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# Doing 'Right From Start' in Biopharma Development

Dialogue Biopharm 2010

# Agenda

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- The Biopharma/Pharma industry
- The challenges in the value chain
- How to reach high quality throughout a biotech product lifecycle

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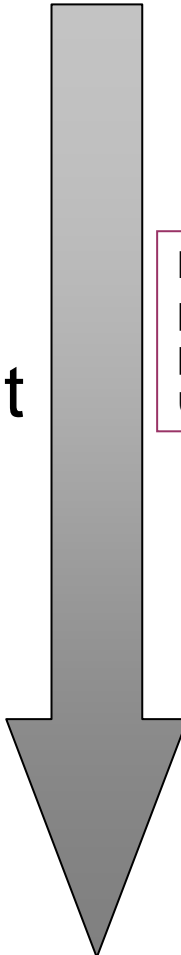
# The Biotech pharma industry:

**A Manufacturing industry with a  
high intense in Research &  
Development**

# The product life cycle

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- Pharmaceutical development
  - Drug substance development
  - Formulation development
  - Manufacturing process development
  - Analytical method development
- Technology transfer
- Commercial manufacturing
- Product discontinuation



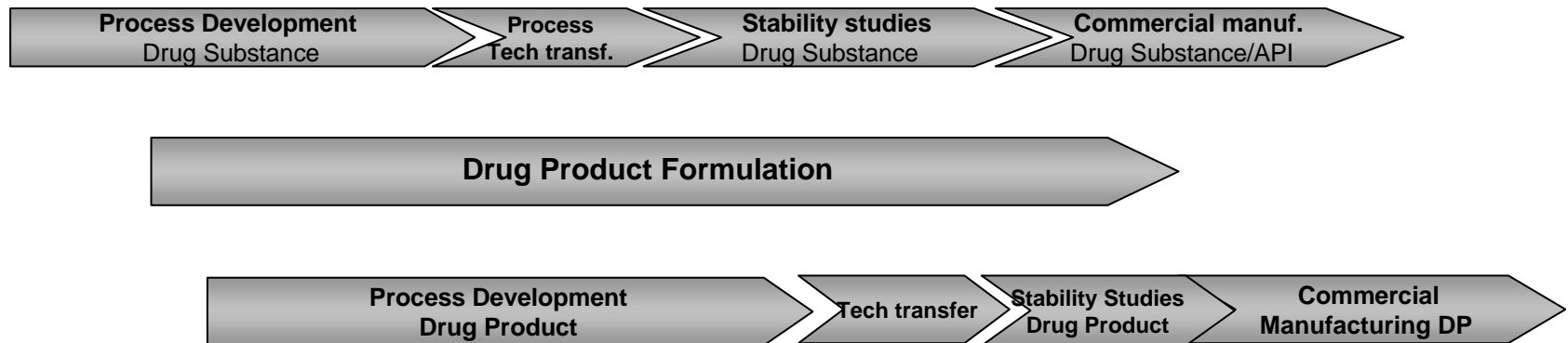
Increased  
process and  
product  
understanding

# The Value Chain for Pharmaceuticals

## 1. Preclinical testing, clinical trials



## 2. Product development and manufacturing



*Time*

# The Pharmaceutical Industry

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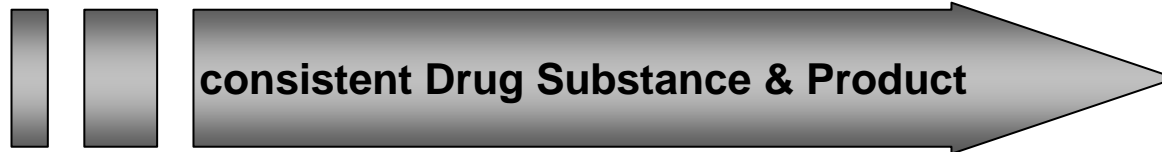
- **”Big Pharma” has 40 % of the industry’s total turnover**
  - **Ex. ca 300 biotech companies in Sweden, whereof 290 have less than 50 employees**
- **Less than 30 new entities/yr (NCE’s) worldwide**
- **Generics – Biosimilars when patent expiry**
- **’Time to market’ increases**
- **Breakthroughs in science**
- **New medical needs**
- **Growing ”new” markets**

# The Challenge

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- Cost reduction
  - 2 of 10 marketed products gain profit higher than cost for R&D (US)
- Quality in product and process development
  - "Right First Time"-attitude
  - 'Quality by design' in products life cycle
- Consistent products throughout the value chain
- Effective coordination between the companies
- Use of knowledge gained from product and process development (both from successes and failures)

# Development & Manufacturing



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# Right from Start -- A Paradigm Shift ??

