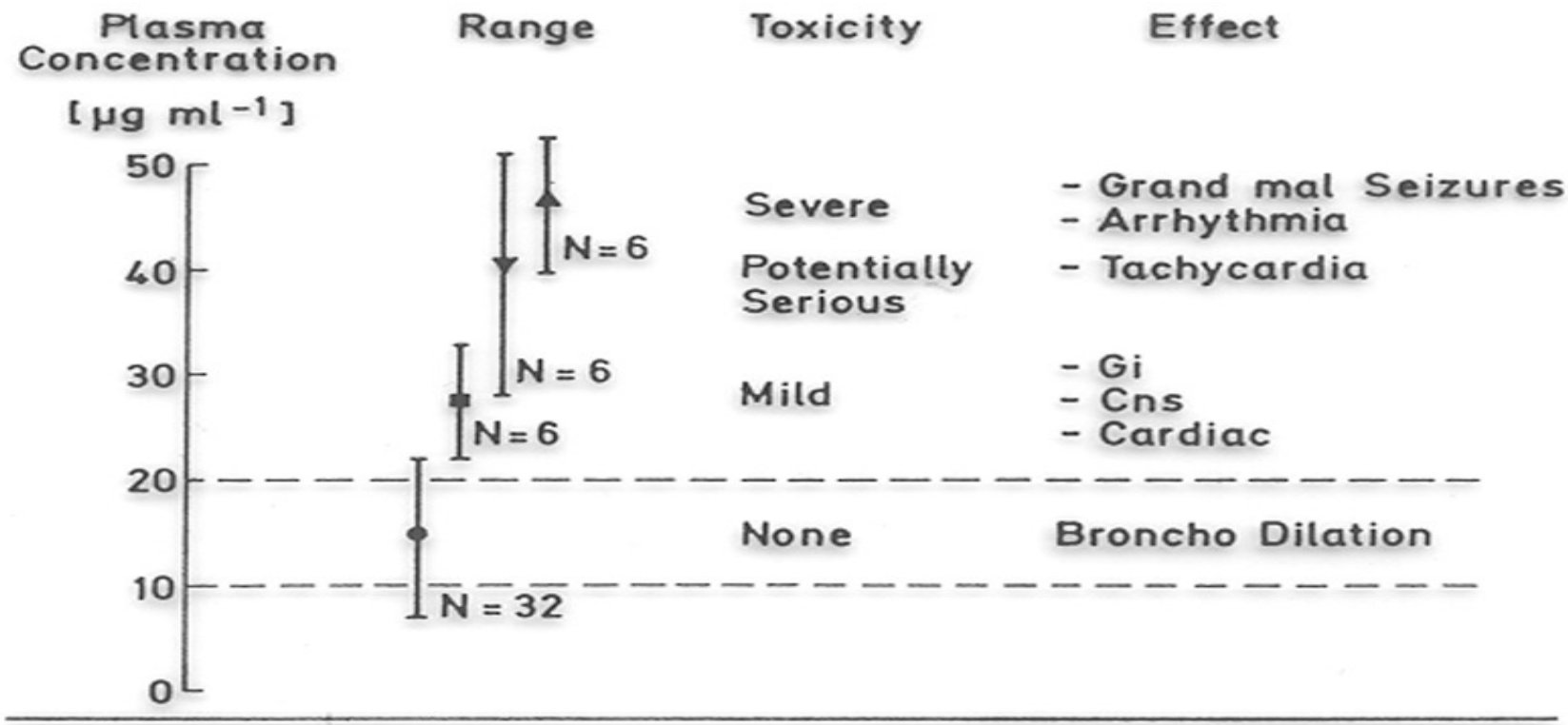
Slide: A. Hussain, ex FDA

© European Compliance Academy (ECA)



© European Compliance Academy (ECA)

Systemic Circulation: Therapeutic window

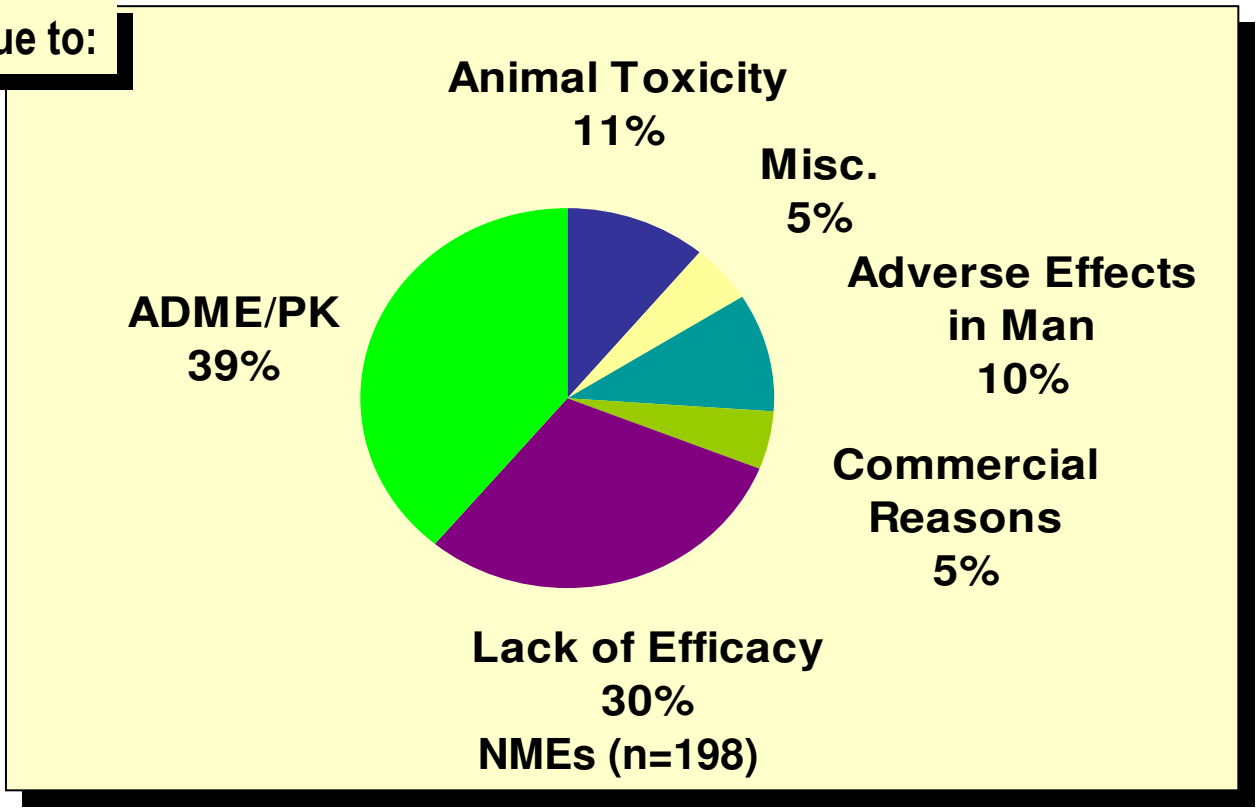


Plasma concentrations of theophylline related directly to the appearance of adverse reactions. Bronchodilation is the therapeutic effect of this drug

© European Compliance Academy (ECA)

Failure of a project: Reasons

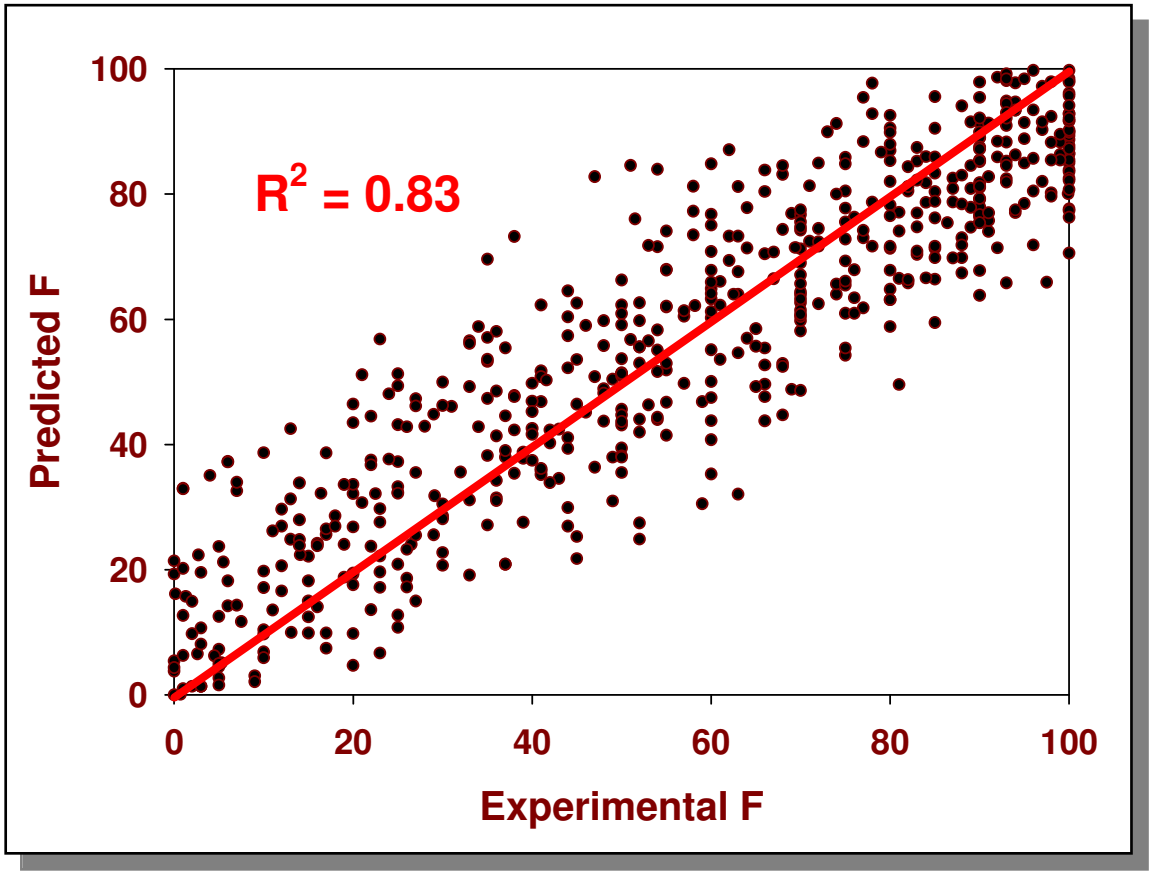
Failures due to:



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

© European Compliance Academy (ECA)

Hurdle: Bioavailability of the drug substance



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

© European Compliance Academy (ECA)

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

© European Compliance Academy (ECA)

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

© European Compliance Academy (ECA)

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.

© European Compliance Academy (ECA)

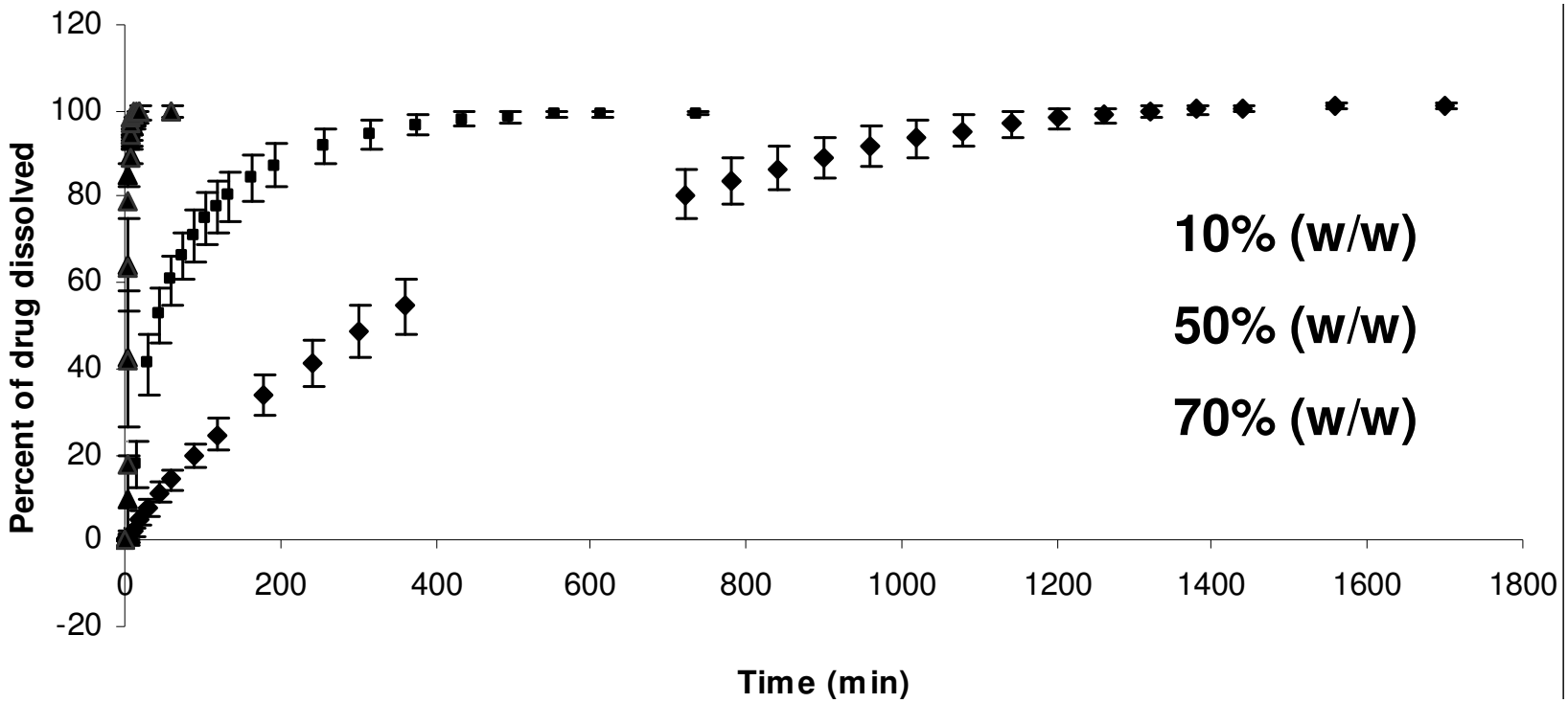
Classical Approach I

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 !)

