


GMP of the 21st Century: Quality by Design

Market access

Key aspects in the Making of Medicines

1. Product: R&D
 2. Process: Manufacturing
 3. Prize: Reimbursement
 4. Patient: Product fit for purpose
- 

"**Good manufacturing practice**" or "**GMP**" is part of a **quality system** covering the manufacture and testing of active pharmaceutical products. Many countries have legislated that pharmaceutical (and diagnostic, medical device, food) companies must follow GMP procedures, and have created GMP guidelines that correspond with their legislation.

Business environment: QbD & R&D

Drivers for innovation in Biotech

1. Key to future growth is convergence of (bio)pharmaceuticals, diagnostics and IT
2. New delivery technologies: intranasal is becoming accepted
3. **QbD** effect: also leading to less validation burden

Products in biotech areas

1. Monoclonal abs approach mimicking the body's host defence should still generate many successful therapies
2. Cell based production methods should revitalize the vaccine area
3. SiRNAs could yield new angles of attack
4. Application of stem cells must deliver revolutionary cures sooner or later

Ref.: Biopharm Int., October 2007, - p 16,17

Business environment: QbD and R&D (cont.)

New FDA commissioner Margaret Hamburg's keynote address at Regulatory Affairs Professionals Society Annual Conference in Philadelphia, September 2009

- “All the billions of dollars poured into research and development in the U.S. **wont mean a thing**”
- “**We must streamline and strengthen the regulatory science**”
- Areas cited where this is being accomplished include FDA's partnership with ICH around **Quality by Design (QbD)**

Conclusion: QbD is the method to innovate pharma industry

QbD issued: why?

Pharma business model crisis

- Time to market is long (> 12J)
- Expensive originator products
- Low consumer orientation
- Moderate quality
- Governmental control by GMP and market authorization
- Moderate safety and efficacy performance
- Marketing and sales practices
- Patent cliff

Result

- Conservative (blockbuster) strategy
- Substitution US 2009 = 66 % generics
- See next slide
- See next slide
- Deterioration into paper quality and a technical bureaucracy
- Phase IV and PMS imposed

- Transparency lack
- Pipeline gap

Message: time for a change

Pharma performance: moderate

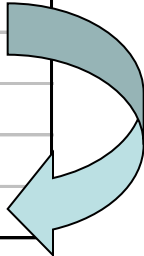
Low consumer directed

Average % of patients for which a group of drugs is ineffective		
		%
Anti depressives		38
Asthma		40
Diabetes		43
Arthritis		50
Alzheimer		70
Cancer		75

Cancer: products with billions of sales/y perform clinical only 5 -10 % above placebo and show a QOL of 0.5 y.

Moderate quality

Sigma	ppm Defects	Yield (%)	Cost of Quality (%)
2σ	308.537	69,2	25-35
3σ	66.806	99,3	20-25
4σ	6210	99,4	12-18
5σ	233	99,98	4-8
6σ	3,4	9.999.966	1-3



Pharma scores high % defects (rejections, recalls): 2-3 sigma. ICT , medical devices and automotive score 6 sigma.

QbD: origin

- Launched through FDA report: “Pharmaceutical cGMPs for the 21st Century (August 2002)”
- Implies a **strategic change towards the presentation of more scientific knowledge** in submissions
- Shortly afterwards FDA issued the guidance document “PAT – a framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance (Pat doc. discusses many principles of QbD); finalized in 2004
- PAT plays a pivotal role in the QbD process

PAT = Process Analytical Technology

QbD: status

1. FDA and EMA regulatory framework have implemented ICH 8,9, 10 docs
2. (Still) optional requirements
3. Rererence docs:
 1. ICH 8: Pharmaceutical development
 2. ICH 9: Quality Risk Management
 3. ICH 10: Pharmaceutical Quality Systems

QbD: what is?

Definition QDb: a **systemic** approach to **pharmaceutical development** that begins with predefined objectives and emphasizes product and process understanding based on **sound science** and **quality risk management**

1. The QbD frame contains concepts and tools - e.g. design space - to practice QbD in a submission file (**design space approval**)
2. The selection of QbD implies the use of **Quality Risk Management** (ref.: ICH 9, Quality Risk Management)
3. The connection to a suitable (bio)pharmaceutical quality system offers opportunities to **enhance science ad risk based submissions approaches**

Message: systemic, science and risk based pharmaceutical development

QbD (extended): what is ?