# The Paradigm Shift ?

Interpretation of  
rules and guidelines



**Product  
and  
Process understanding  
from start of product development**

**Quality by design**

- **What's stated from authorities – representatives from Big Pharma ?**
- **Which of the rules/guidelines do I have to follow – when ?**

- **Critical process parameters ?**
- **Product Specification ?**
- **Product stability profile ?**
- **Process stability ?**

# Properties to be considered in the Value Chain

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- **Active Pharmaceutical Ingredient (API)**
  - control of material
  - manufacture
  - characterisation
  - control of drug substance
  - stability
- **Pharmaceuticals**
  - composition
  - development
  - manufacture
  - control of excipients
  - control of drug product
  - container closure
  - stability

IMPD=Investigational medicinal product dossier  
CTA=Clinical trial application  
MAA=Marketing Authorisation application

(IMPD för CTA, Module 3 for MAA)

# Examples of incomplete documentation in Application for Clinical trials (IMPD)

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- No analytical method or control of impurities
- Unstable pharmaceutical formulation
- No Specification – no references for assay of product
- The analytical method do not correlate to declared in vivo - conditions

# Overall objectives in product- and process development

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- **Active Pharmaceutical Ingredient (API)**
  - High purity in finished bulk product
  - High yields(productivity)
  - Stable and reproducible processes
- **Pharmaceuticals**
  - No degradants created during the process
  - No contamination – during process
  - Reproducible processes – Same product properties

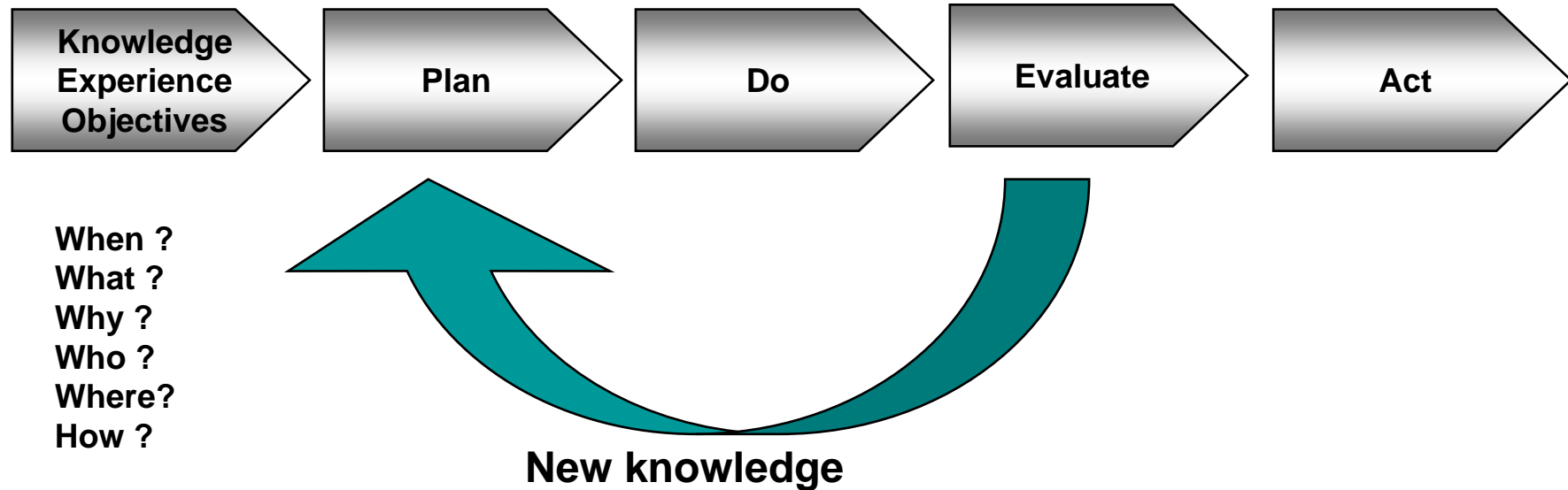
# Enablers to a Pharmaceutical Quality system