© European Compliance Academy (ECA)

Drug A: Dissolution rate of capsule formulations

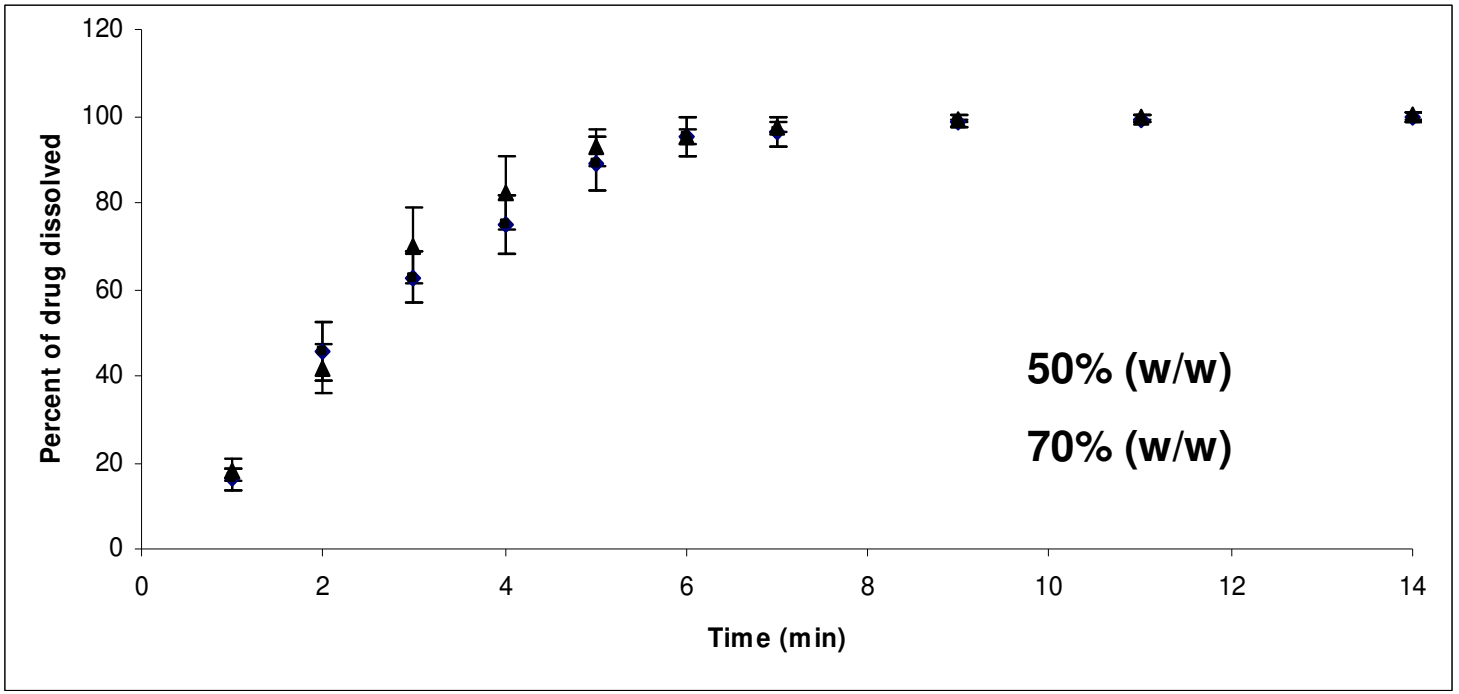
Capsule formulations were not robust being sensitive to the drug load (16, 79 and 109 mg, respectively 10% w/w, 50% w/w and 70% w/w.



© European Compliance Academy (ECA)

Drug A: Dissolution rate of tablet formulations

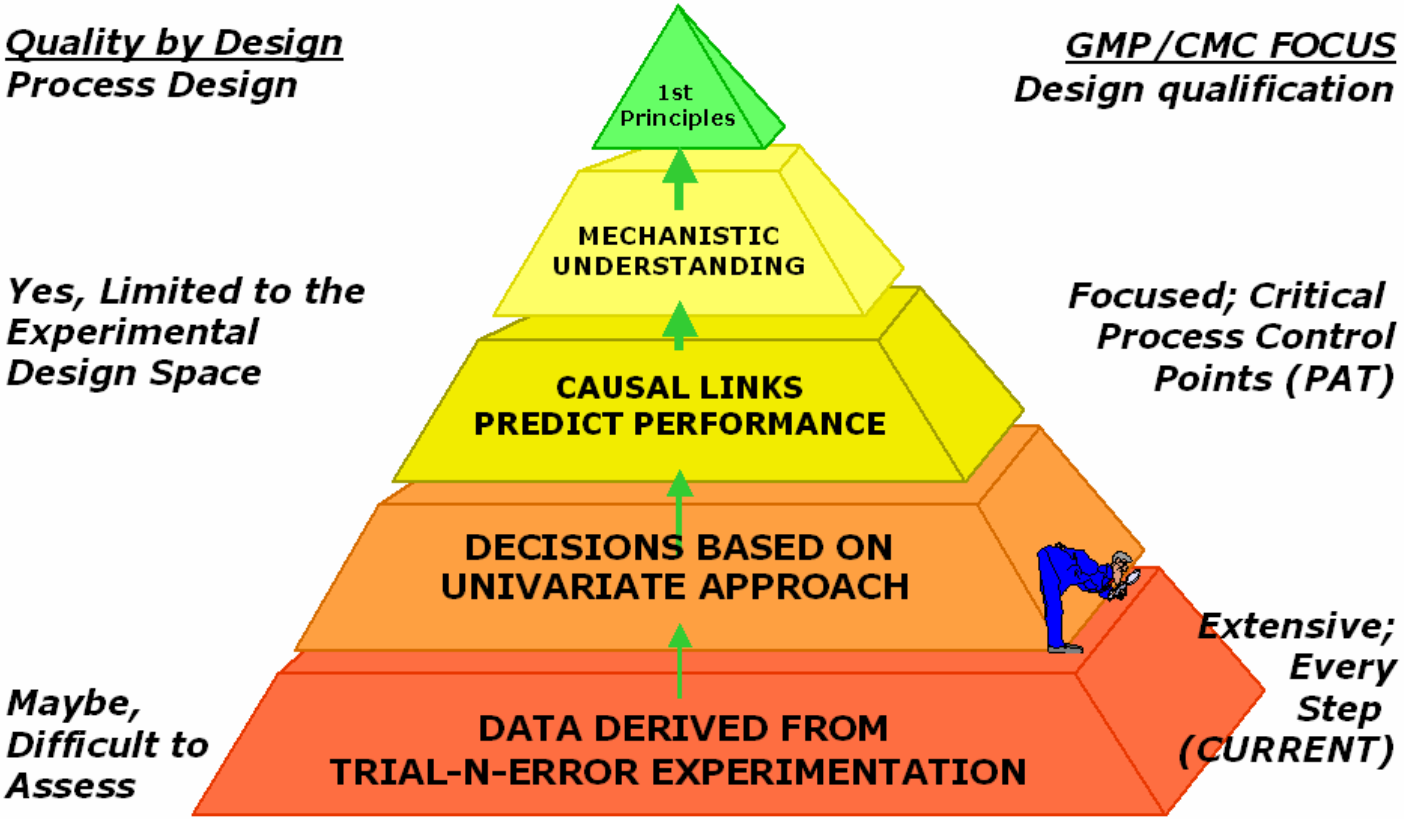
Tablet formulations have been robust and not sensitive to the drug load: 77mg, 109 mg drug substance, respectively 50% w/w, 70% w/w.



Reference: PhD Thesis Johannes von Orelli

© European Compliance Academy (ECA)

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



© European Compliance

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?

© European Compliance Academy (ECA)

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

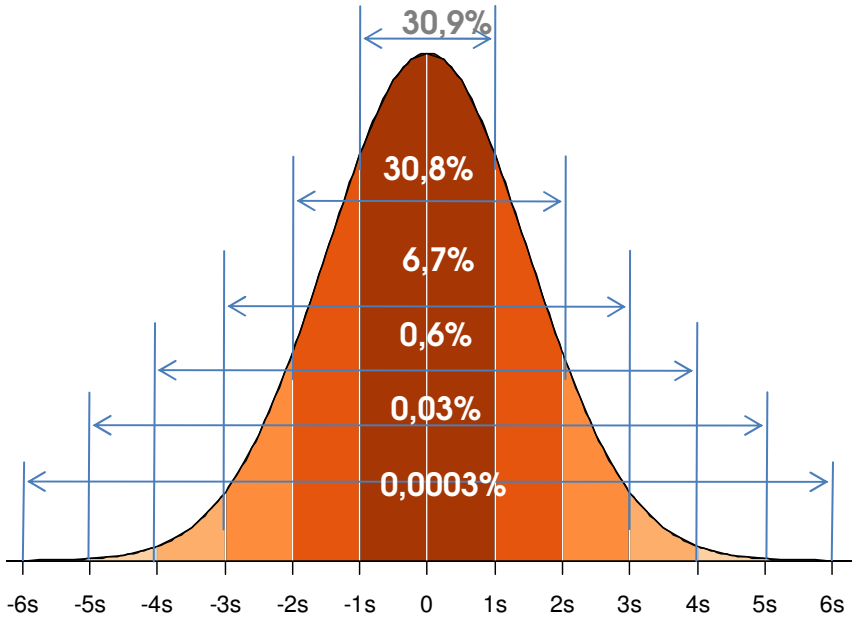
Performance of a process → Sigma value

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!

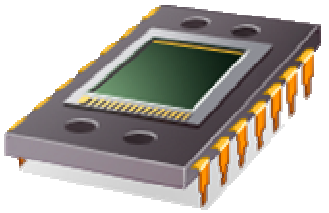
$$f(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{x^2}{2\sigma^2}}$$



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!)

© European Compliance Academy (ECA)

Common approach to keep costs under control

The 20% / 80% Rule:

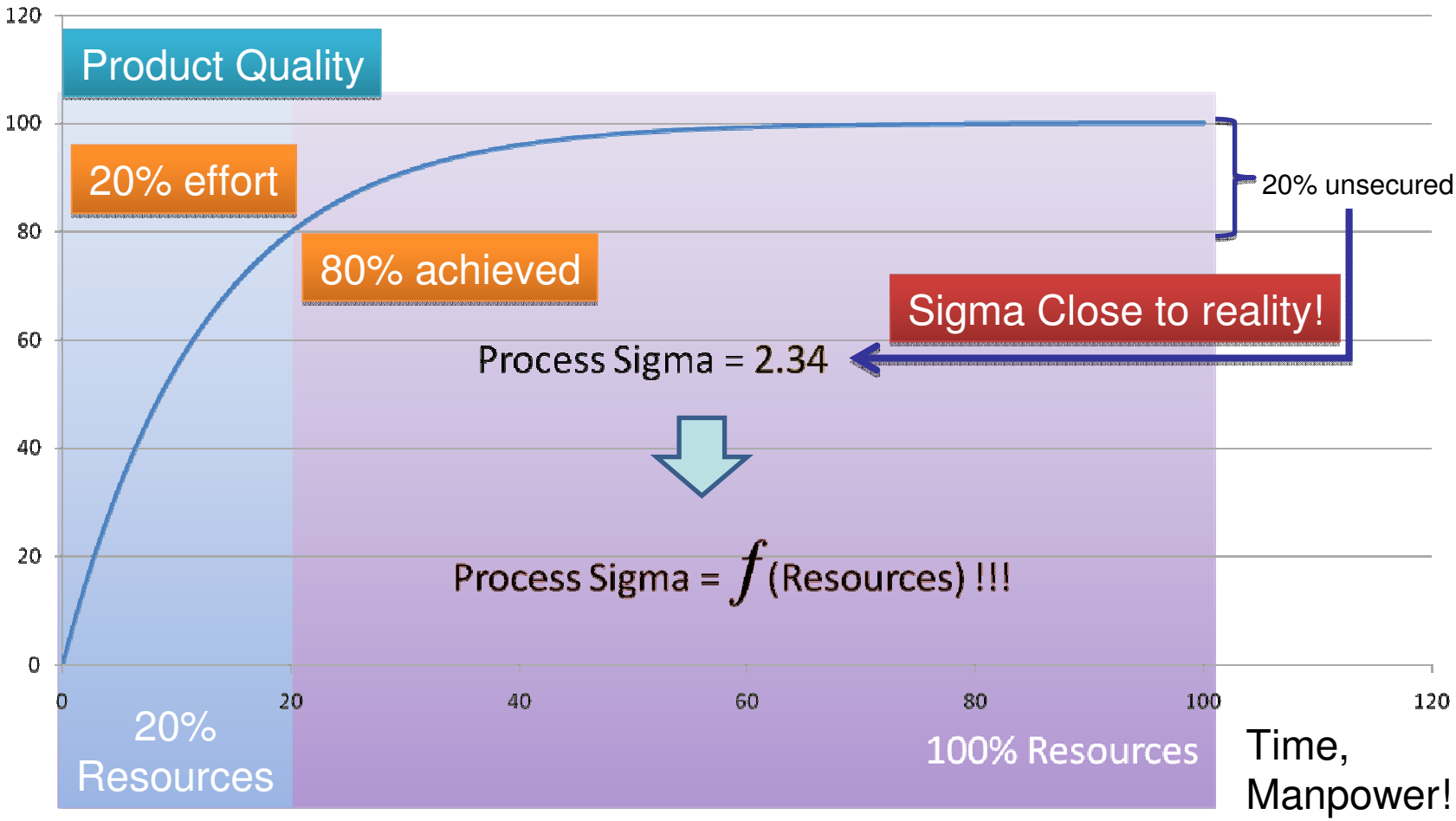
With 20% of time and effort dedicated to a project
80% of the goals can be achieved!

