Process Analytical Technology
Community of Practice

Germany/Austria/ Switzerland Affiliate
ENGINEERING PHARMACEUTICAL INNOVATION

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Quality by Design – Konzepte in der Pharmaindustrie

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Global ISPE PAT CoP (Community of Practice) Co-Chair

Regional PAT CoP D/A/CH Chair

werum SOFTWARE & SYSTEMS

Quality by Design und PAT – Konzepte in der Pharmaindustrie

- Charakterisierung der Pharmaindustrie
- Optimierungspotenziale in der Pharma
- Das “ANDERE” PAT
- PQLI – Die ISPE Initiative
- PAT im Internationalen Spannungsfeld

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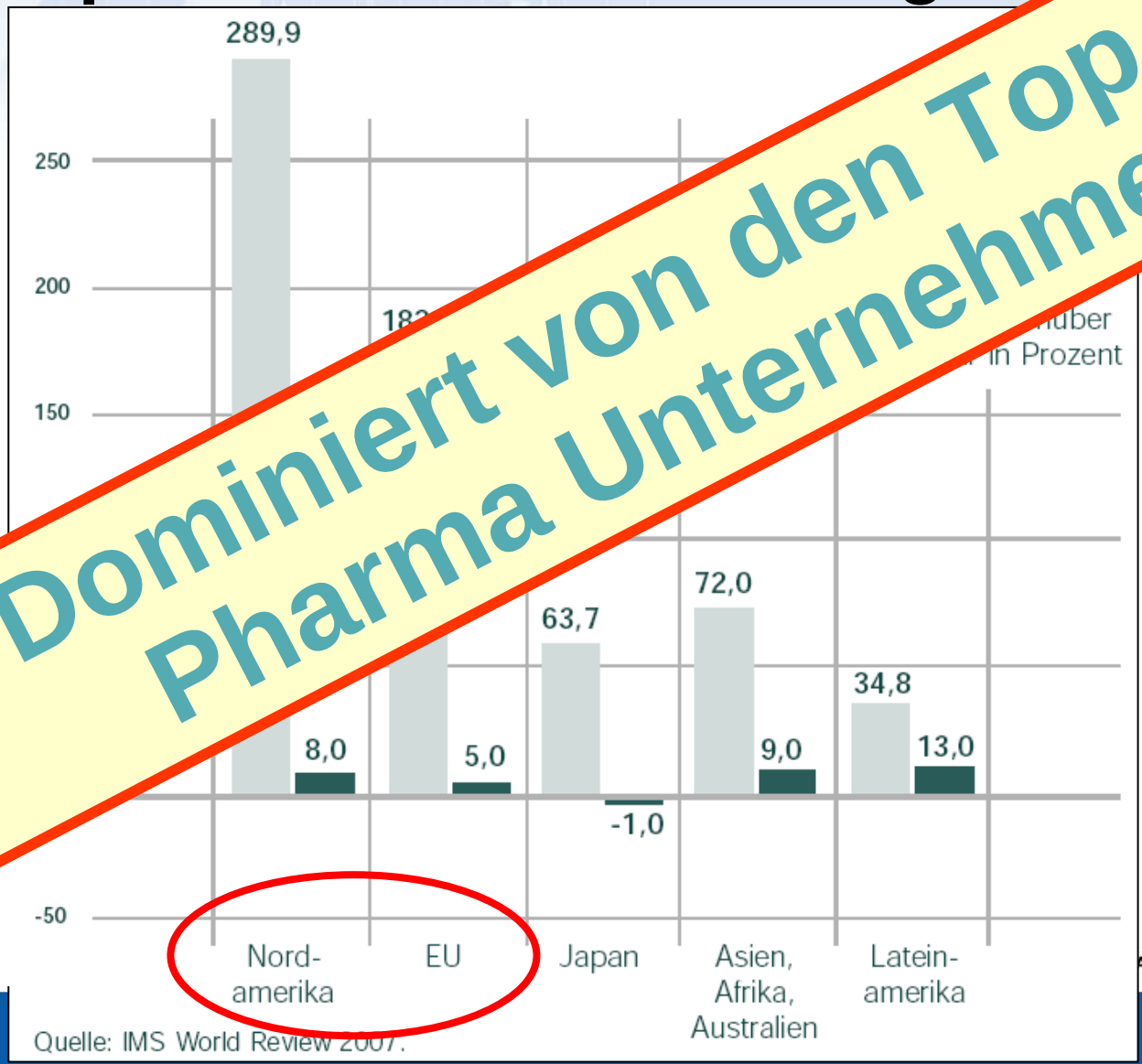
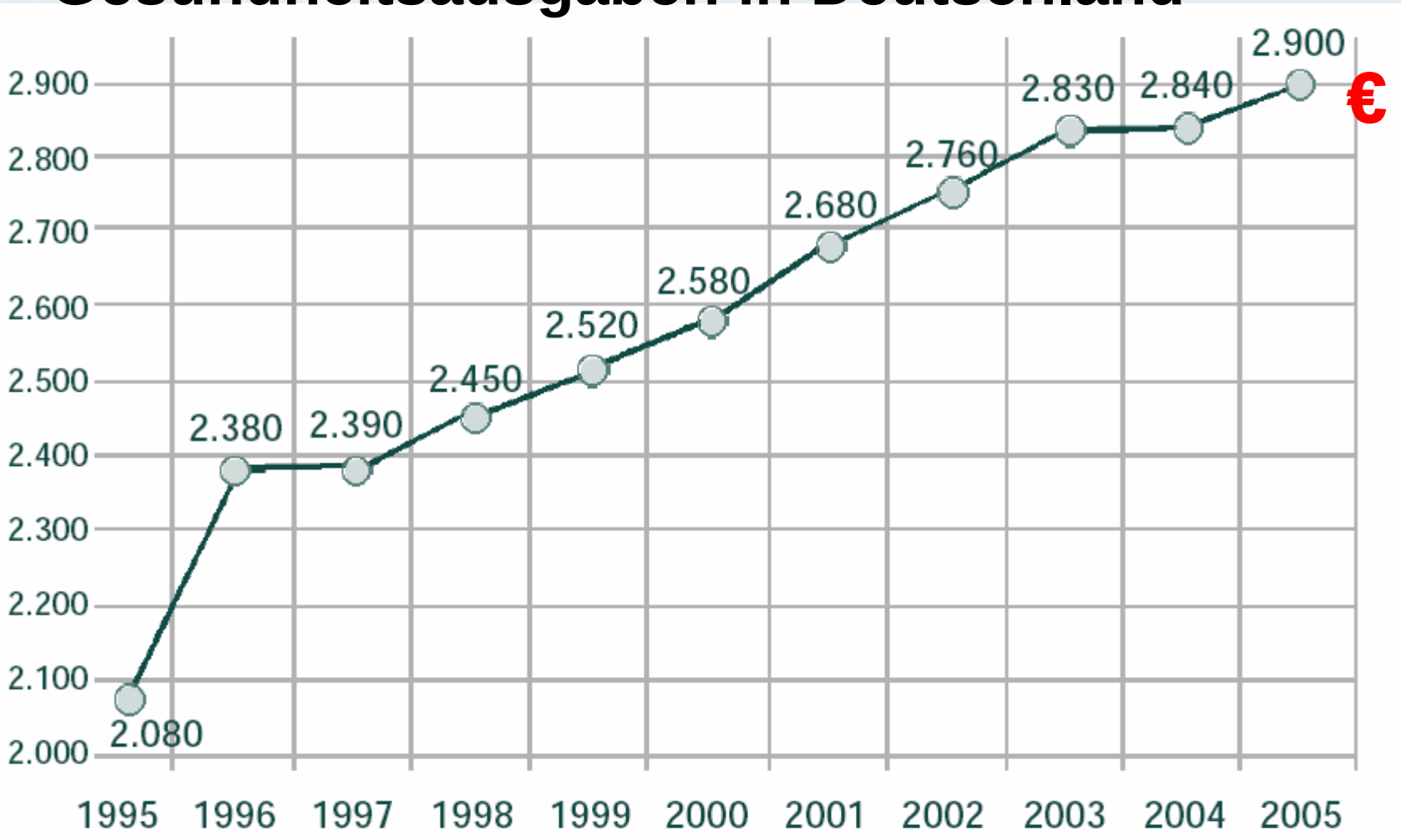
Weltpharmamarkt nach Regionen