Purpose:

- “to **design** a quality product such, that the manufacturing of it **continuously** delivers a drug product **suited for its purpose**”

Note:

this is the general quality principle



Meaning:

the **PATIENT** comes first

Ref: Q8 (R1) June 2009, p2

QbD: basics

- a **systemic** development and manufacturing by **use of prior knowledge**,
- **risk assessment guided design control**,
 - **combined molecular and system biology based diagnostics - therapy solutions for disease treatment**,
 - **through the total life cycle of a product (continuous improvement)**.

Implications:

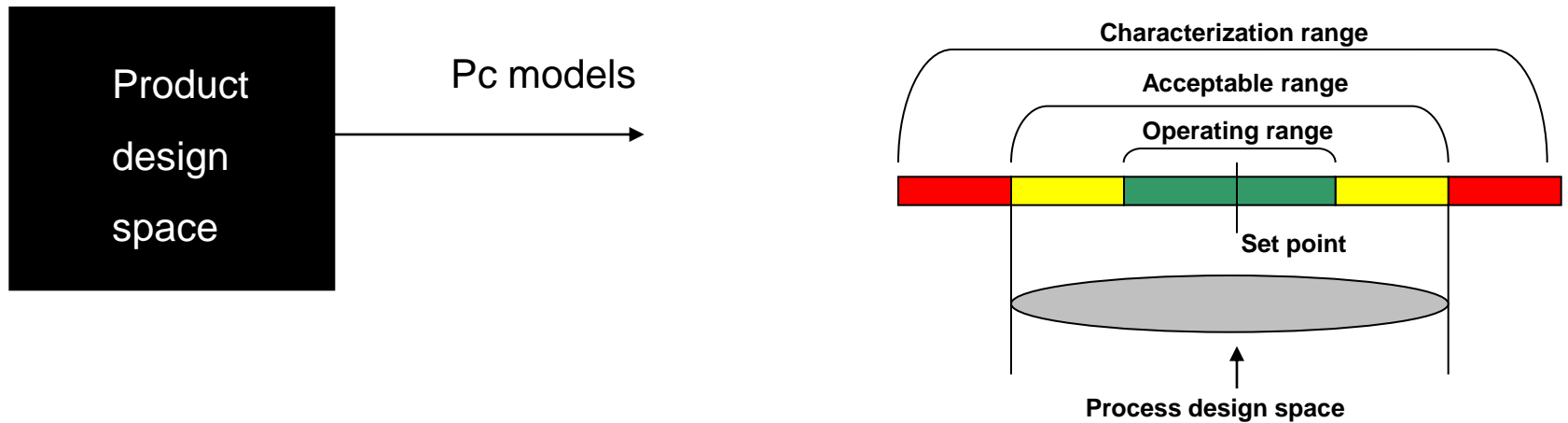
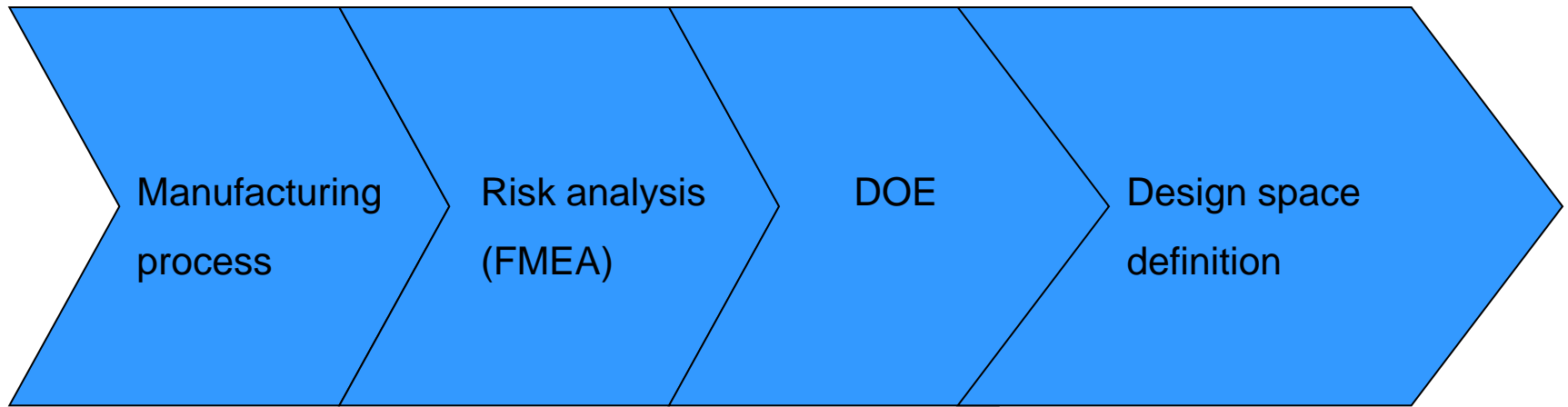
- **Quality using statistics (farewell tot trial and error)**
- **Quality back to the roots: product suited for its purpose**
- **Quality is dynamic: continuous improvement**
- **Quality must be build in**
- **Quality means first time right**
- **Quality patient (consumer) directed**