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!

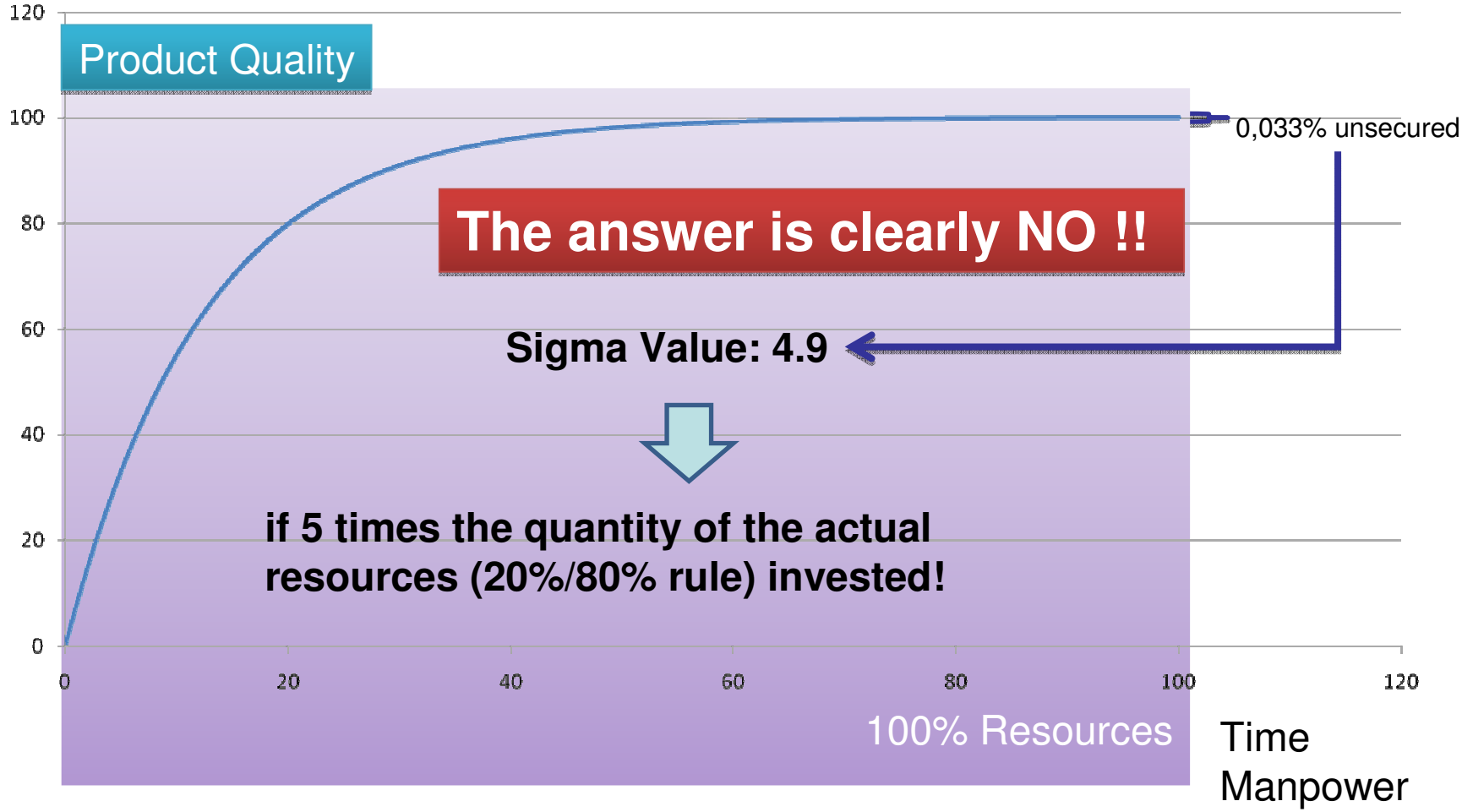
© European Compliance Academy (ECA)

Sigma Value – function of resources



© European Compliance Academy (ECA)

Can Six Sigma be achieved with conventional tools?



© European Compliance Academy (ECA)

21

PWC Pharma 2020: Vision e-Development

New Tools are required!!

- 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!

© European Compliance Academy (ECA)

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.

© European Compliance Academy (ECA)

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).**

© European Compliance Academy (ECA)

Boeing 777 and Airbus 380 were fully designed in-silico

© European Compliance Academy (ECA)

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

© European Compliance Academy (ECA)

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

How can we do that for pharma?

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

Prerequisites and primary requirements I:

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.

© European Compliance Academy (ECA)

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 II:

a)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

© European Compliance Academy (ECA)

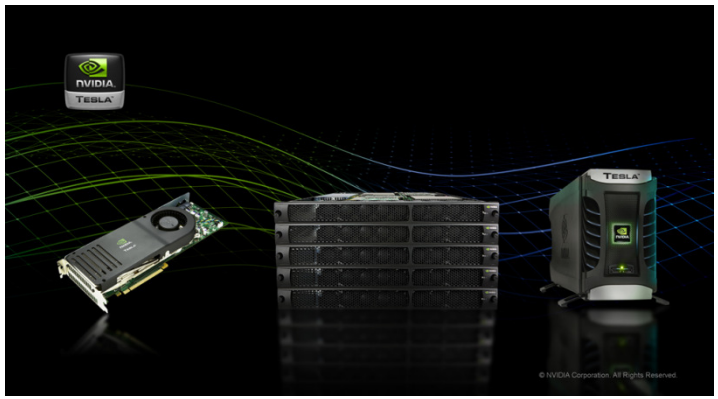
Designing a solid dosage form: *in silico* approach II?

How can we do that for pharma?

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

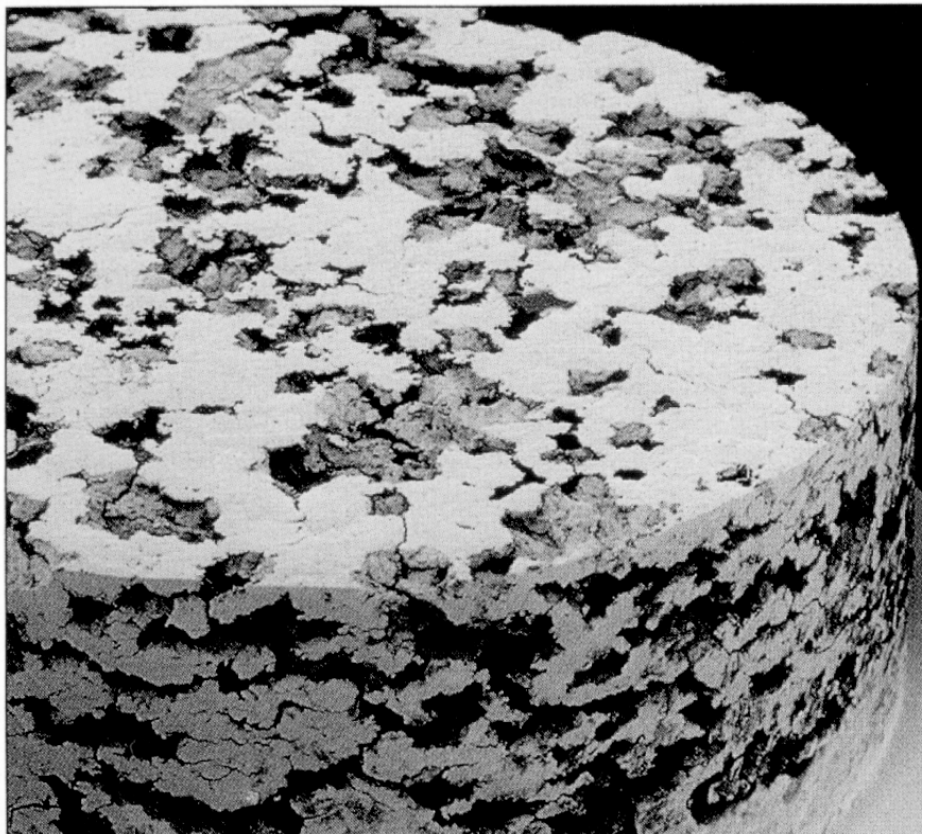
Prerequisites and primary requirements II:

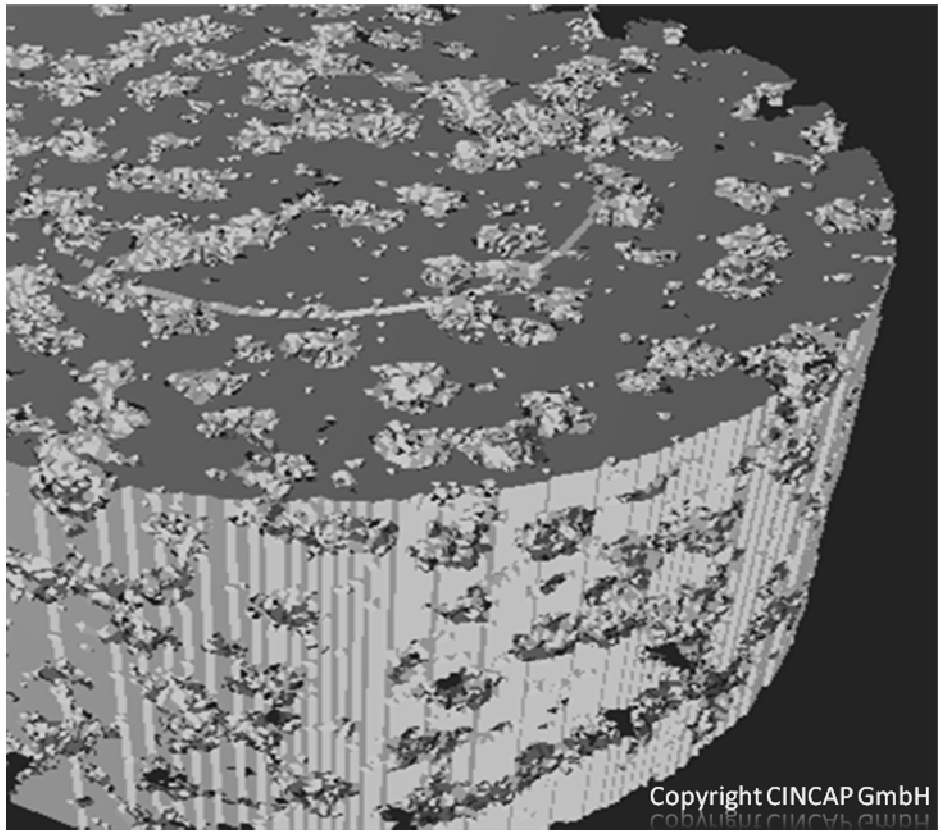
b) Availability of the corresponding hardware, i.e. A supercomputer.