Quelle: IMS World Review 2007.

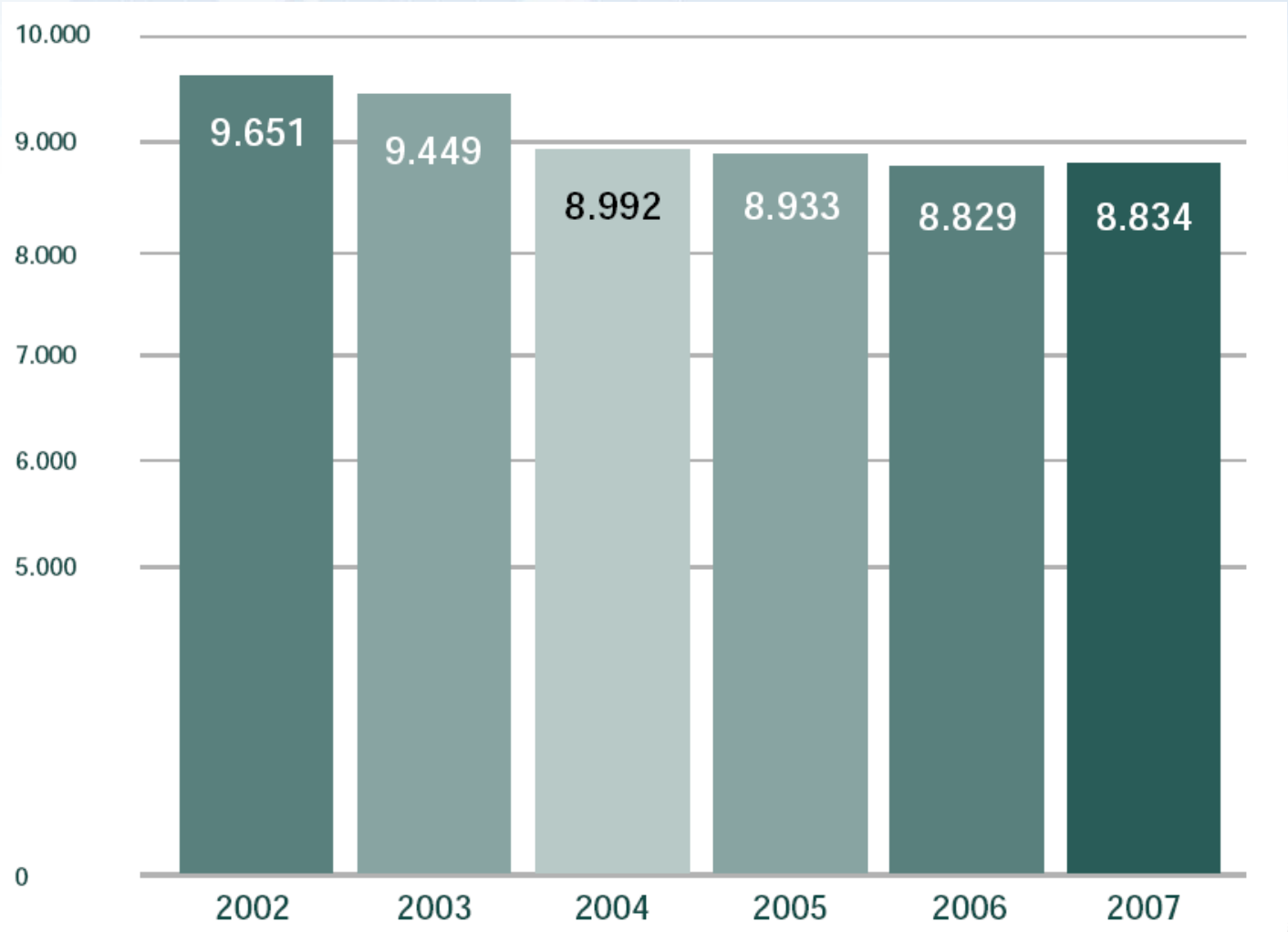
Dominiert von den Top 20 Pharma Unternehmen

Pro Kopf Entwicklung der Gesundheitsausgaben in Deutschland



Quelle: Statistisches Bundesamt, 2006.

Pharma Präparate in der „Rote Liste ®”



Quelle: „Rote Liste®", 2007.

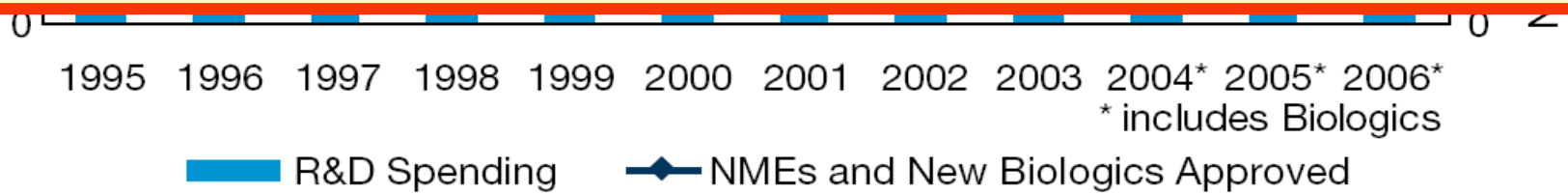
Immer Weniger mit Mehr...