QbD in action

1. Collect as much as possible relevant scientific information ("science")
2. Define purpose and goal of the experiments by Risk Assessment
3. Define measure values of the Critical Quality Attributes (CQAs); these are also the dependable process variables
4. Brainstorm over the Critical Process Parameters (CPPs); these are also the independent variables
5. Select 2-7 of the CPPs, that will be used in the experiment
6. Select for every CPP the levels or boundaries
7. Select a statistic model (by Design of Experiments)

Ref: Torbeck, L.D. Biopharm. International, May 2009, 52-59

QbD approach



QbD: what does it bring?

1. Time to market reductions: 12 - 6 years realized by amongst others
 - First time right
 - Continuous improvement over the total product life cycle
 - Absence of design freeze (no variation issues)
 - Less validation burden
 - Real time controls (less batch controls)
2. Contributes substantially to realize the better, cheaper and safer mandate

QbD: is it needed?

Wages:

The costs in the EU to employ someone are \$ 300.000.
In China \$ 100.000 (source: US multinational)

How to compete than?

Create trade barriers

or

inovate, perform better and stay ahead

QbD: innovate, be better and stay ahead

1. Potential savings (Ref.: R. Baker, Bovis Lend*)

Action	Savings (%)
Eliminate scale up (see MAB dossier)	4
Invest later in production	8-10
Removal of undercapacity (30%)	8-10
Improvement of logistics	10
Reduction of waste/rejections	7
Manufacturing space usage: generic/branded = ½	?

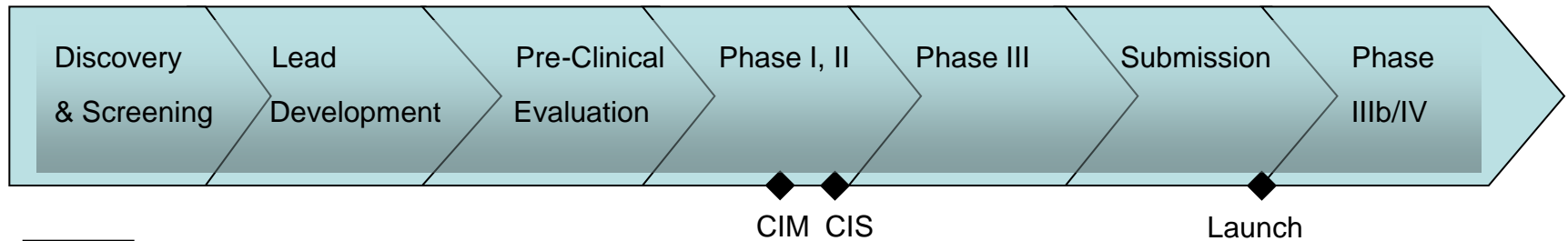
2. Lean assets management: Toyota Production Systems bij MSD (Ref: Cees Mens*, 10% savings/year of 2004 with a concurrent increase of production volume of 71%)

ALL comes together in QUALITY by DESIGN

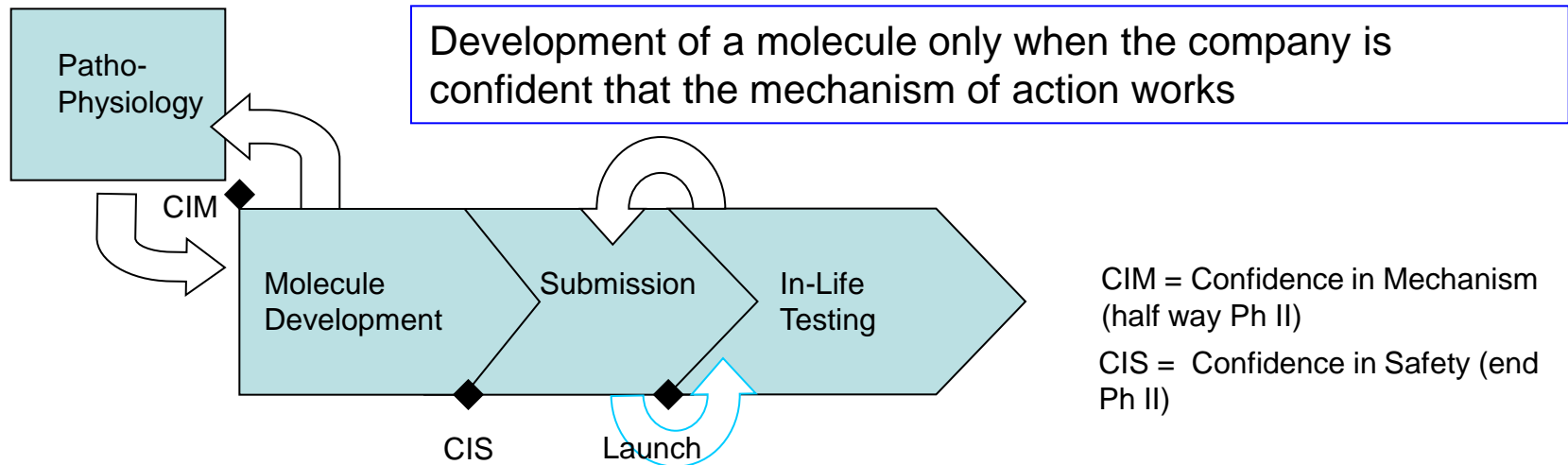
* presentations Lean Asset Management in de Farma en Biotech Industrie, ISPE NL, 20 Maart 2009