© European Compliance Academy (ECA)

Leached Matrix Controlled Release Tablet: Real: left ; Computer Generated System: right

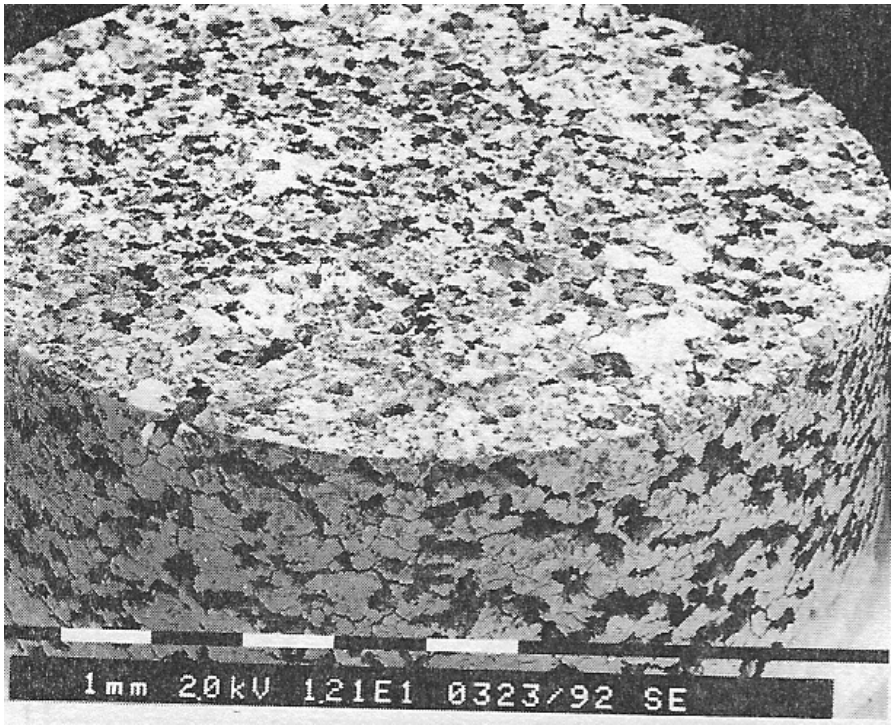




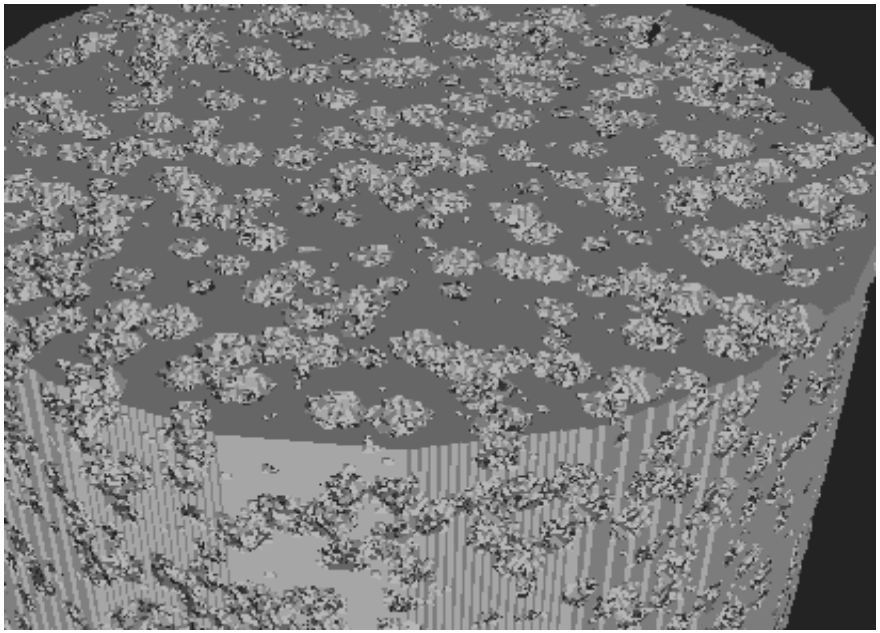
Reference for real product: PhD Thesis J.D. Bonny

Leached Matrix Controlled Release Tablet:

250-355 µm



280-400 µm

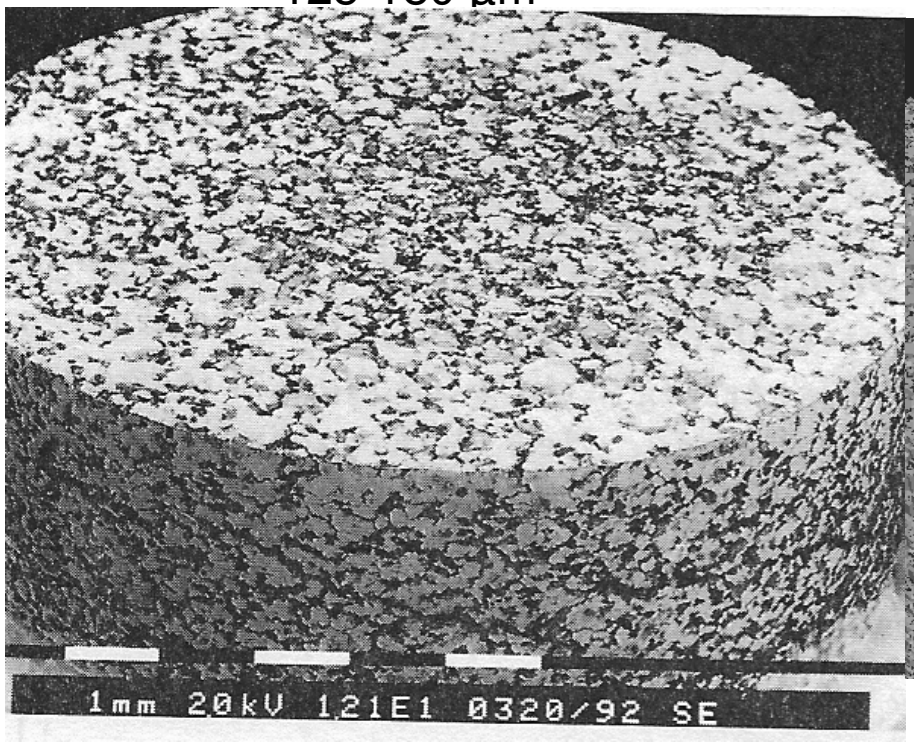


Real – left (PhD Thesis J.D. Bonny)
Computer Generated System - right

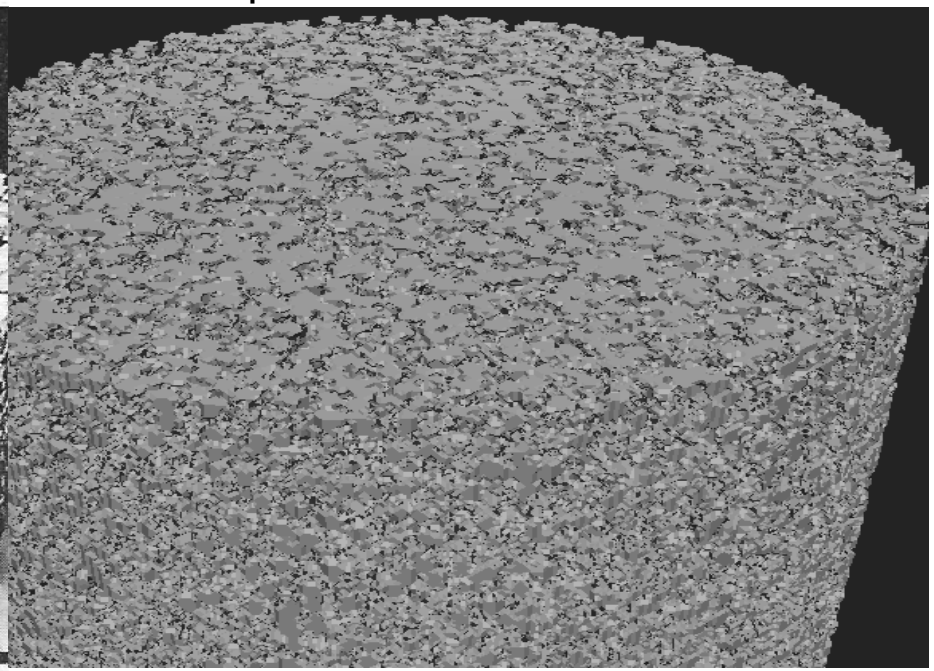
© European Compliance Academy (ECA)

Leached Matrix Controlled Release Tablet

125-180 µm



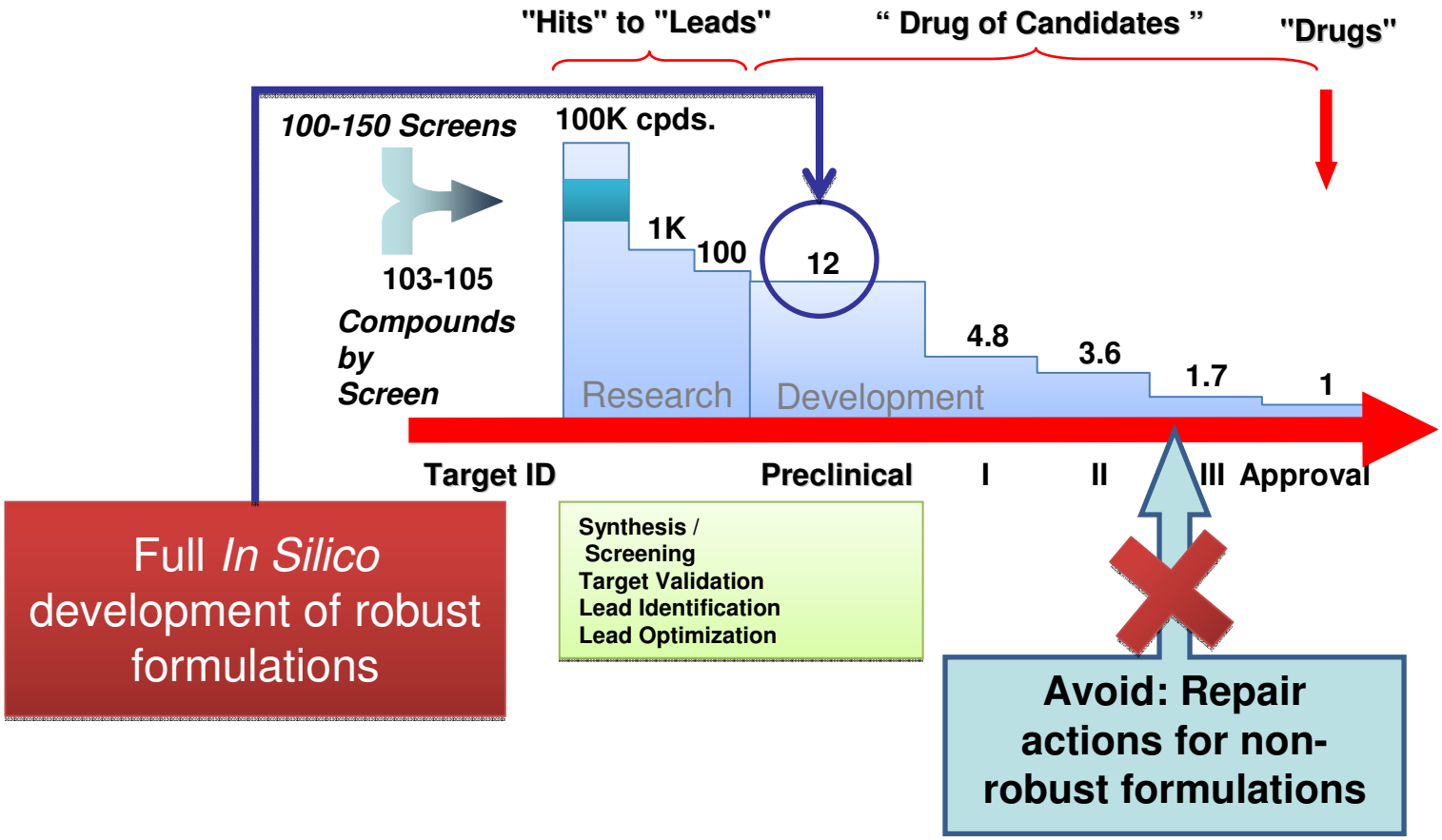
150-200 µm



Real – left (PhD Thesis J.D. Bonny)
Computer Generated System - right

© European Compliance Academy (ECA)

Idea: Full in-silico development of the marketed dosage form of 12 drug candidates for Clinical Phase I instead in the phase II / end of phase III !!