Figure 2: R&D spending has soared but the number of NMEs and biologics approved by the FDA is down

"Ratio from innovation to market approval is 250 to 1"

"Only 30% will recover development costs"

Source: *Pharmaceutical Research and Manufacturers of America & Pharmacoeconomics*



Sources: FDA/CDER Data, PhRMA data, PricewaterhouseCoopers analysis
Note: Data on R&D spending for non-PhRMA companies are not included here, because they are not available for all 11 years

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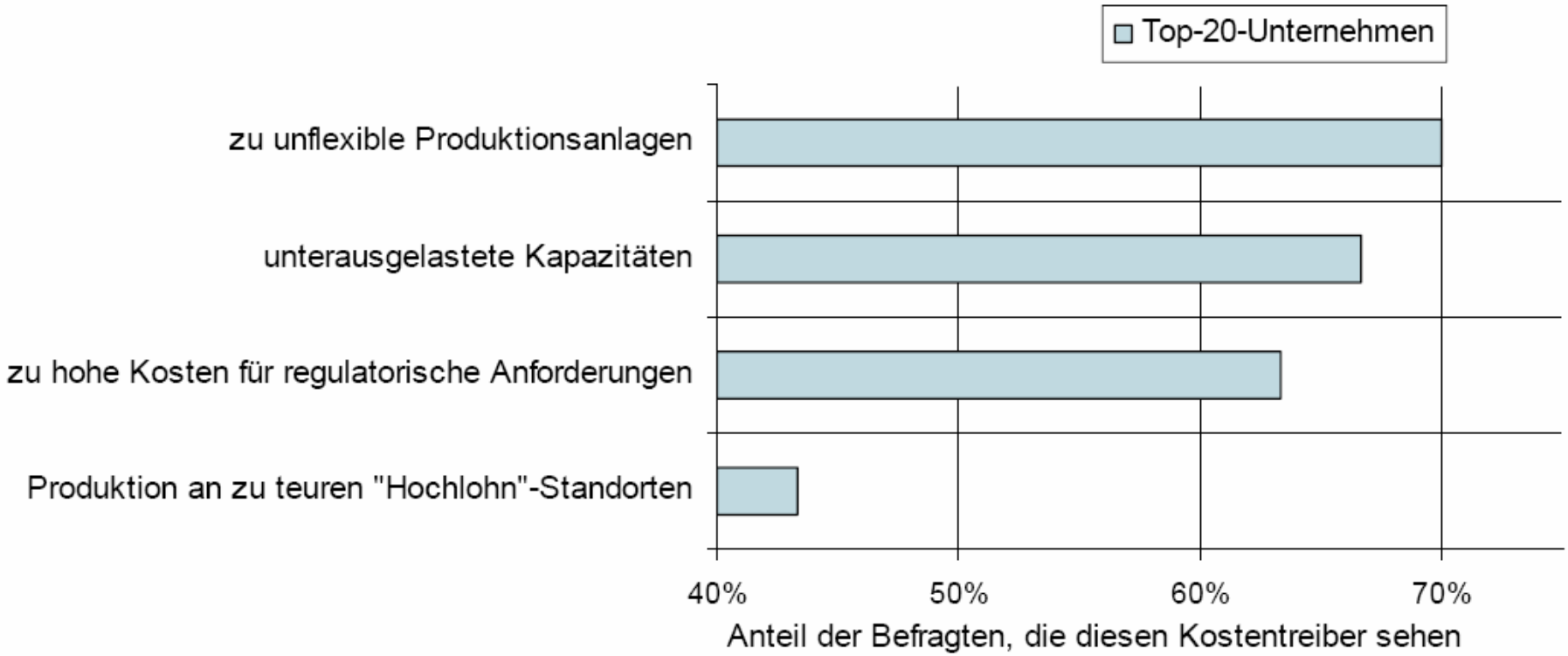
Die Pharma GMP Produktion

- Hohe regulatorische Anforderungen
  - GMP - „Gute Manieren beim Produzieren“
  - Validierung der Produktionsprozesse
- Herstelldokumentation mit Papier
  - GMP - „Give Me Paper“
- Hohe Qualitätsanforderungen
  - GMP – „Give More Paper“

Some Benchmarks	Pharma Industry Today	A winning pharma company	World class plant
STOCK TURN –total turnover of the site at manufacturing price divided by all the stock on the site on the same basis. The stock includes finished goods, work In progress and purchased raw materials.	3 to 5	14	50
On Time In Full delivery. This is the percentage of orders that are satisfied On Time In Full, with zero defects. Note that if there is one defect in an order, the OTIF is zero percent.	60% to 80%	97	%
Right First Time –percentage of the products at the point of manufacture that are delivered right first time with no defects. Any recycling, blending or other adjustments are excluded from the Right First Time figure.		%	99.4%
Cpk – a statistical process control measure of the variability of th… A six - sigma figure corresponds to only four defects per mil… while a two-sigma figure corresponds to 308,000 defect… products. It is measured on a logarithmic scale.		2	3.5	3.2
OEE Overall Equipment Effectiveness – T… …tively the manufacturing equipment is used. It … …uct rate multiplied by the quality rate m… …liability. A figure of 100% implies that the plan… …hour of the day making perfect product. A fig… …e plant could achieve ten times the output …	30%	74%	92%
CYCLE T… … total time from commencing manufacture to d… …customer which in many cases is the factory	720	48	8
SA… …0,000 HOURS – This is the number of reportable accidents, gre… …equal to three days absence per hundred thousand working hours.	0.1	0.05	0.001

VDMA Studie...Die Schwachstellen

Tetragon Consulting



Quelle: VDMA-Studie Anforderungen der Pharmaindustrie 2006

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The 2 PATs

PAT as Process Analytical Technologies

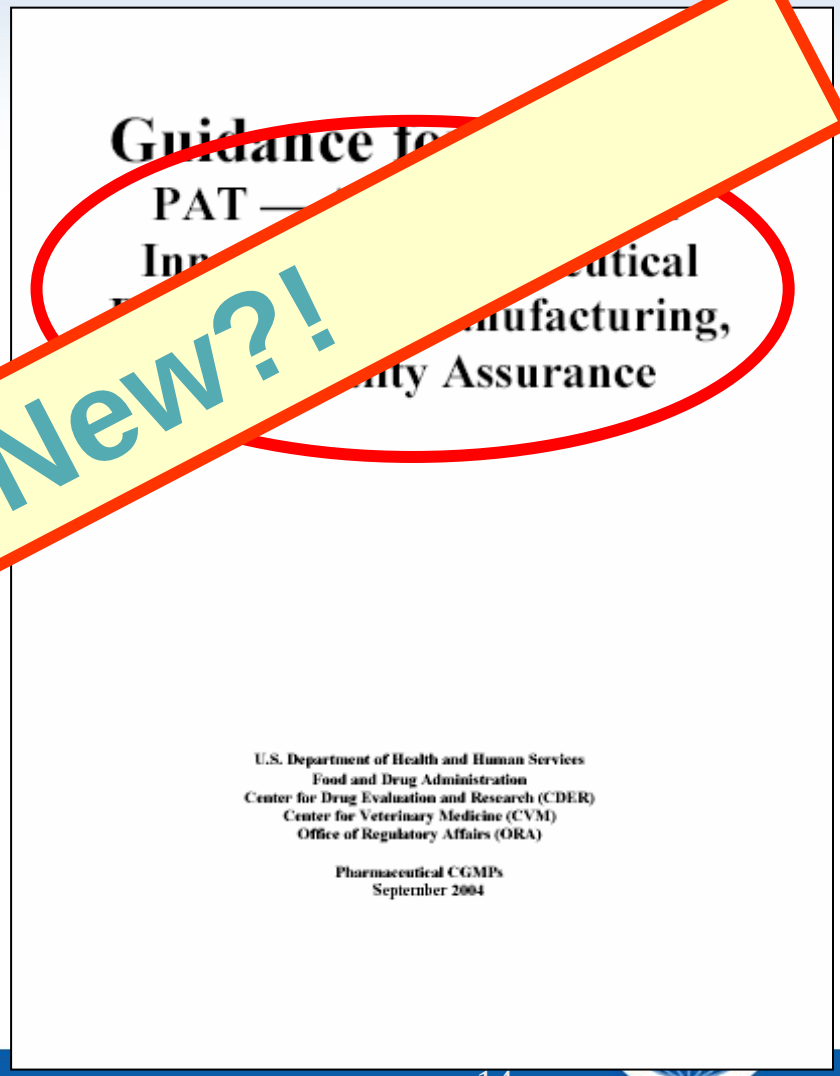
- Done since 20 years, nothing new

PAT - FDA science based approach

- Quality by design
- Process understanding
- Risk based approach

Start der FDA Initiative...