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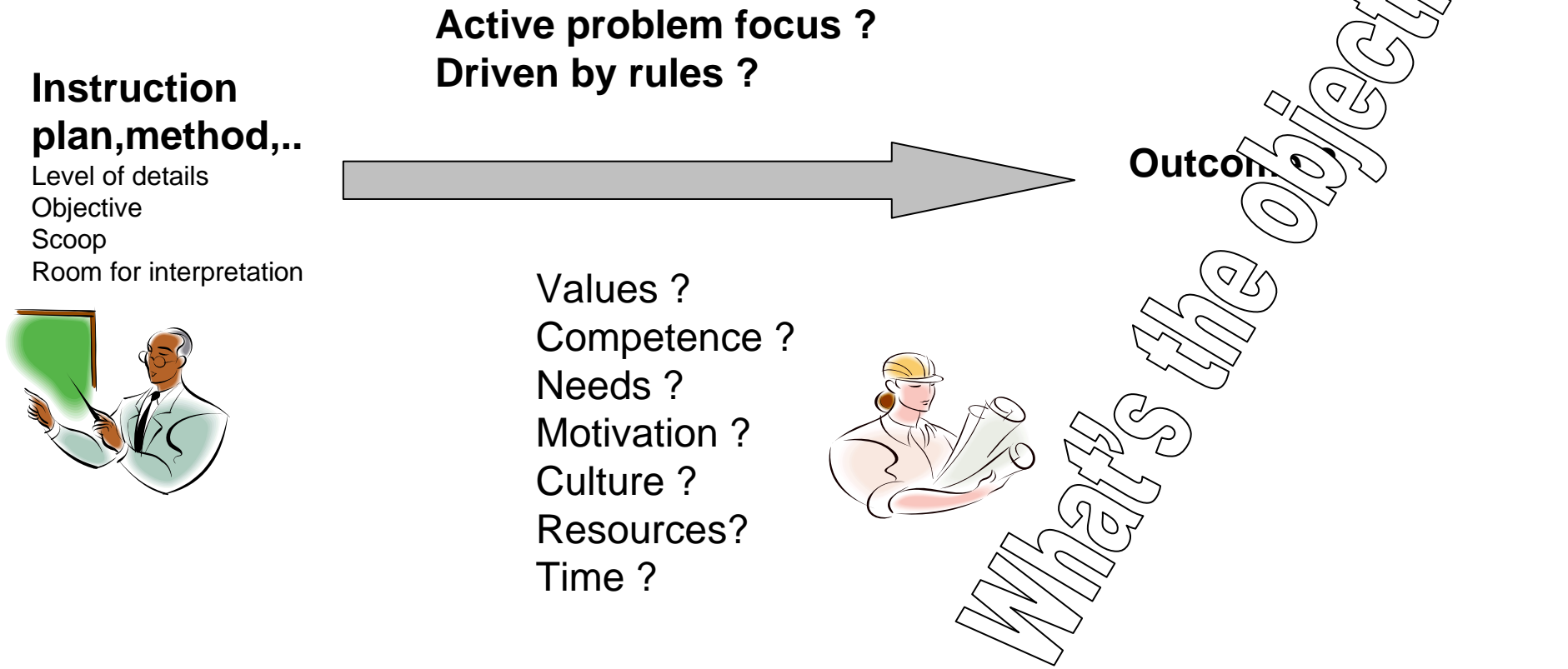
- Effective product and process knowledge management
- Integrated Quality Risk Management

# Quality System

Often a written procedure aiming to make it easier to meet quality objectives



# How to get quality in activities?



# Routine vs creative problem solving

Method Knowledge in respect to..	A Routine	B Driven by the problem	C Based on competence, experiences... (crossfunctional)
Influence Effect	<i>Known</i>	<i>Known</i>	<i>Unknown</i> ?
Cause	<i>Known</i>	<i>Unknown</i> ?	<i>Unknown</i> ?
Actions	<i>Known</i>	<i>Unknown</i> ?	<i>Unknown</i> ?

# ”New” quality systems

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- **FDA ”21<sup>st</sup> Century GMP”**
  - Process oriented GMP
  - More effective quality systems
  - Validation - based on risk management
  - Use of Process Analytical Technology(PAT)
- **ICH-guidelines (International Conference of Harmonisation)**
  - ICHQ8 Pharmaceutical Development
  - ICHQ9 Quality Risk Management
  - ICHQ10 Quality Systems
  - **ICHQ11 Development and Manufacture of Drug Substances (step 2; 2010)**

