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F-CAD, Six Sigma Optimization and Cost Savings

Vision and statements for a computer-aided approach
to achieve Six Sigma performance
in solid dosage form design
and to reduce costs

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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

CINCAP QbD Orientation

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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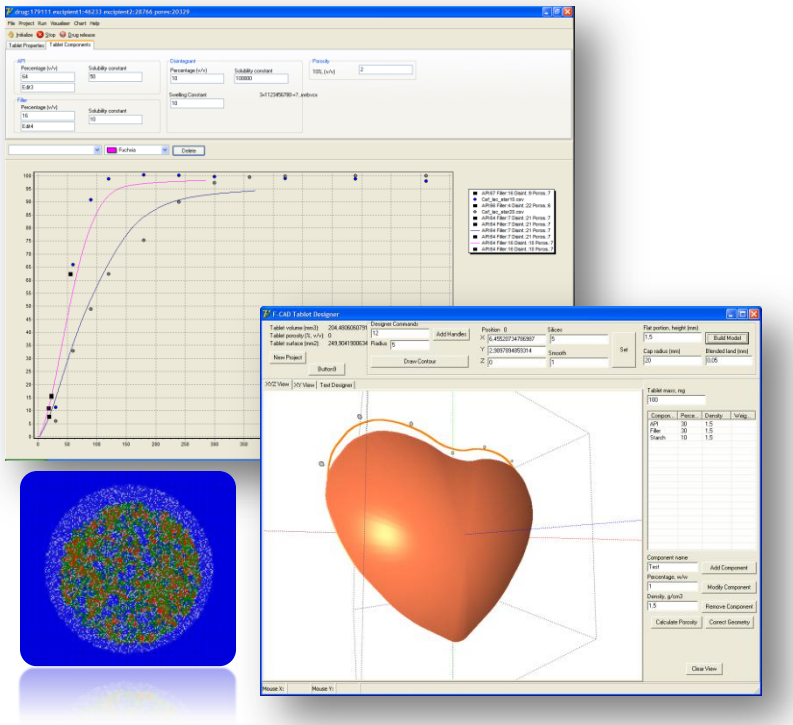
VES and F-CAD Screenshots



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

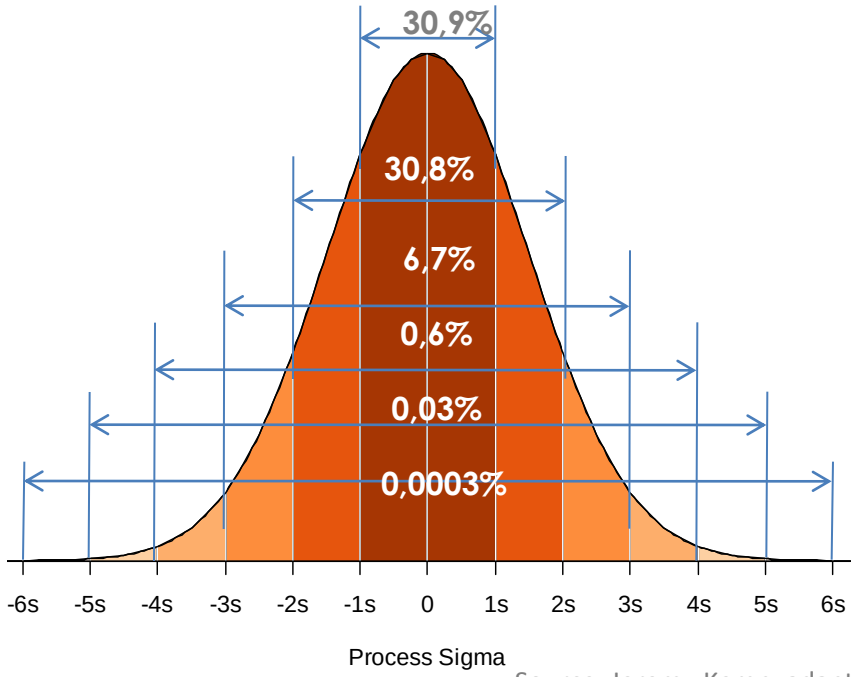
Performance of a process → Sigma value

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!

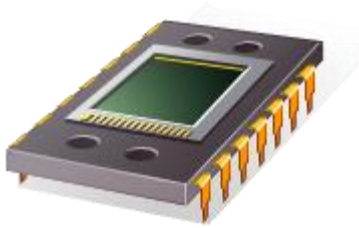
$$f(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{x^2}{2\sigma^2}}$$



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!