© European Compliance Academy (ECA)

F-CAD as Toolbox for computer-aided formulation design

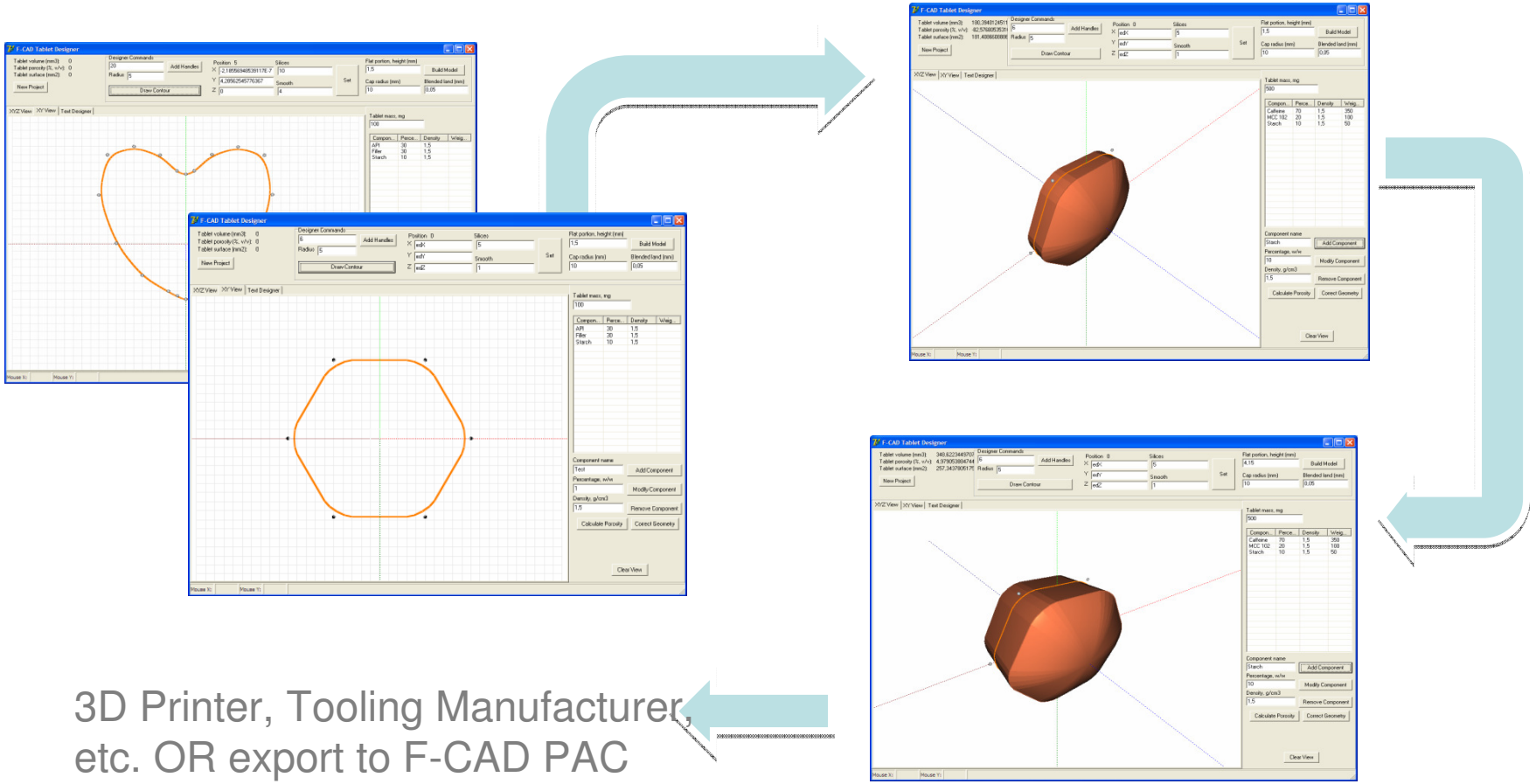
Important issue:

In order **to close the gaps** between Marketing, Pharmaceutical R&D, Clinical Supply, Clinical Phases, Pilot Plant Manufacturing, Scale-up Activities, Full Scale Manufacturing,
it is recommended
to start to use F-CAD already in the pre-clinical phase!

Thus the connectivity between the departments can be improved as a result of applying F-CAD!

© European Compliance Academy (ECA)

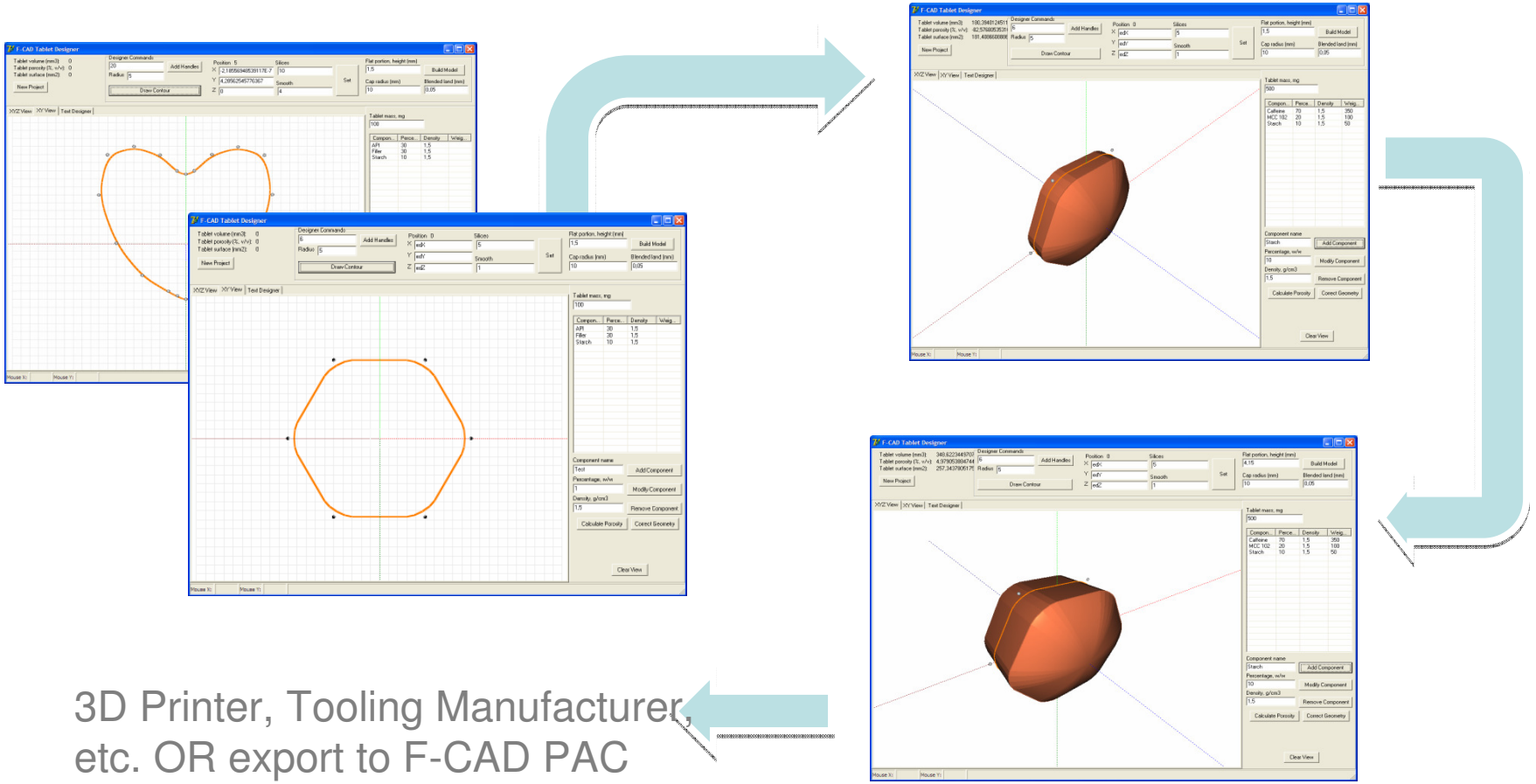
F-CAD Tablet Designer



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

© European Compliance Academy (ECA)

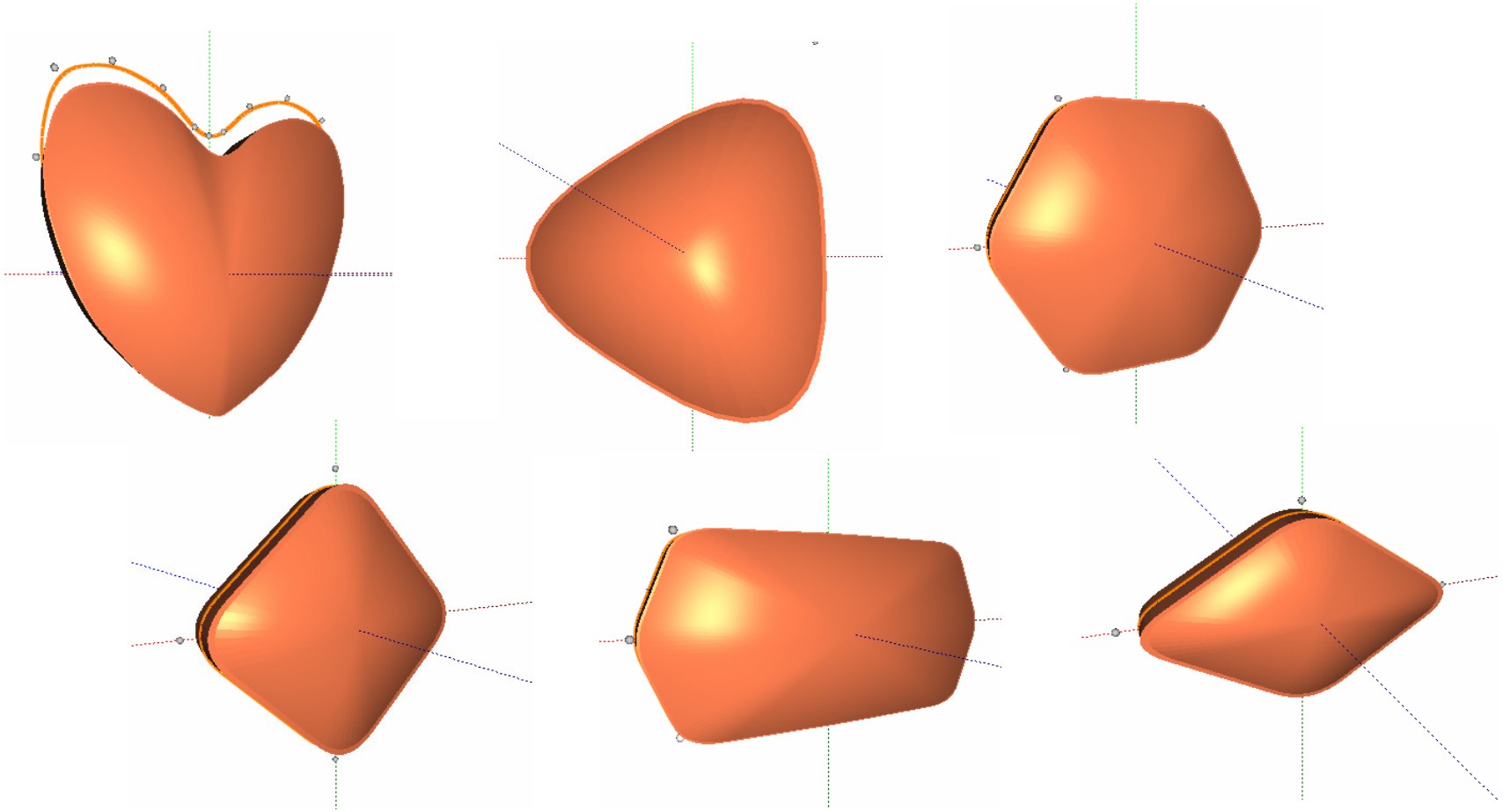
F-CAD Tablet Designer



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

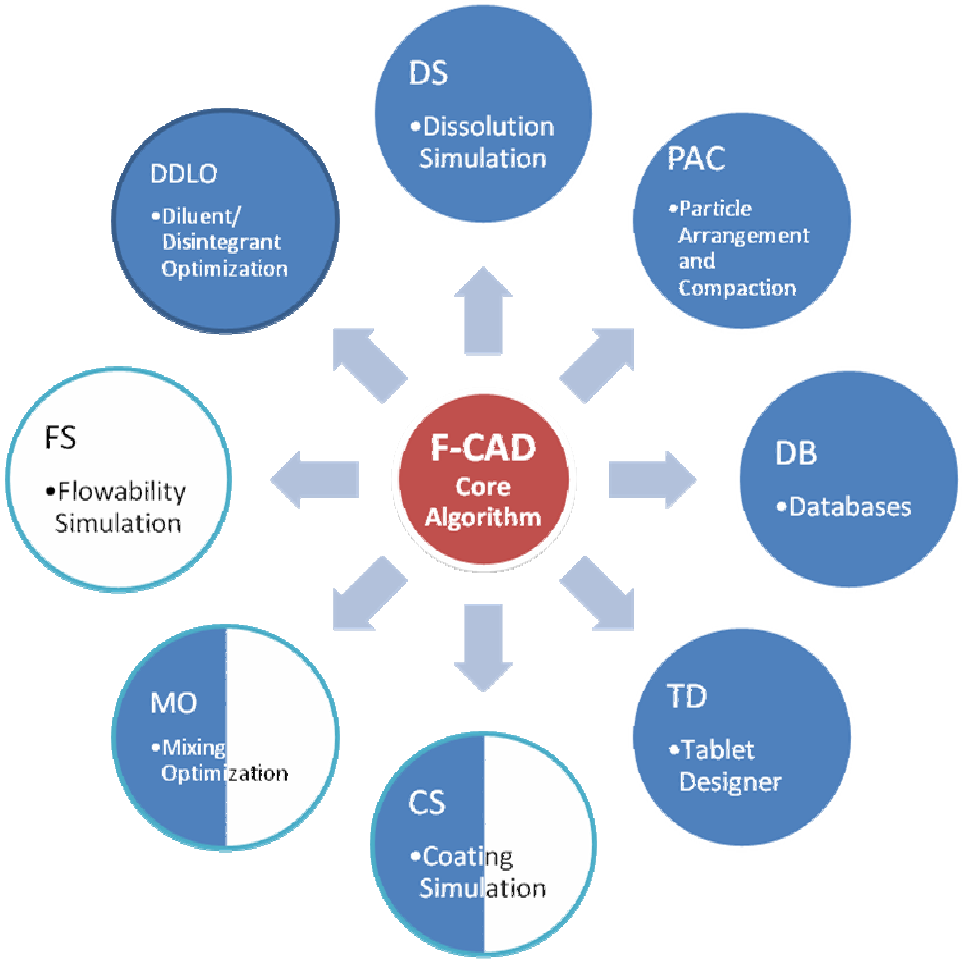
© European Compliance Academy (ECA)