# ICH Quality Guidelines

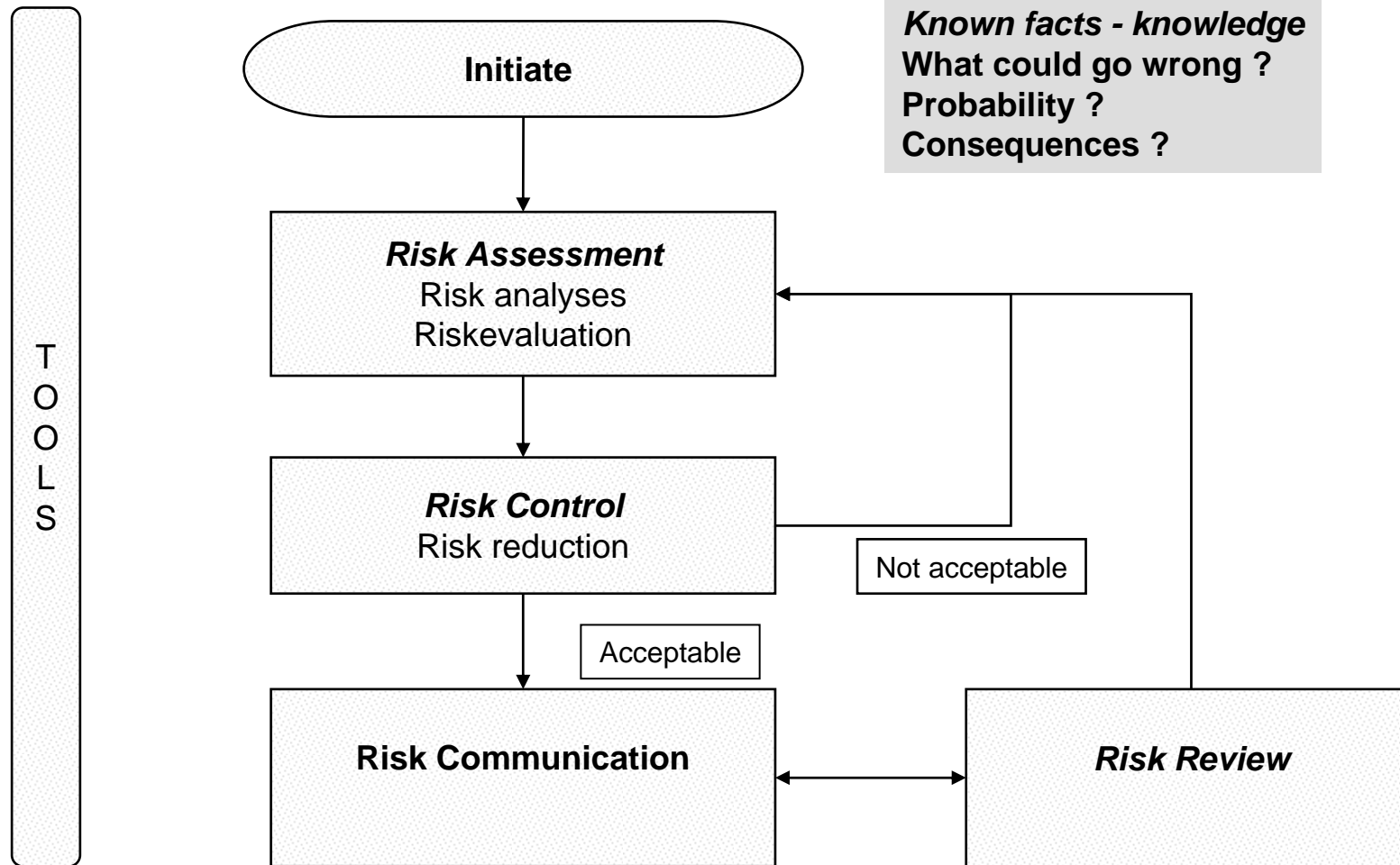


- Q1 (A-F) Stability
- Q2 Analytical Validation
- Q3 (A-C) Impurities
- Q4 (A,B) Pharmacopoeias
- Q5 (A-E) Quality of Biotechnological Products
- Q6 (A-B) Specifications
- Q7 Good Manufacturing Practice ;EU-GMP del II (fd Annex18)
- Q8 Pharmaceutical Development
- Q9 Quality Risk Management ; EU-GMP, Annex 20
- Q10 Pharmaceutical Quality System
- Q11 Development and Manufacture of Drug Substances (chemical entities and biotechnological/biological entities)
  - Step 2 (consensus paper) planned , 2010