The goal of the PAT approach is to ensure patient health by the availability of safe, effective, and affordable medicines.


Guidance fo
PAT —
Inn
utical
nufacturing,
ity Assurance

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

Pharmaceutical CGMPs
September 2004

Nothing New?!

Launched September 2004

What PAT is...

"PAT is considered to be a system fo
designing, analysing, and contro
manufacturing through timely m nts
of critical quality attributes rmance
attributes... with the suring final
pr ty"

Scientific goals!

hat is new?

Quality by Design

Process Understanding

Risk Based Approach

PAT Guidance for Industry

PAT - A Framework for Innovativ… and Quality Assu…

- Continuous Q…
- Real Ti… …ATR
- Ri…

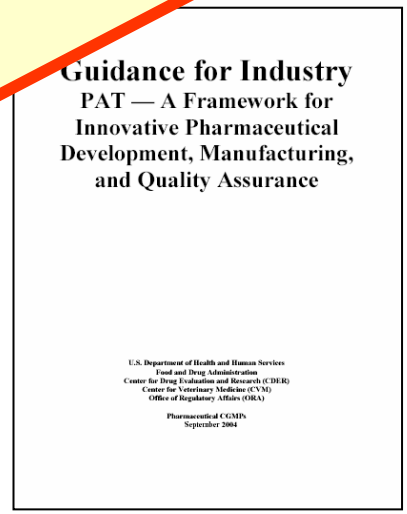
…to remove human error

…, scrap and re-processing

…production cycle times

…y using in-line, on-line and at-line measurements – rather than lab measurements

- Reduce costs



Commercial goals!
PAT equals Lean!

"Creating QbD/PAT Management Awareness"

Authority view	Commercial Management view
More pharmaceuticals	•Time-to-market •More Innovation
with higher quality	•Reduced documentation •Optimized communication between authorities and industry •Guaranteed quality level ("unit-to-unit")
at lower cost	•Decreasing cost of production by improved productivity
	Further on: Competitive advantage Image improvement Existing data and resources can typically be used

Authorities view corresponds to Commercial Management view and the common goals can be reached by QbD / PAT as an innovative way of thinking in manufacturing pharmaceuticals.

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Was ist die ISPE?

- ISPE steht für
  - International Society for Pharmaceutical Engineers
- 25 Jahre in 2005
- Affiliates in der ganzen Welt
  - D/A/CH (seit über 10 Jahren) ~1100 Mitglieder
  - US (15 Chapter)
  - Nordic
  - UK/Irl, Singapore, Japan, Turkey
  - etc.
- Insgesamt über 25.000 Mitglieder

ISPE PAT CoP D/A/CH - History

- Founded May 23rd, 2005
- Approx. 100 Member in regional PAT CoP mailing list
  - 900 Members in Global ISPE PAT CoP
- 7 Meetings:

1.	23.5.2005	Mannheim	(Ger)	(48)
2.	12.9.2005	Mannheim	(Ger)	(42)
3.	16.11.2005	Darmstadt	(Ger)	(32)
4.	8.-9. 3. 2006	Frankfurt	(Ger)	(28)
5.	22.-23.5.2006	Hamburg	(Ger)	(30)
6.	27.-28.11.2006	Vienna	(A)	(18)
7.	7. – 8.5.2007	Frankfurt	(Ger)	(20)
7a.	25.10.2007	Frankfurt	(Ger)	(8) Brainstorming Session
8.	17.1.2008	Ingelheim	(Ger)	Next Meeting

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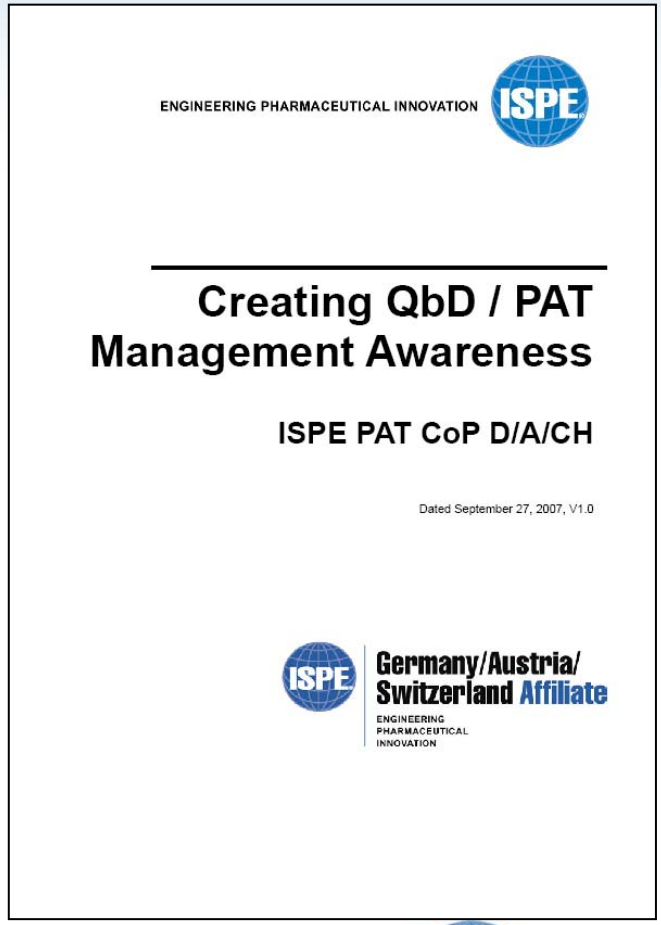
"Creating QbD/PAT Management Awareness"