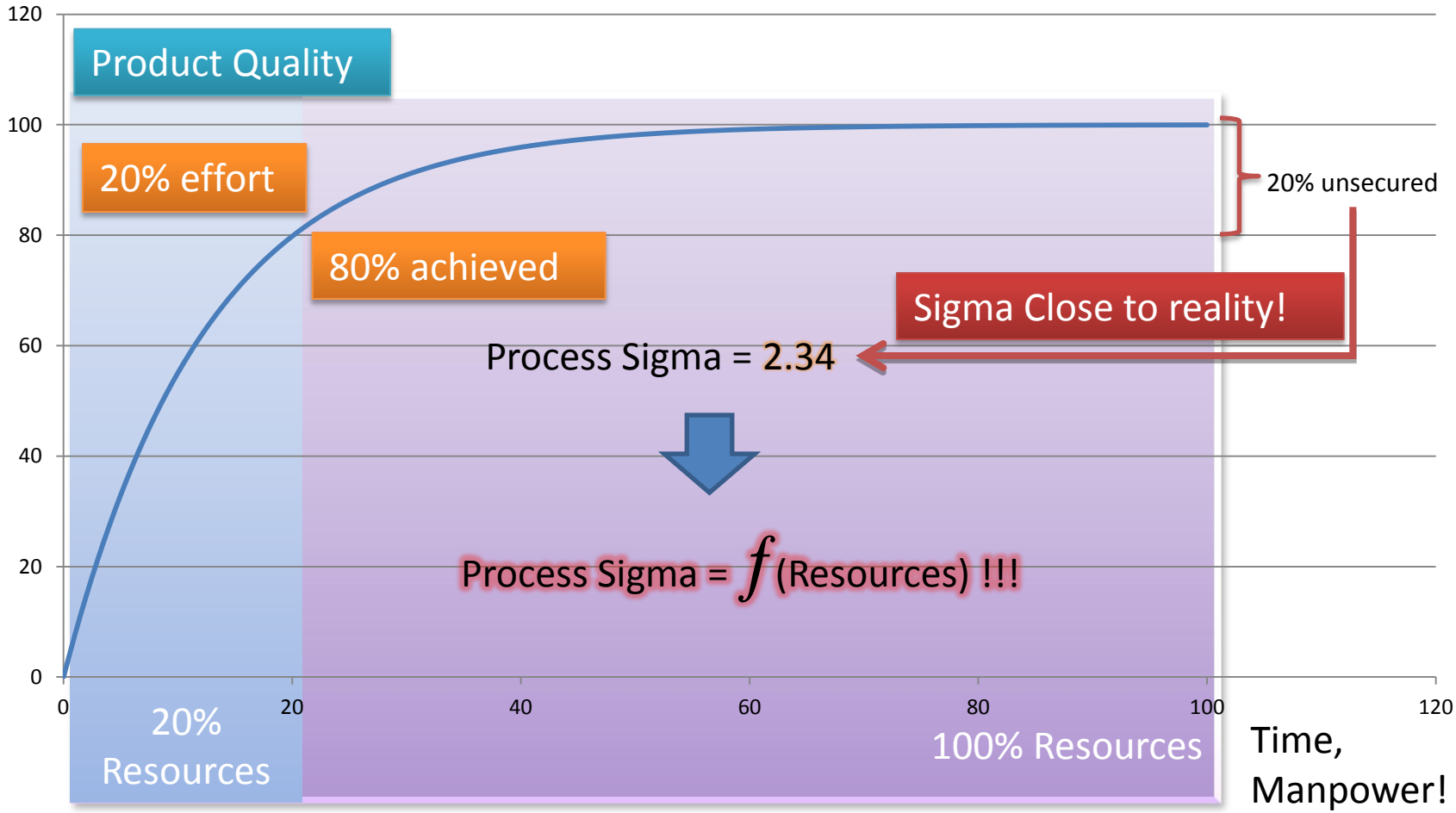
Common approach to keep costs under control

The 20% / 80% Rule:

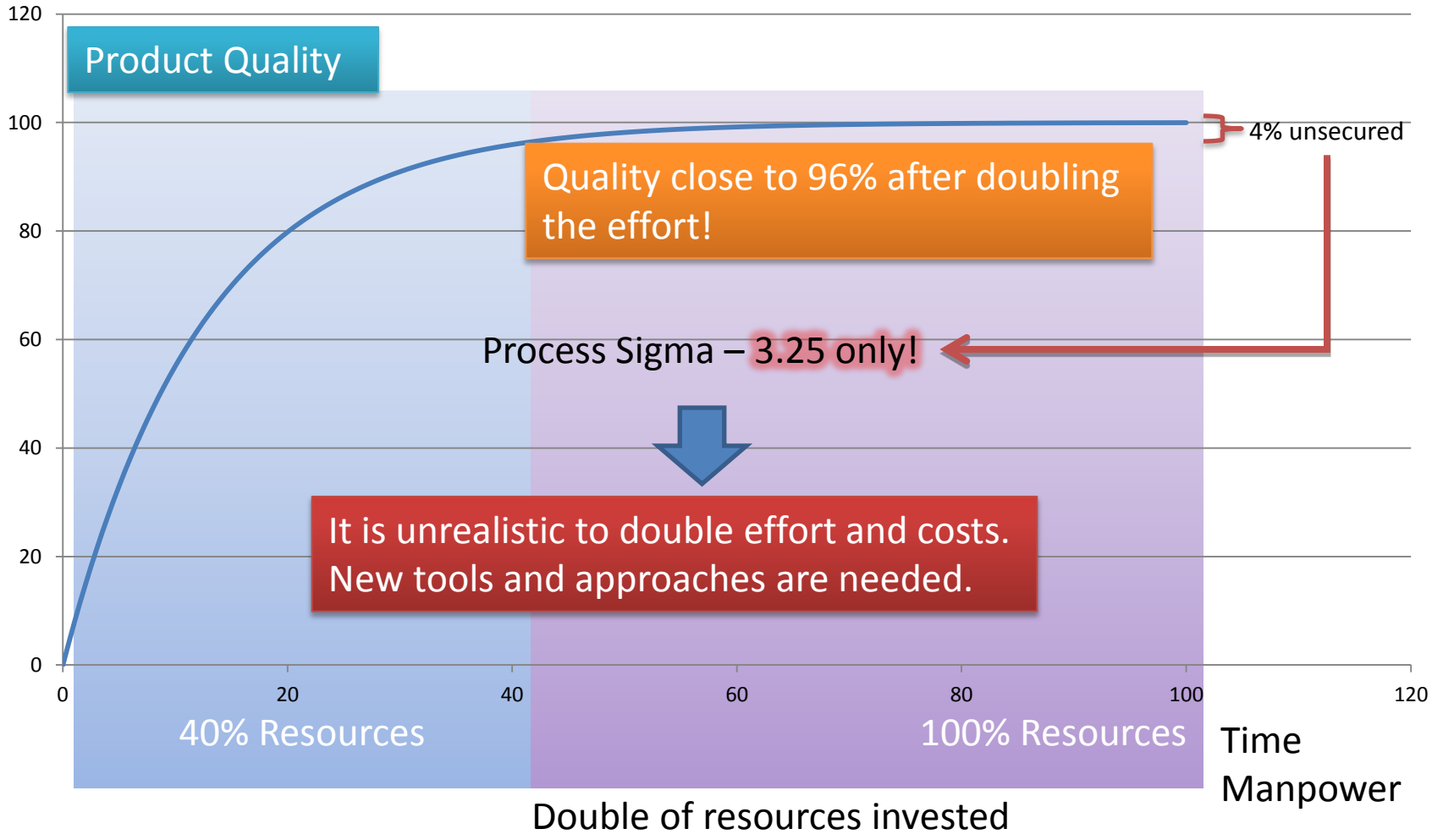
With 20% of time and effort dedicated to a project
80% of the goals can be achieved!
This rule has its great merits and allows to optimize efficiency!
Is this approach adequate for an optimal Quality by Design?
Can we afford a 6 Sigma Quality? What is the Quality in case of the 20%/80 % Rule?

Let us make an estimate!