Custom Shapes with F-CAD Tablet Designer



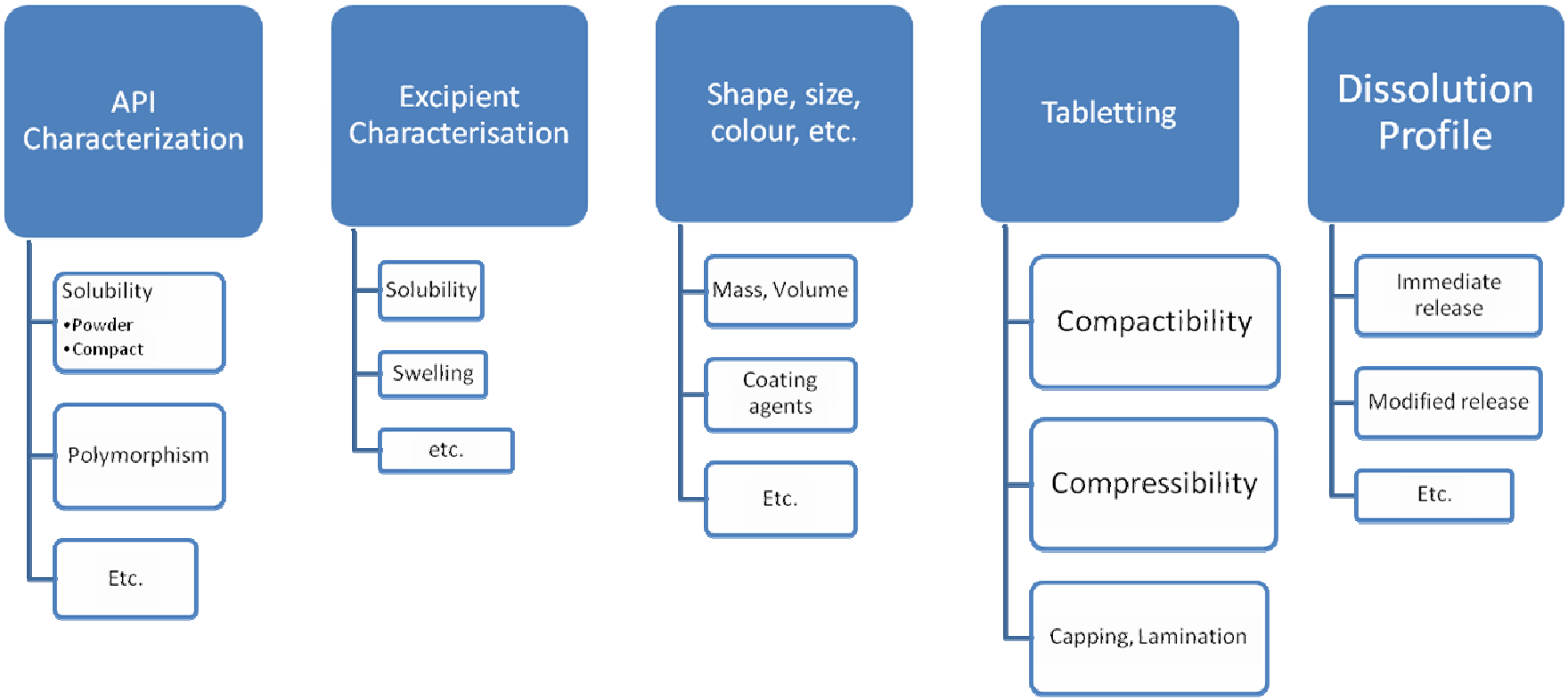
© European Compliance Academy (ECA)

F-CAD Modules



© European Compliance Academy (ECA)

Formulation development with F-CAD



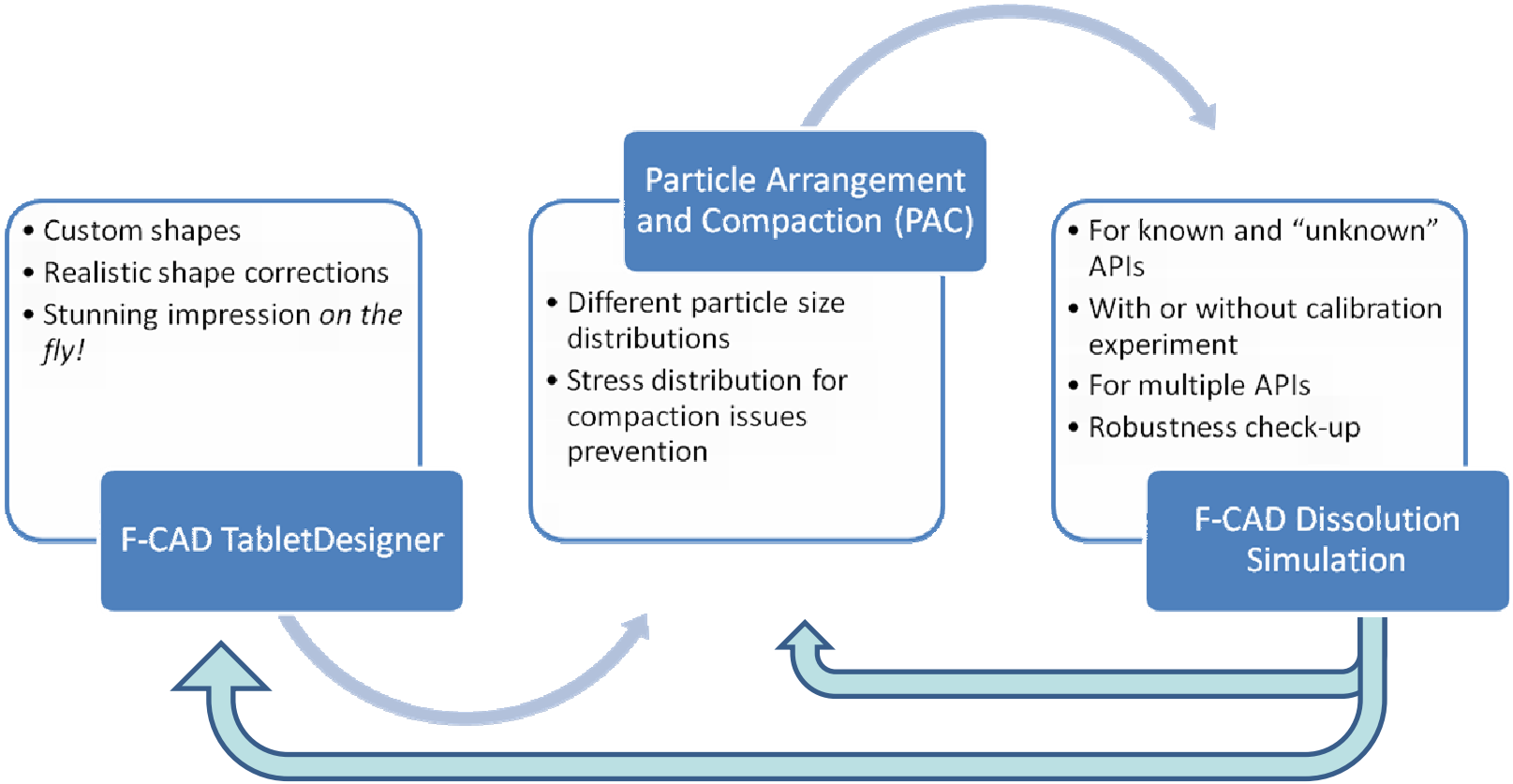
© European Compliance Academy (ECA)

F-CAD - QbD

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

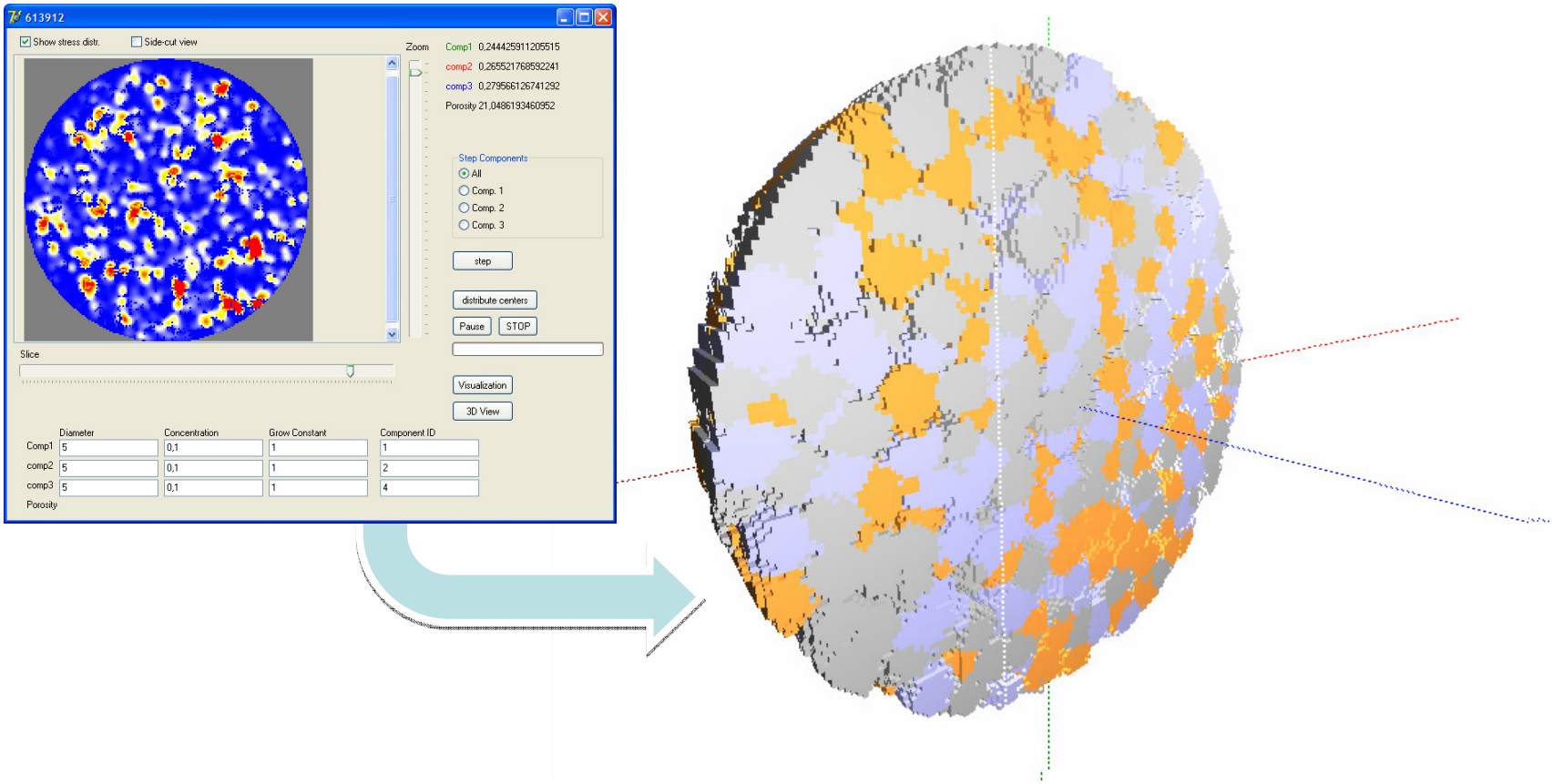
© European Compliance Academy (ECA)

F-CAD modelling process



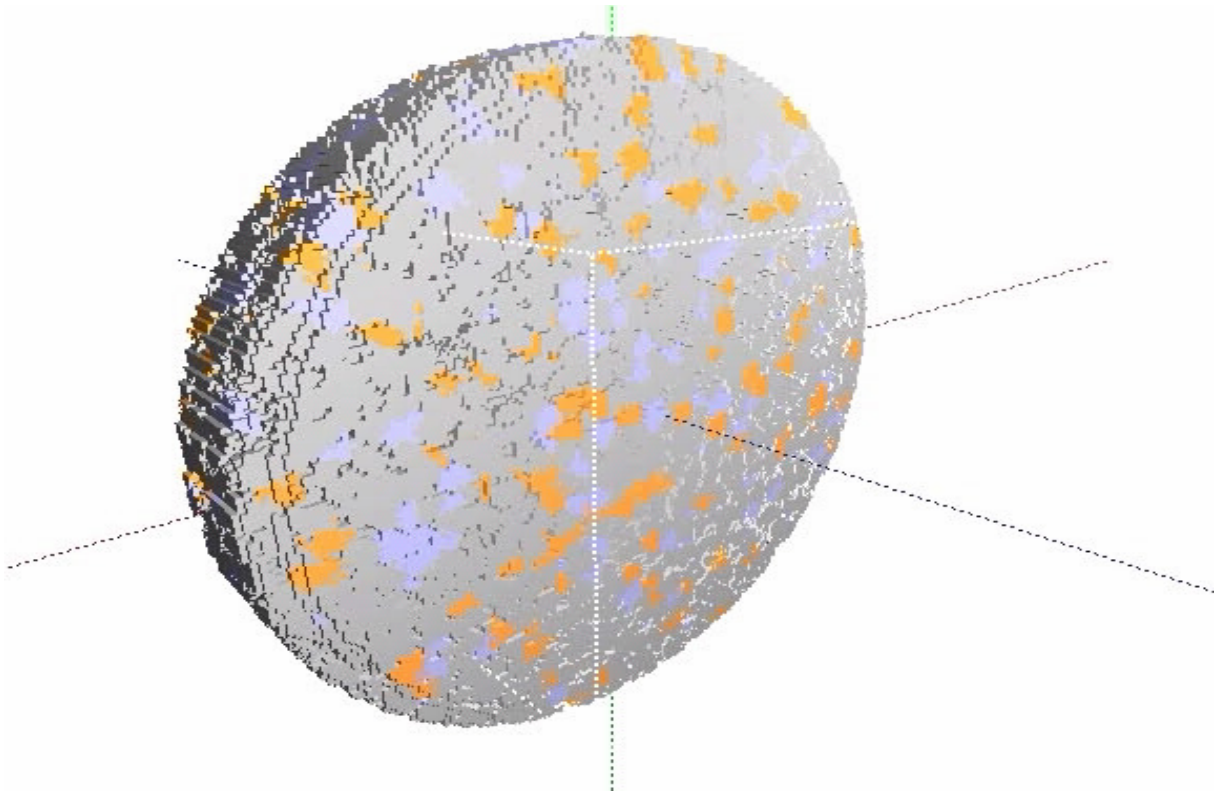
© European Compliance Academy (ECA)