PWC view on the supply & availability of medicines

Today



2020

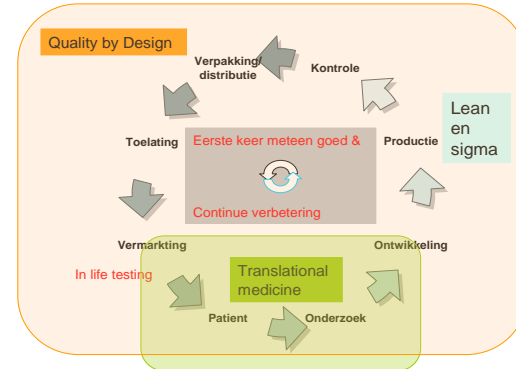
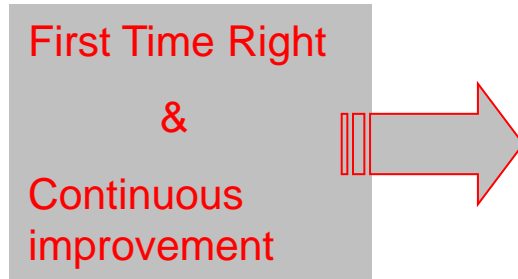


Ref.: PWC Pharma 2020: The vision, [Which path will you take?](#)