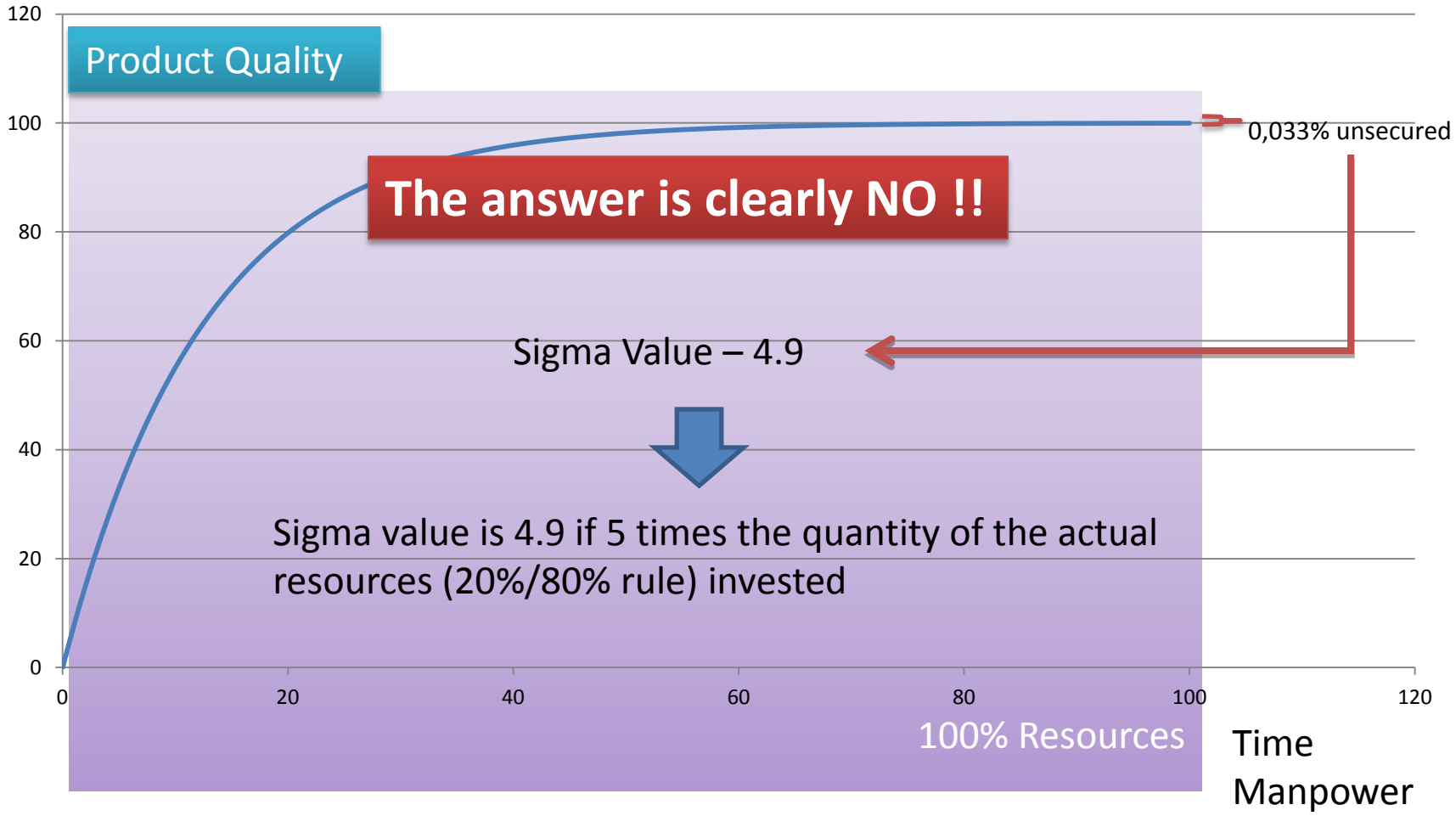
Sigma Value – function of resources



Can we afford to double effort and costs?!



Can Six Sigma be achieved with conventional tools?



New tools and approaches are needed!

- The Concept of F-CAD developed by CINCAP
- F-CAD is different from any existing e-tool such as
  - Expert System
  - Artificial Neural Network
  - Collection of existing formulations etc
- F-CAD is based on
  - Physical laws
  - Percolation Theory
  - Process Understanding
  - Particulate Formulation Design

New tools and approaches are needed!

- F-CAD takes into account
  - Microscopic structure (packing of particles)
  - Stochastic mixture of particles
  - physico-chemical properties of the drug substance(s)
  - biopharmaceutical properties of the drug substance(s)
  - physico-chemical properties of the excipients
  - unit operations (pharmaceutical processes)

New tools and approaches are needed!