F-CAD PAC – Particle Arrangement and Compaction



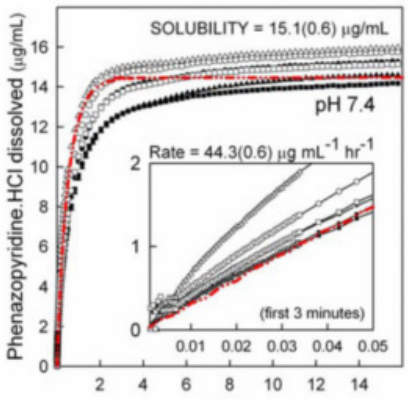
© European Compliance Academy (ECA)

Resulting compact

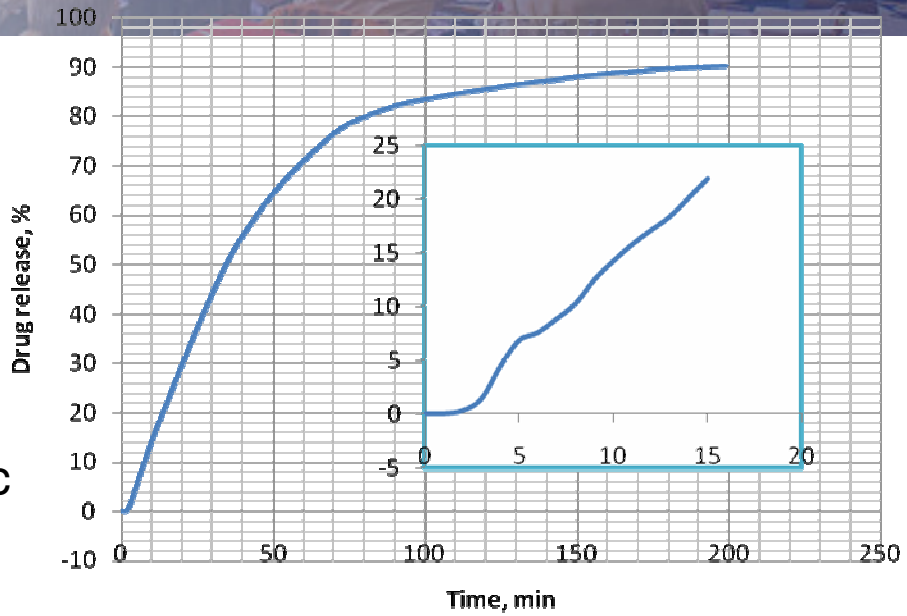


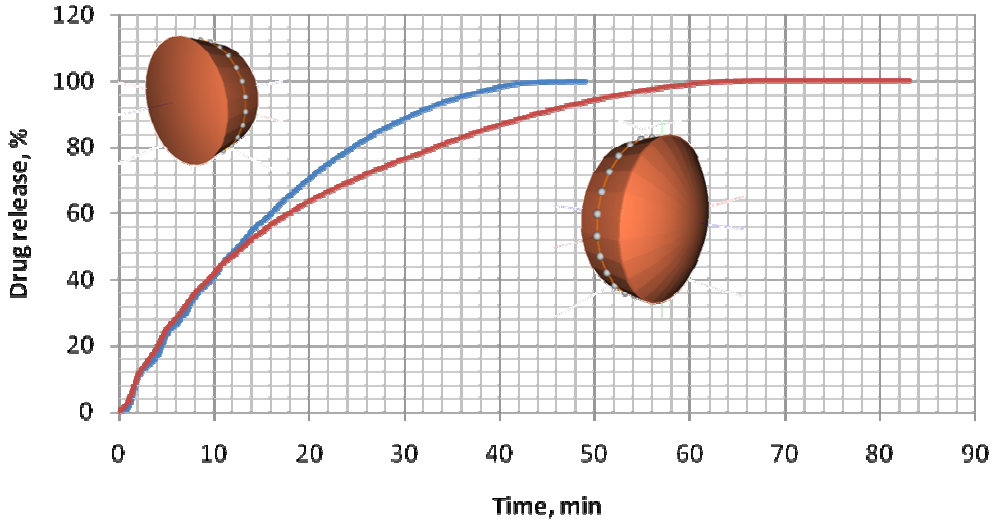
© European Compliance Academy (ECA)

F-CAD DS – *in silico* Profiles



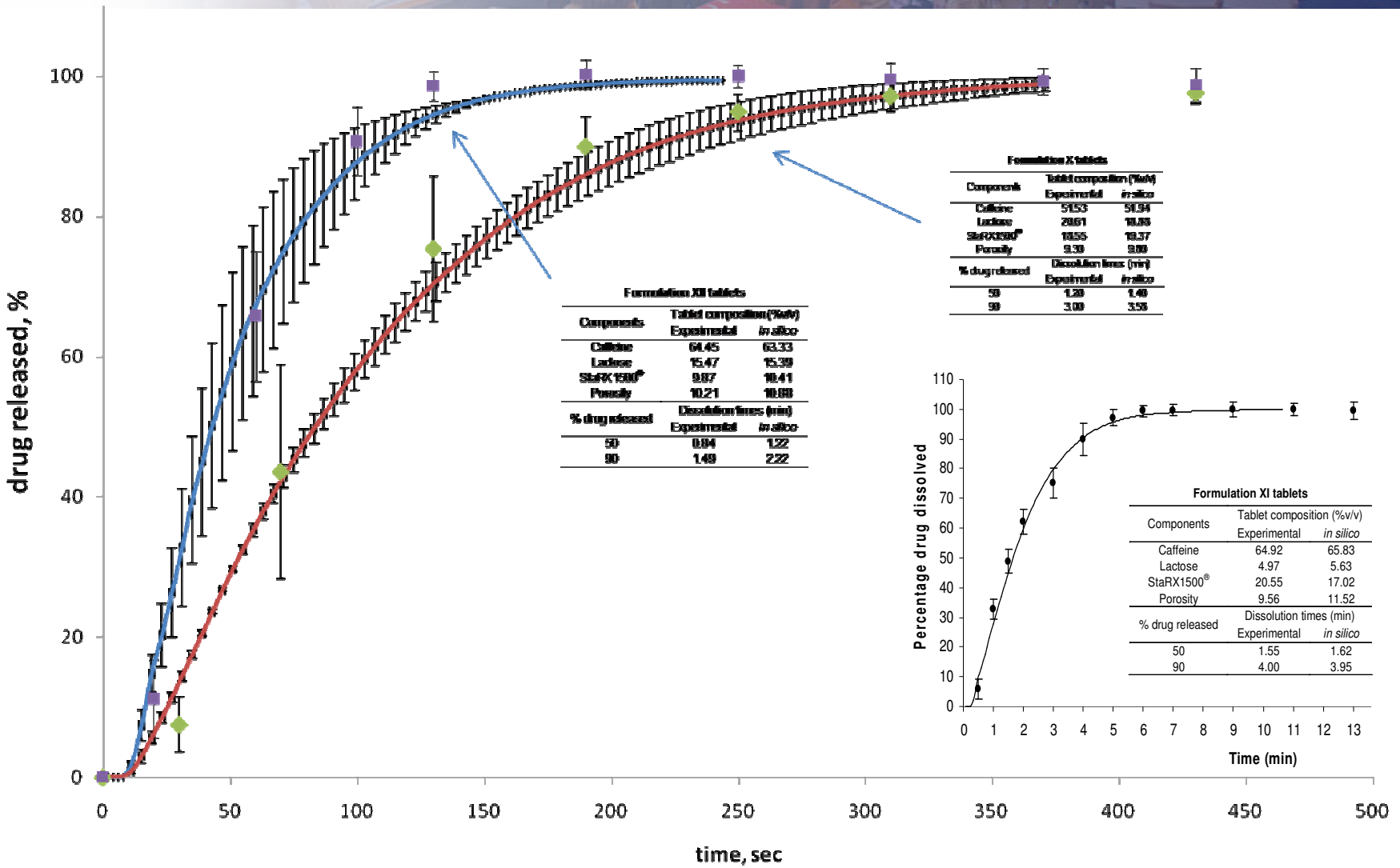
© Heath Scientific





© European Compliance Academy (ECA)

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



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

Components	Tablet composition (%v/v) Experimental	*in silico*
Caffeine	51.53	51.94
Lactose	28.61	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	3.55

Formulation XI tablets

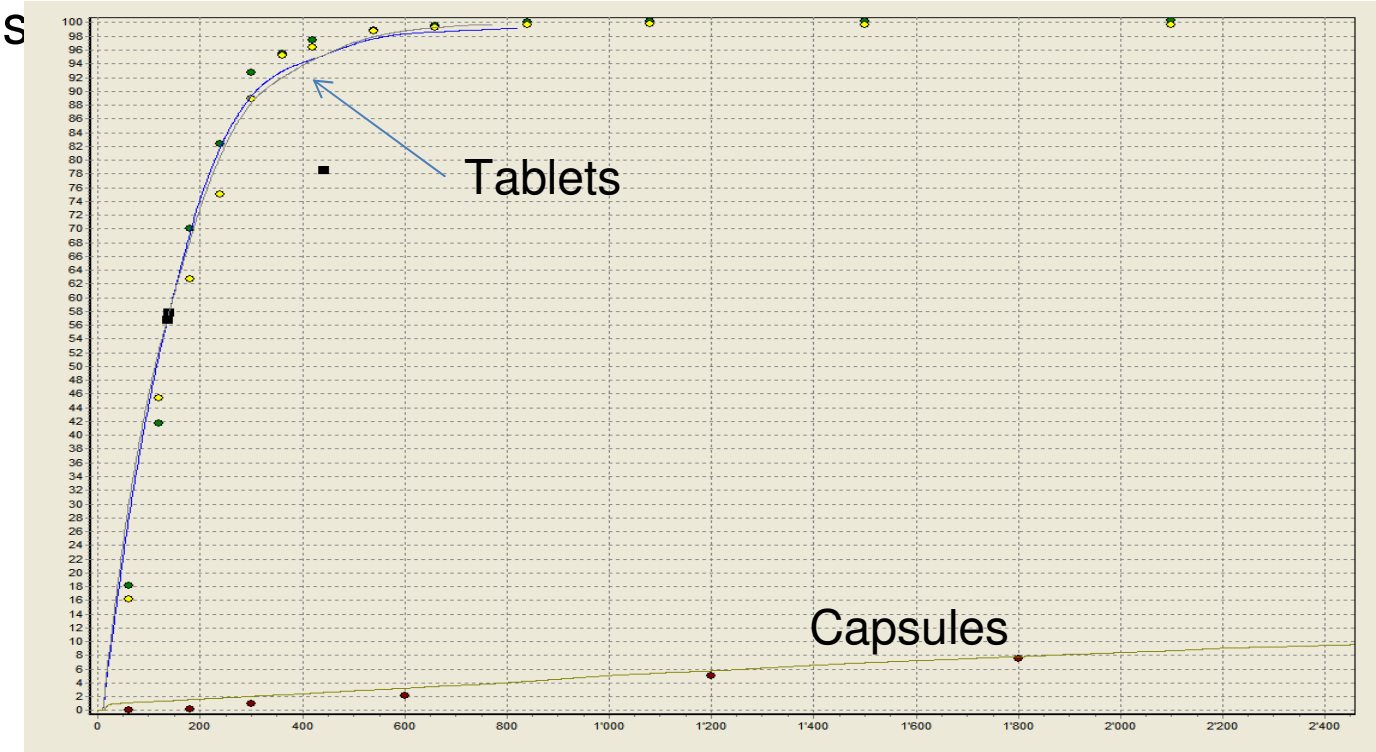
Components	Tablet composition (%v/v) Experimental	*in silico*
Caffeine	64.92	65.83
Lactose	4.97	5.63
StaRX1500®	20.55	17.02
Porosity	9.56	11.52
% drug released	Dissolution times (min) Experimental	*in silico*
50	1.55	1.62
90	4.00	3.95