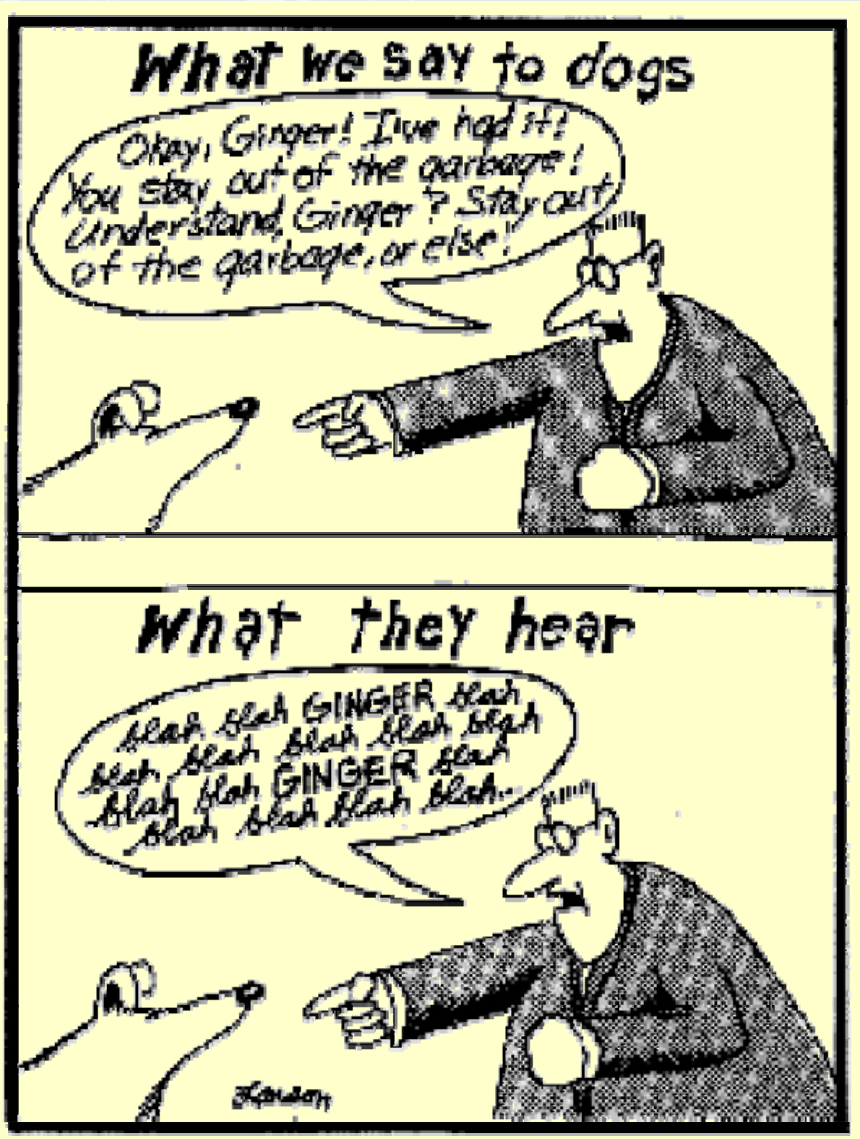
- Address upper management
- Based on case studies
- Presentation to Pharma Companies
  - Pharma Companies out of the PAT CoP
  - Core team for presentation
- Generate / Launch PAT projects



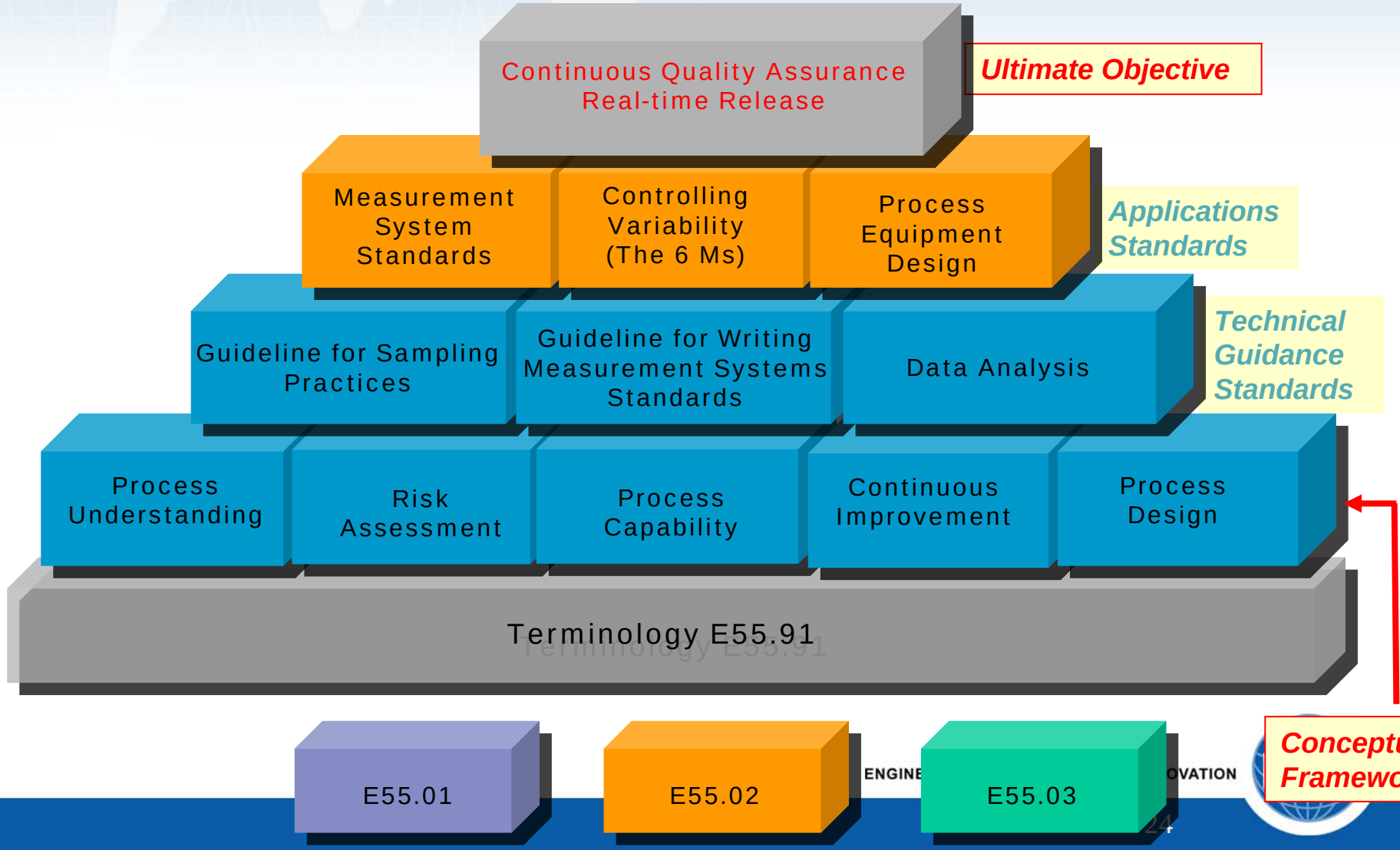
Statt PAT ist das das bessere wording...
PQLI Product Quality Lifecycle Implementation

- *The ultimate vision for PQLI is to deliver to the industry a comprehensive and practical knowledge base of deliverables covering the application of QbD.*