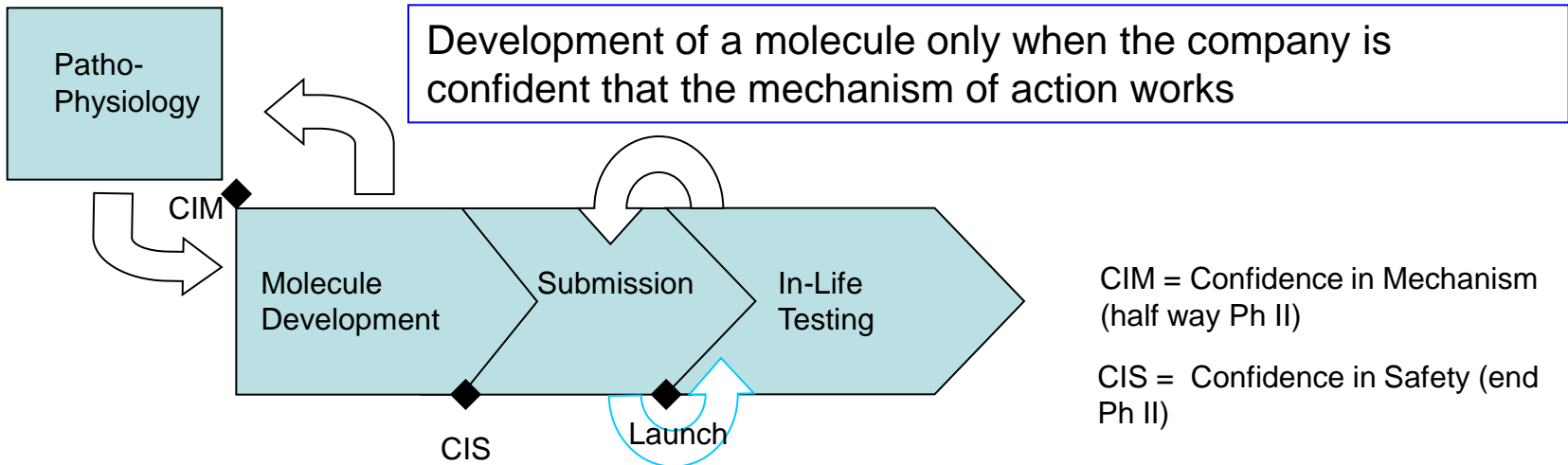
PWC view & QbD

Ontwikkeling en maken van een geneesmiddel: nieuw ^{BioFarmind}

Approach & Tools



2020

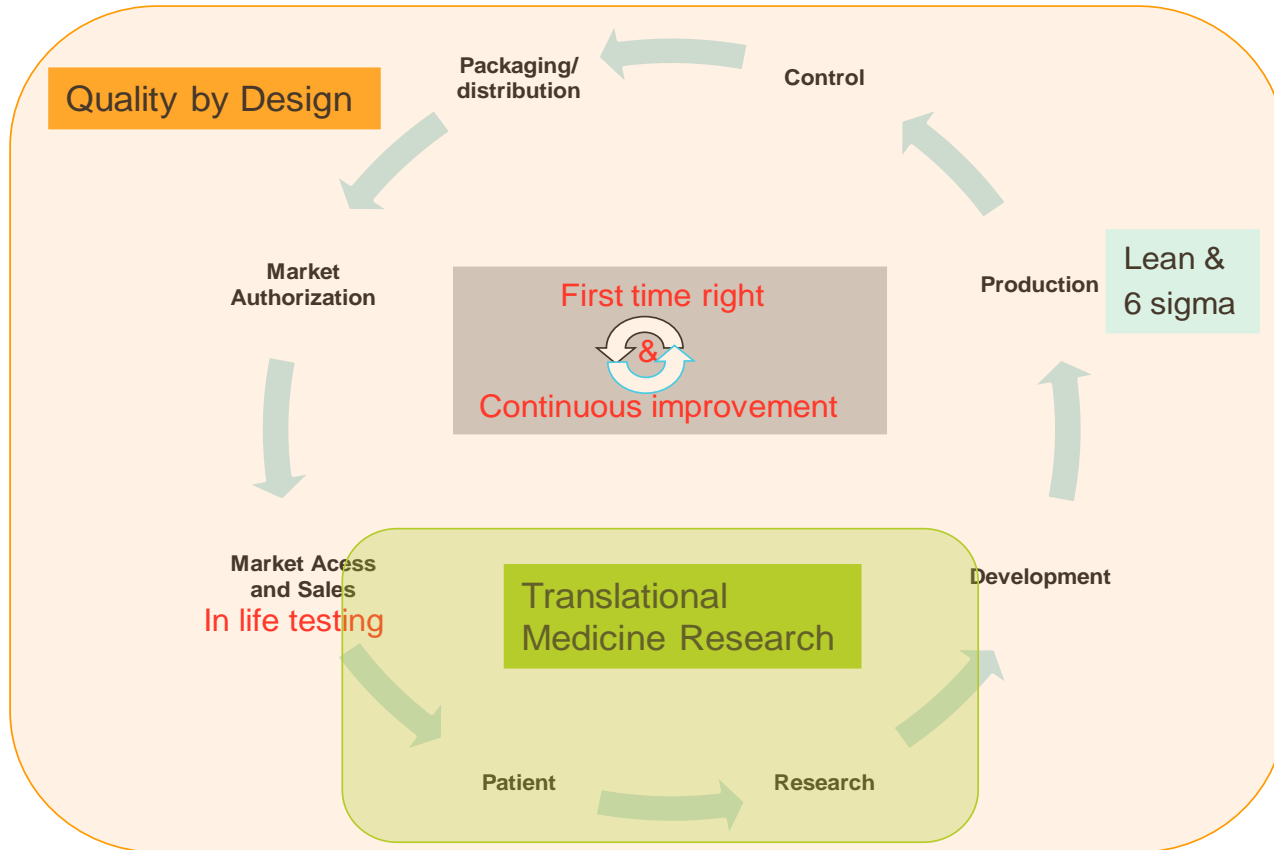


CIM = Confidence in Mechanism (half way Ph II)

CIS = Confidence in Safety (end Ph II)

Ref.: PWC Pharma 2020: The vision

Development & production of a biopharmaceuticals : new



Pharma perspectives: eR&D

By 2020, the pharmaceutical research and development process may be:

- shortened by - **even**- two-thirds
- success rates may dramatically increase
- clinical trial costs could be cut substantially

Ref.: PricewaterhouseCoopers report "Pharma 2020: Virtual R&D, which path will you take?"

Because