- **F-CAD can be compared to**
  - Concepts used in the aircraft-industry
  - In-silico design of aircrafts such as Boeing 777/ Airbus 380
  - e- Design of the first aircraft prototype is able to fly

- **The goal of drug delivery systems are similar to the goal of aircrafts delivering passengers and goods**
  - at the right time
  - to the right site
  - with the highest possible safety
  - i.e. Keeping quality and quantity of the deliverables intact

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

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!

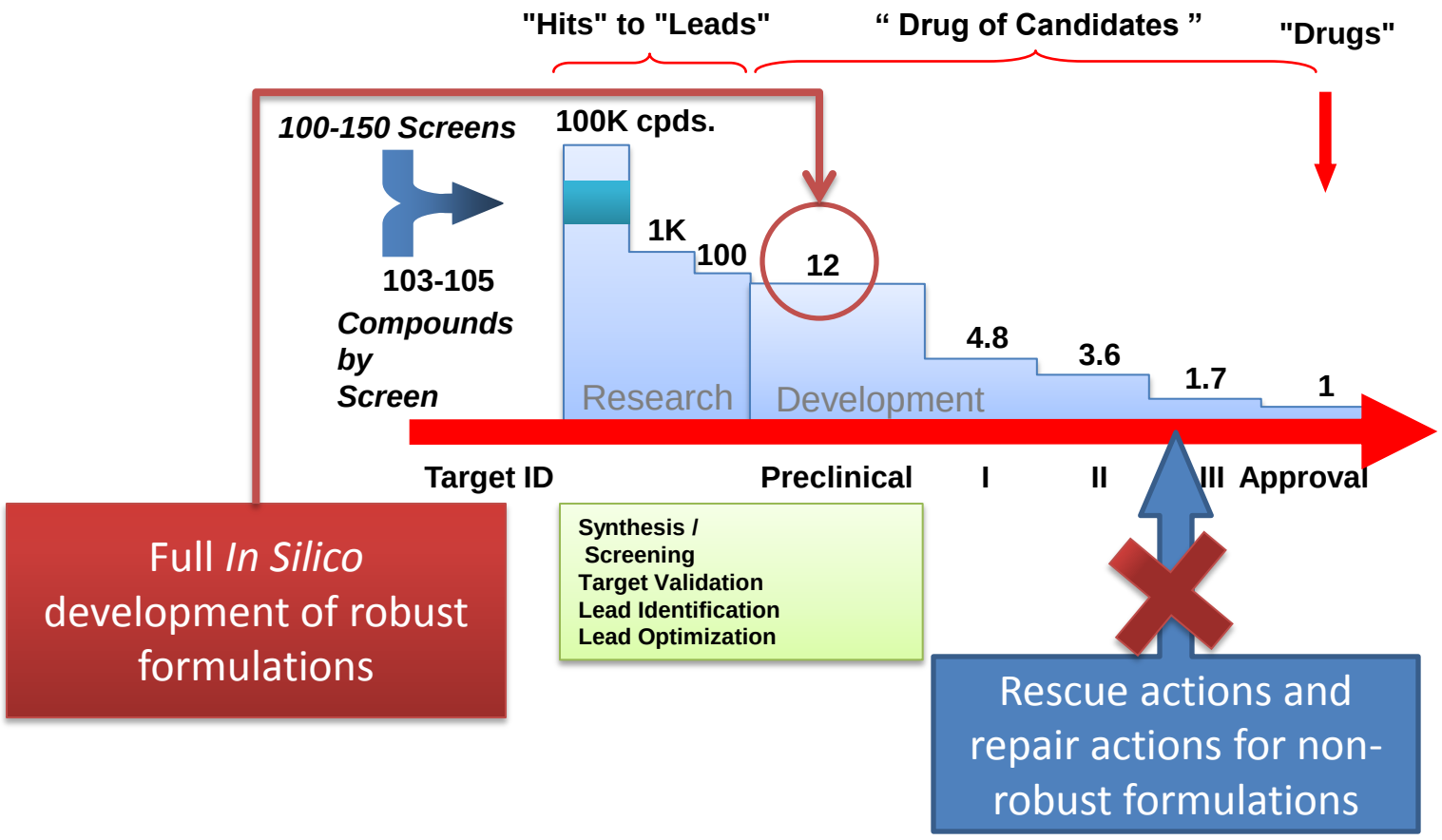
- **The F-CAD experiments are close to reality, but can be done with much lower costs and much much faster. Thus hundreds of formulations can be studied in a short time to find the best option!**

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 !

Slide: A. Hussain, FDA



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
- **Substantial costs savings**

Thank you for your attention!

Audience Q&A