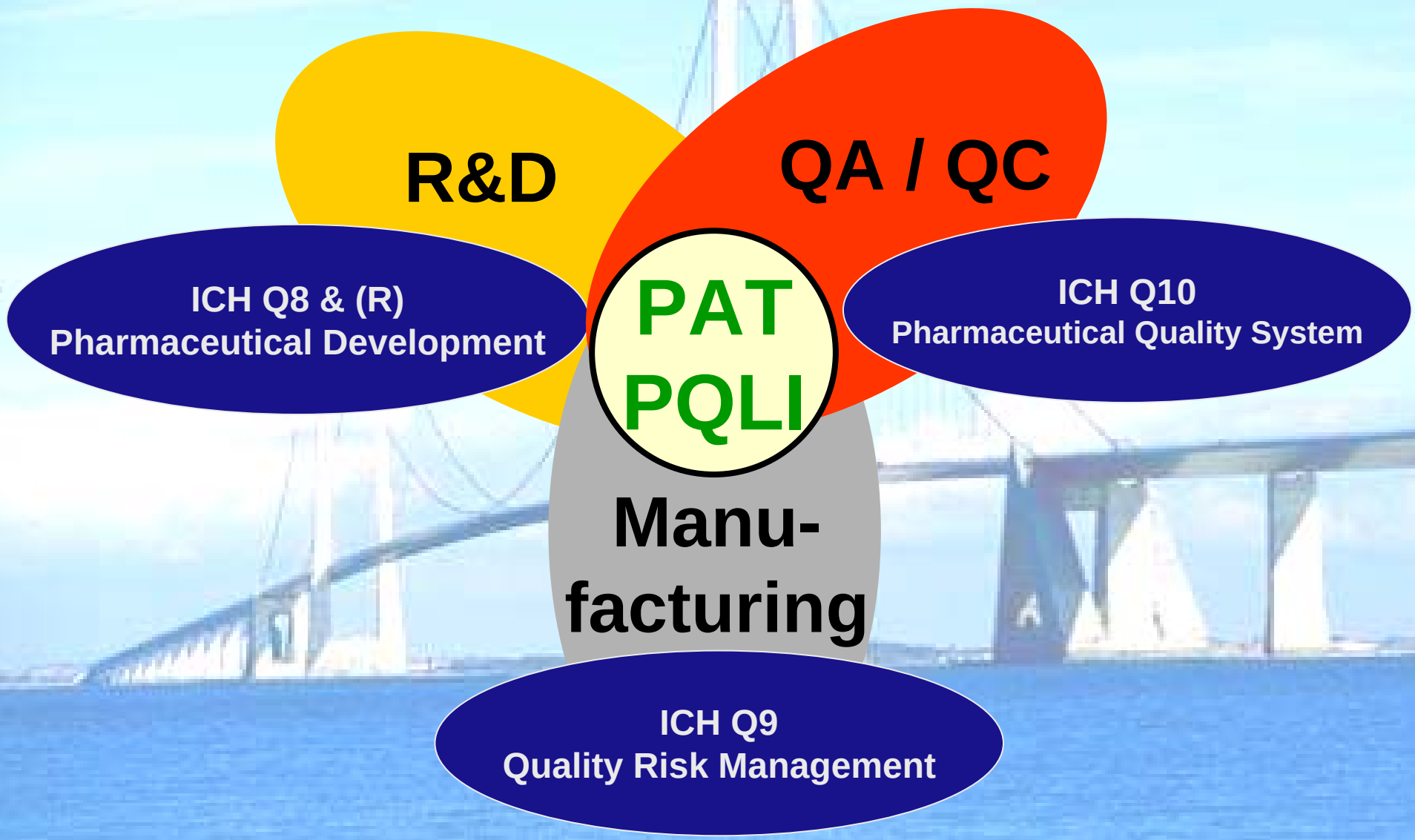
Speaking the Right (QbD / PAT) Language



PAT Definition- Building Blocks - ASTM E55



PQLI – The Bridge...
Impact on all Business Areas



Approaches to Pharmaceutical Development

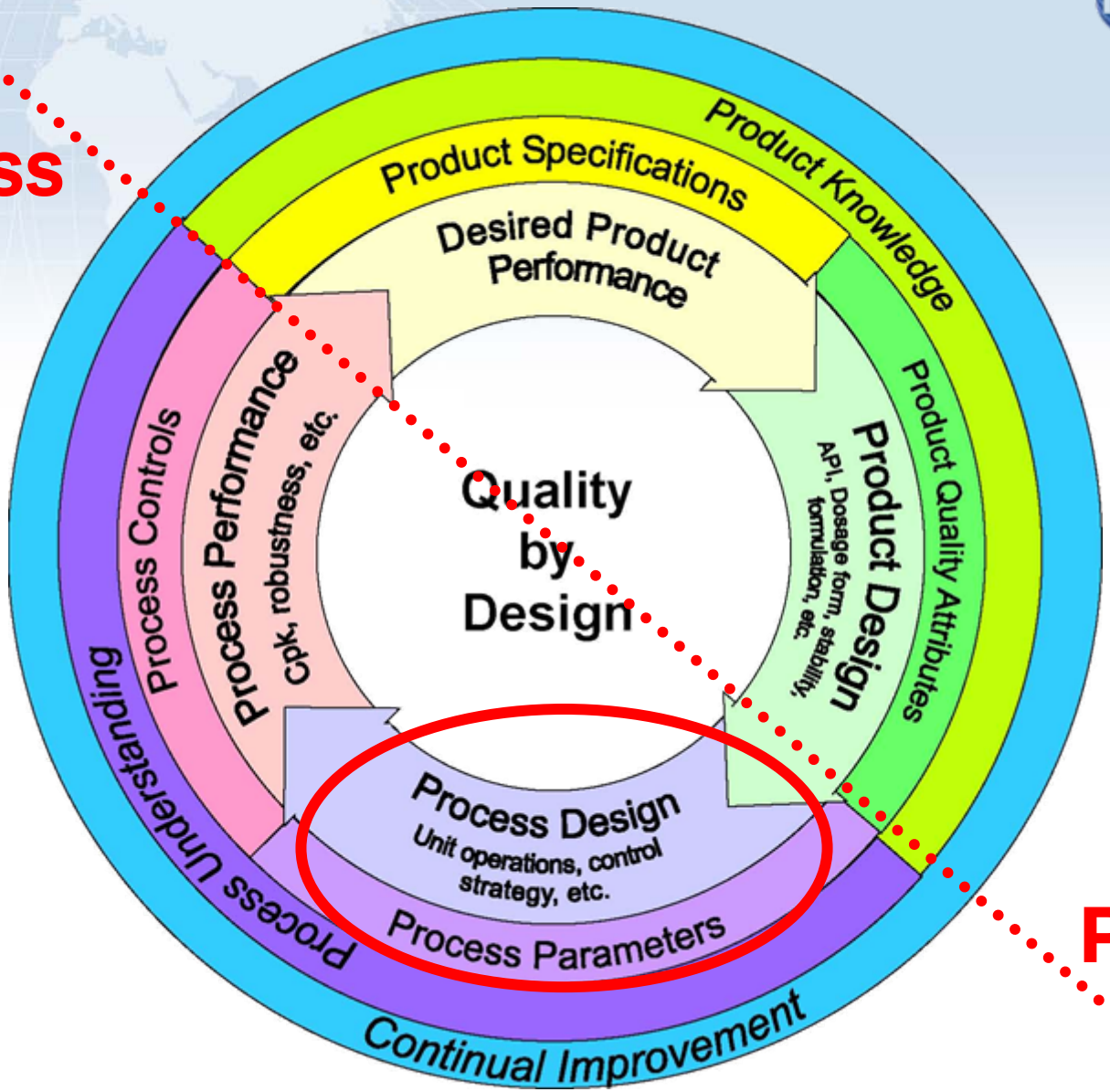
Aspects	Current	QbD
Pharmaceutical Development	Empirical, Random, Focus on optimization	Systematic, Multivariate experiments, Focus on control strategy and robustness
Manufacturing Process	Fixed	Adjustable within design space, supported by robust quality systems
Process Control	Some in-process testing	PAT utilized, Process operations tracked and trended
Product Specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on desired product performance
Control Strategy	By testing and inspection	Risk-based control strategy , real-time release