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

© European Compliance Academy (ECA)

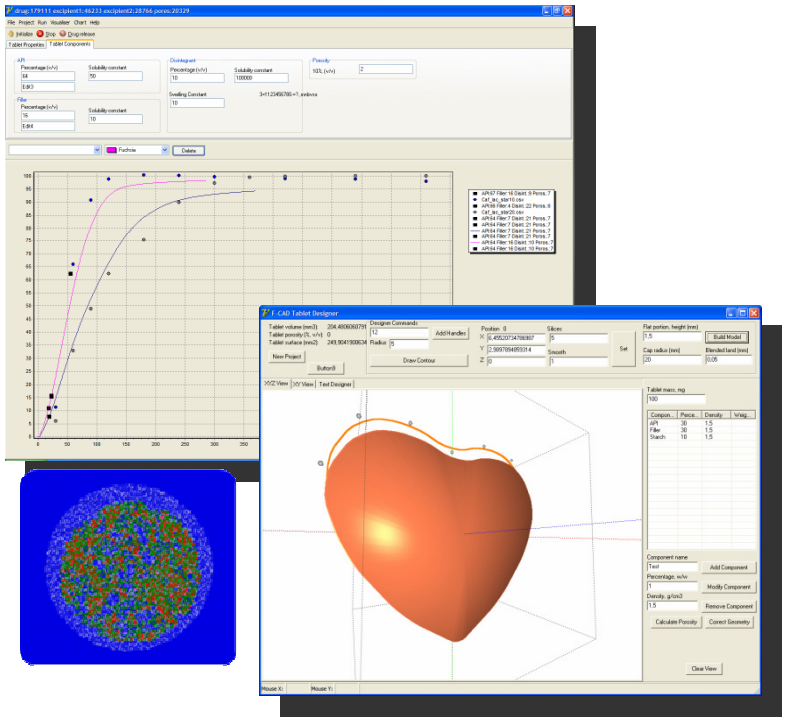
Capsule/Tablet simulation with F-CAD

- System s



© European Compliance Academy (ECA)

VES and F-CAD Screenshots



Orientation: Quality by Design (QbD)

F-CAD Robust Formulation!

Formulation R&D

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

Production

VES Operator Training

- tual Equipment Simulation (VES)
- tinuous Education + Personalized
- ing
- mum human error

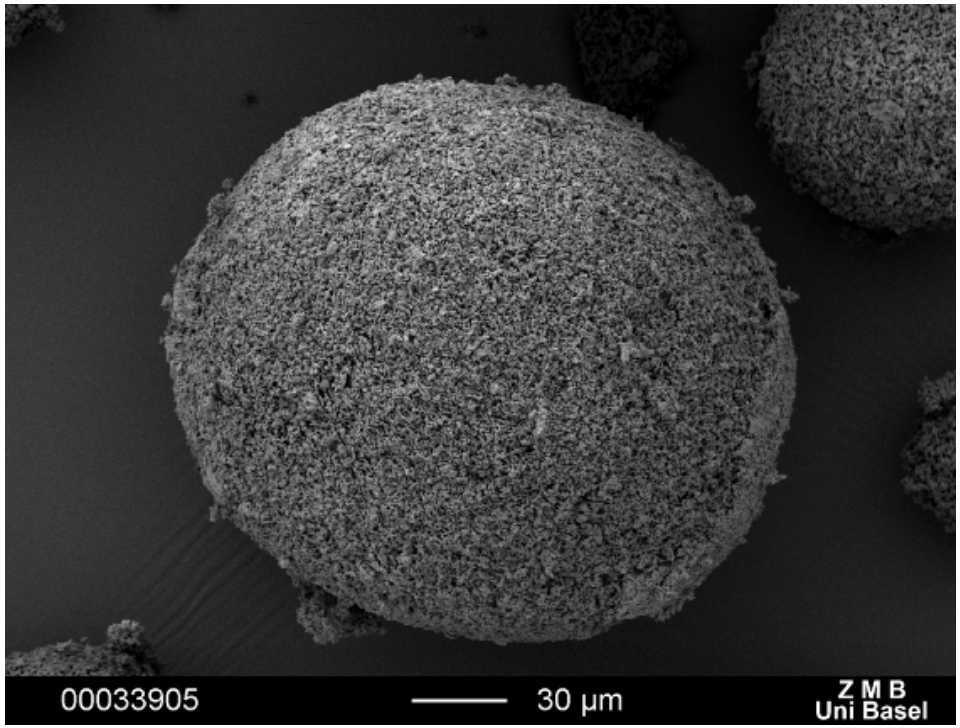
© European Compliance Academy (ECA)

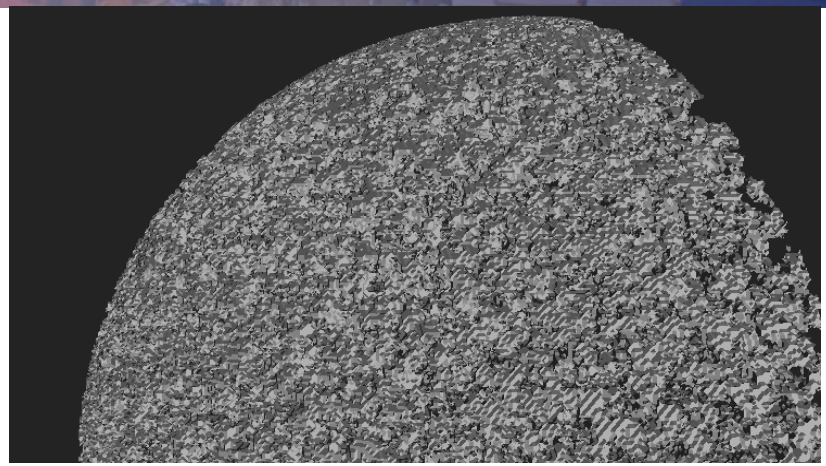
Benefits of F-CAD

- Significant development **costs reduction**
- **Improves 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…. such as **Nanocomposite Pellets** with the correct aerodynamic diameter **for Inhalation** or e.g. **instant soluble** for **Injection** of **biopharmaceuticals** etc**.**

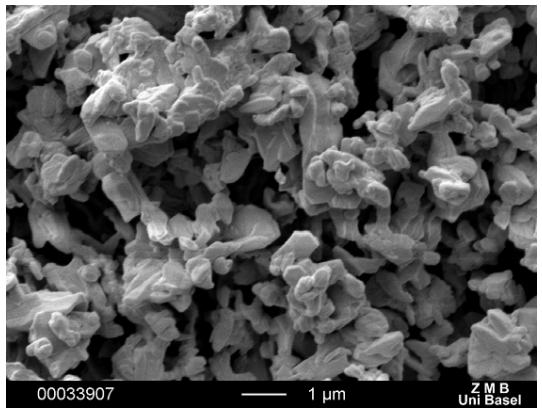
© European Compliance Academy (ECA)

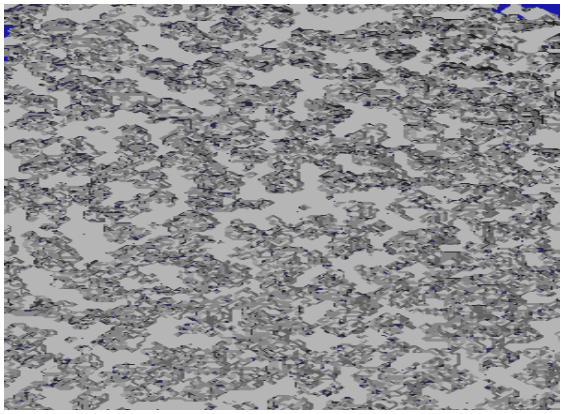




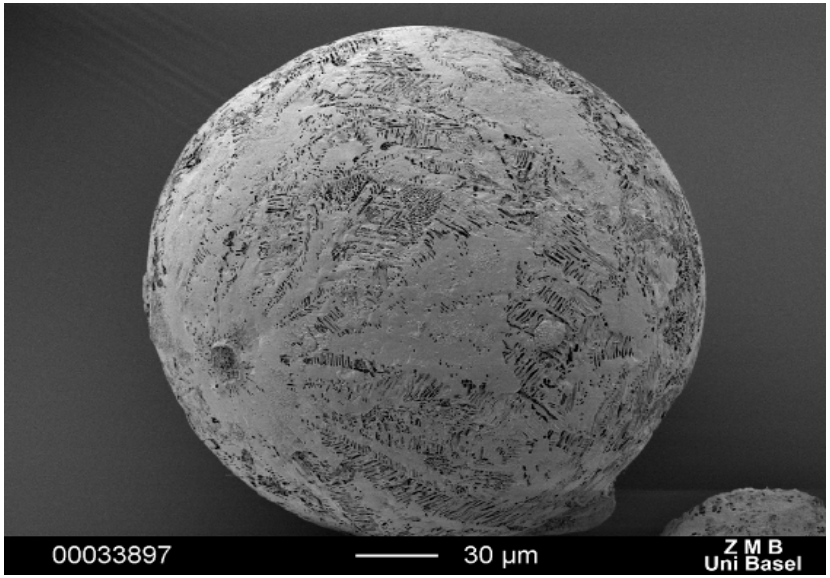
Spray freeze dryed Mannitol pellets with ca. 80% porosity as a drug Carrier, Left: PhD Thesis M. Plitzko; Right: Computer generated nano - comp. pellets by F-CAD (www.cincap.ch).

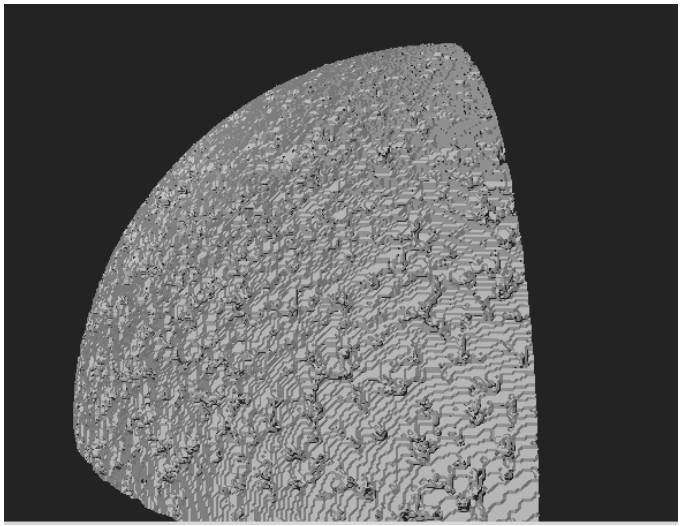
Nanocomposite Pellets as drug carriers for instant soluble Injections Or for Inhalation of Biopharmaceuticals, see www.ifiip.ch

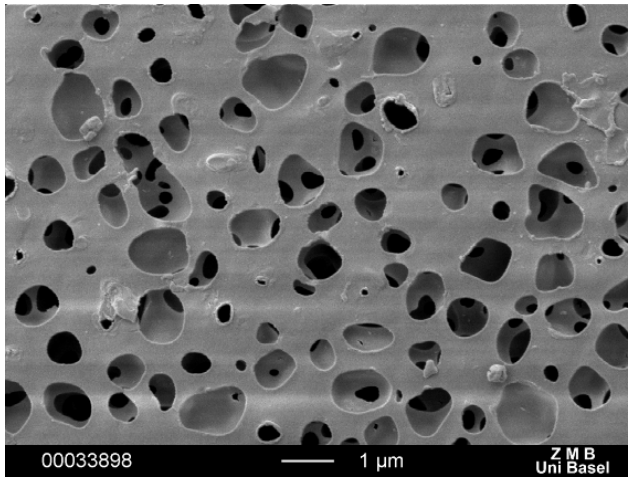




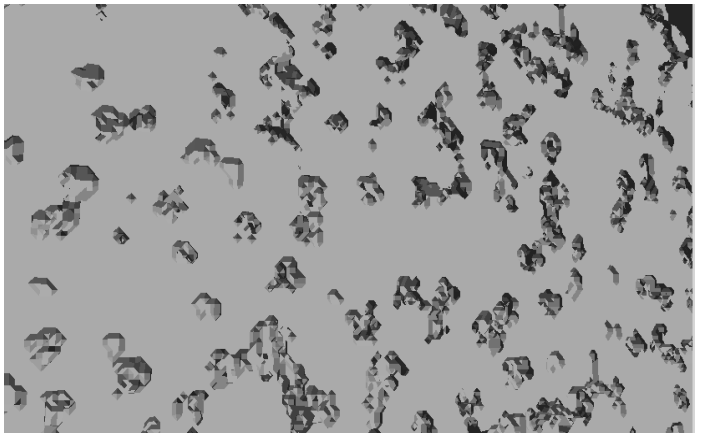
© European Compliance Academy (ECA)







Left: Ref. PhD Thesis M.Plitzko, Right: F-CAD



Real and computer generated Nano-composite Dextran pellets as drug carriers.

© European Compliance Academy (ECA)

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.

© European Compliance Academy (ECA)

F-CAD - QbD

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

© European Compliance Academy (ECA)

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.

© European Compliance Academy (ECA)

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.**

© European Compliance Academy (ECA)

55

Thank you for your attention!

Audience Q&A

© European Compliance Academy (ECA)