Pharmaceutical Manufacturing in the 21st Century – An FDA Perspective
Moheb Nasr, ISPE Annual Meeting 2006

Quality by Design

- ...a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding based on sound science and quality risk management.
- ICH Q8 (R)
  - Im Wesentlichen Erweiterung um QbD

Process



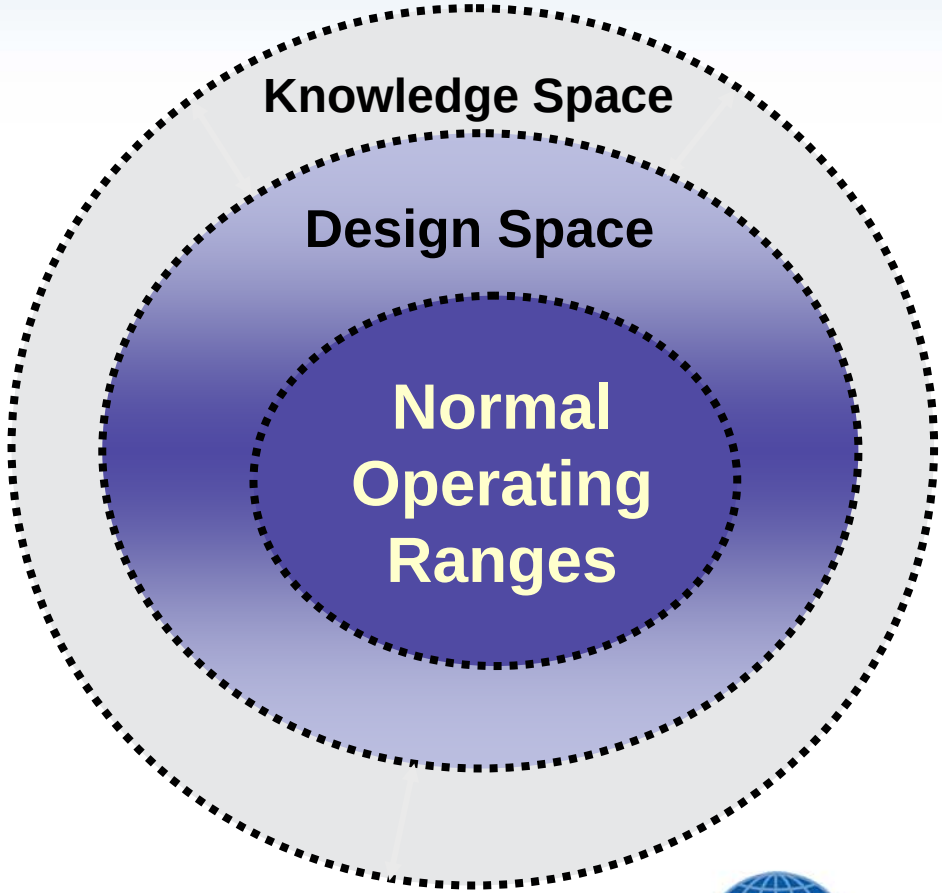
Product

Quelle:
Moheb M. Nasr, Ph.D., CDER, FDA, *MOHEB.NASR@FDA.HHS.GOV*

The ´Control Strategy´ for QbD

- The control Strategy will ensure the product is manufactured within the Design Space to meet all CQAs

- The control strategy for a CQA is the selection and combination of different types of controls applied to the manufacturing process & associated systems to assure the right product quality and that the risk of manufacturing failure is acceptably low



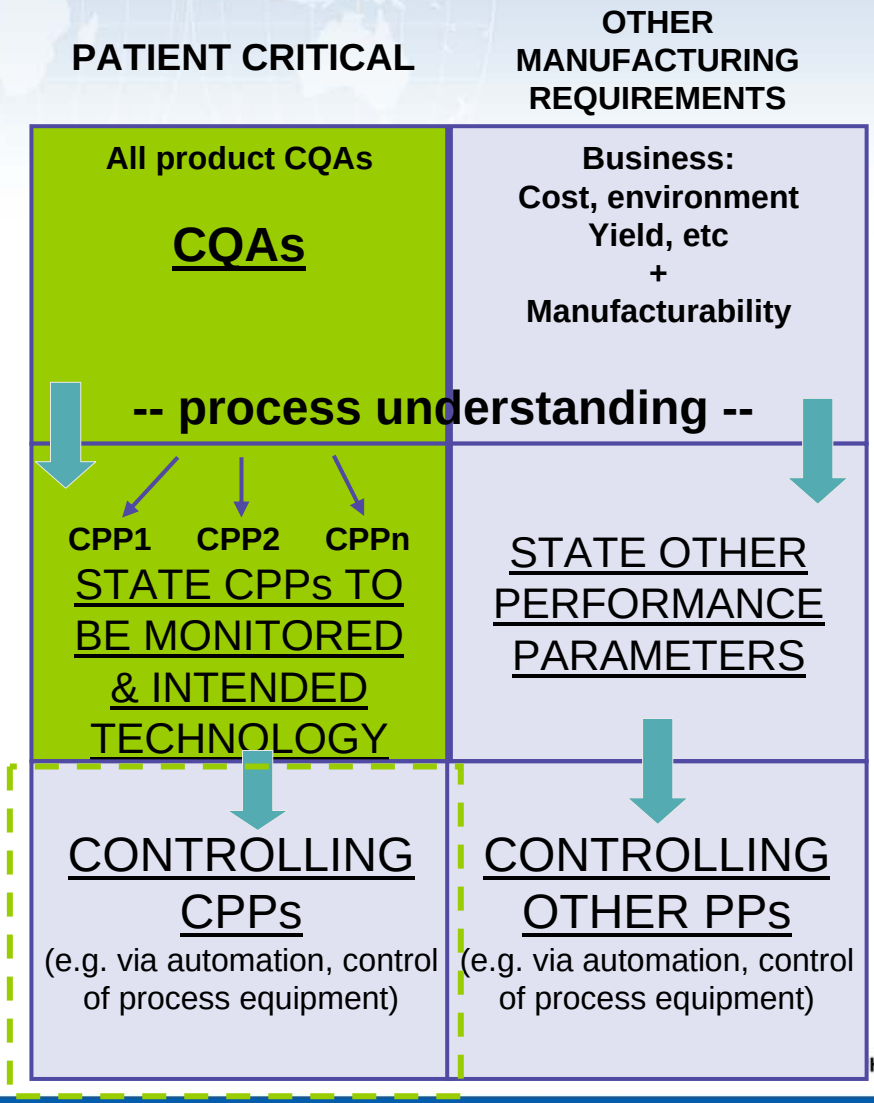
Design Space

- Design Space: the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is **not** considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

  (ICH Q8)

PQLI - Control Strategy (draft)

In practice, consider both patient critical and business issues



Specific detail included in submission

Level 3 information provided, as required, to support Level 2

Level 2 = Outline of Process Model (i.e. What CPP values or CQAs to be measured & proposed methods)

Level 3 = Details of Process Model + Control Model (Controls CPPs)

ISPE PQLI Workshops...

Industry & Regulators are participating

- US FDA
- Europe EMEA and National Regulators
- Japan

- ISPE Las Vegas PQLI Conference
  - November 5th, 2007
- ISPE Copenhagen PQLI Workshop (incl. Regulators)
  - April 9th-11th, 2008
- Proposed ISPE Washington PQLI Workshop
  - June 2nd, 2008

To be coordinated with ICHs own implementation work

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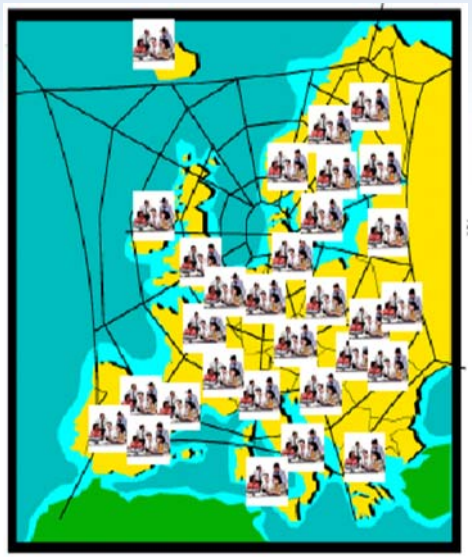
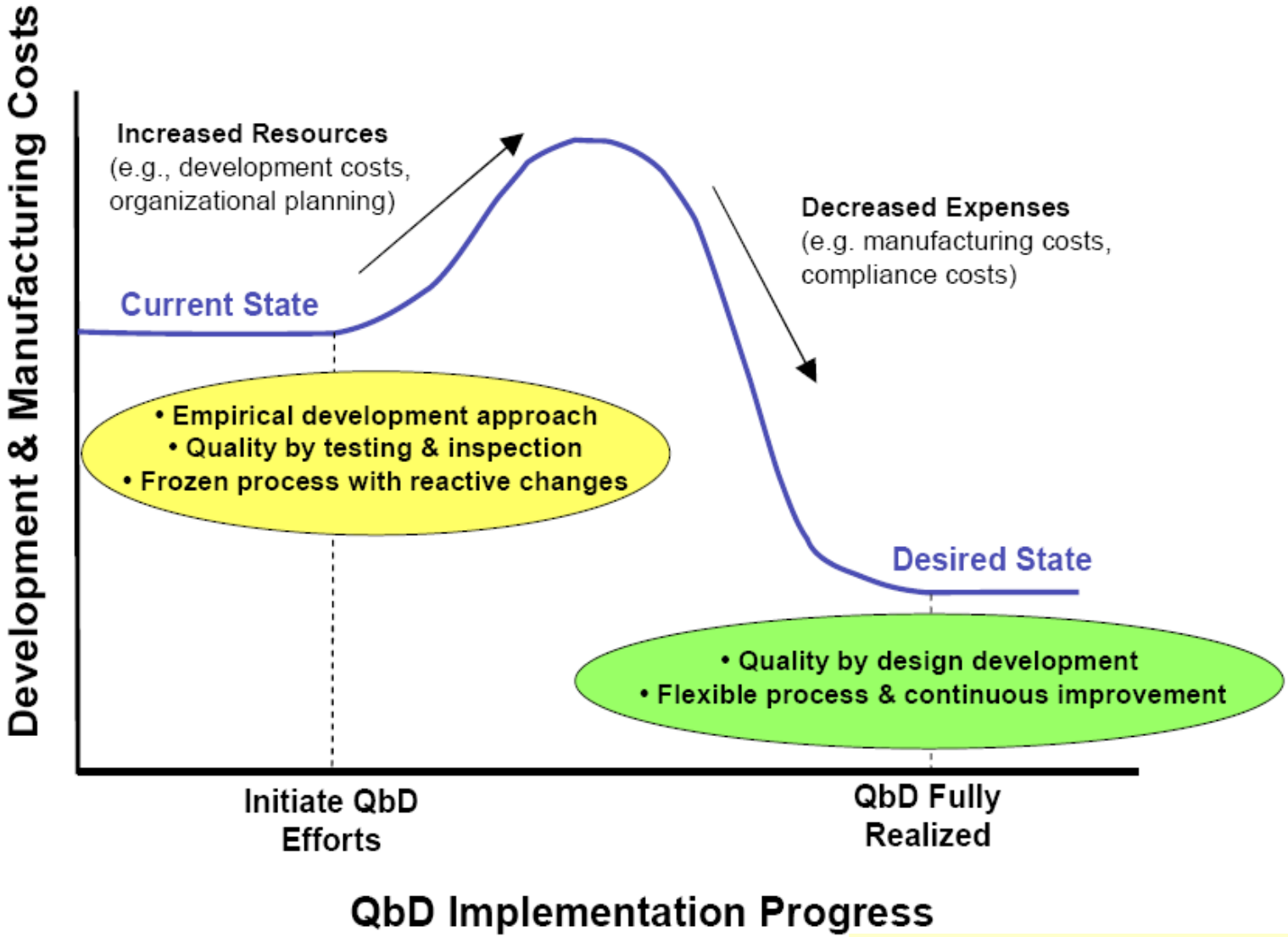
Herausforderungen der Initiative...

- European EMEA PAT Team
  - Virtual
  - Around 28 Agencies...
- Japan
- US
  - One FDA...



Cost and Benefit of QbD



Source: Pharmaceutical Manufacturing in the 21st Century – An FDA Perspective
Moheb Nasr, ISPE Annual Meeting 2006

Zusammenfassung

- Mutation der Prozesse
  - Potenzial: von 2,5 Sigma hin zu 6 Sigma
  - Steigerung des Prozessverständnisses
- Ausnutzung der regulatorischen Flexibilität mit QbD / PQLI / PAT
- Komplexe Herstellprozesse z.B. im Wirkstoffbereich “schreien” nach klassischer PAT
- ABER:
  - Internationale Harmonisierung der gesetzlichen Anforderungen bleibt ein Hemmschuh
  - Auch inerhalb der FDA kontrovers diskutiert

Vielen Dank !

Christian Wölbeling

Coordinator PAT - CoP D/A/CH
Global ISPE PAT CoP Steering Committee Co-Chair

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