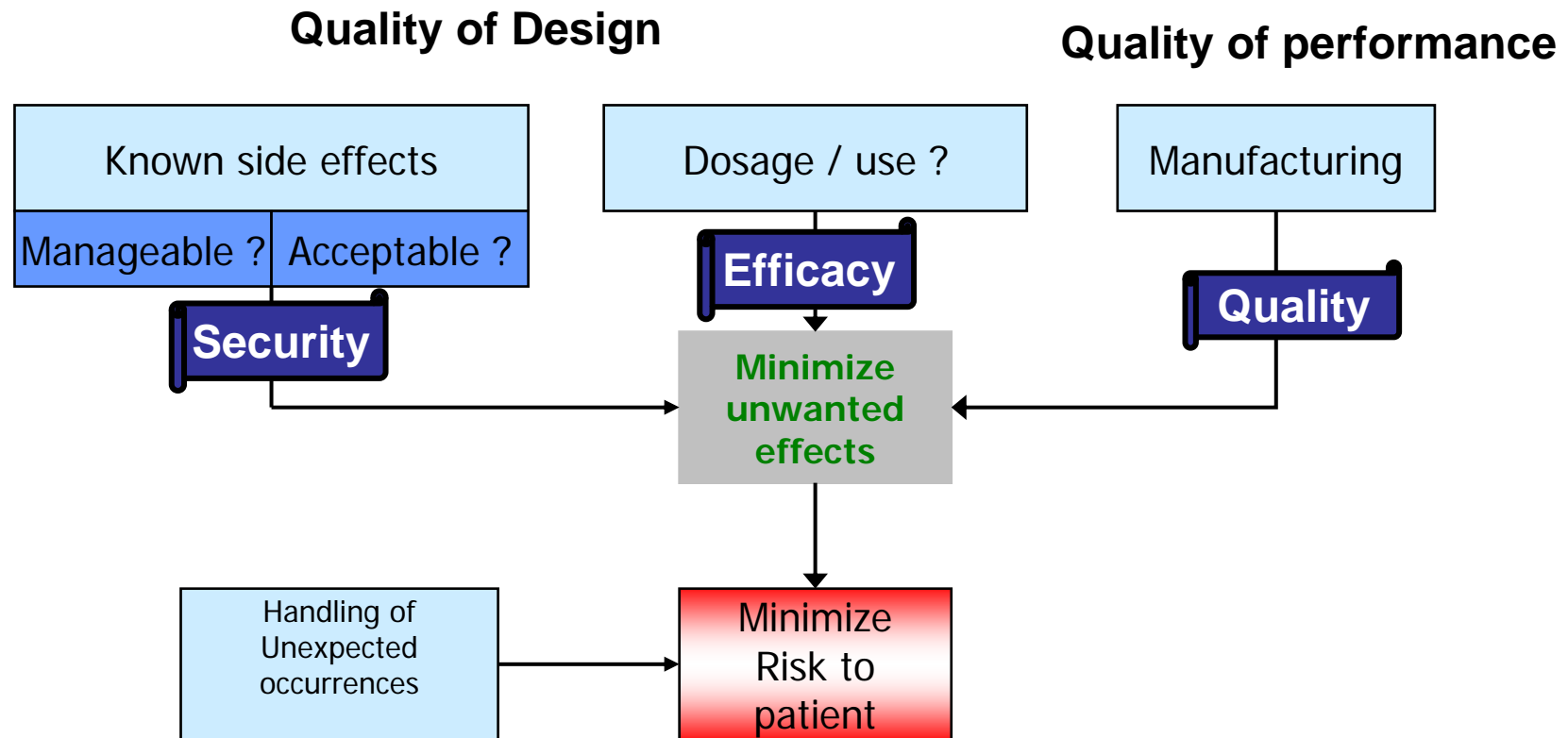
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# Risk Management ICHQ9 (EU-GMP Annex 20)

# Quality Risk Management



# Quality of product and Risk Management



# Methods and tools used in risk management

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- Methods to describe the process
  - Flowcharts;
  - Check Sheets
  - Process Mapping
  - Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram)
  - Statistics from process reviews
- Tools
  - Failure Mode Effects Analysis (FMEA)
  - Failure Mode, Effects and Criticality Analysis (FMECA)
  - Fault Tree Analysis (FTA)
  - Hazard Analysis and Critical Control Points (HACCP)
  - Hazard Operability Analysis (HAZOP)
  - Preliminary Hazard Analysis (PHA)
  - Risk Ranking and Filtering

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# Pharmaceutical Development ICHQ8

# Objective of ICHQ8 Pharmaceutical Development

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- ....provides an opportunity to present the knowledge....use scientific approaches and quality risk management to the development of a product and its manufacturing process.

# Elements in ICHQ8

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- Quality Target Product Profile(QTPP) eg.:
  - Intended use; dosage
  - Drug product quality criteria
  - Container Closure System
- Critical Quality Attributes (CQAs)
  - Identified by knowledge, experience and risk assessment – material and process parameters
- Select a manufacturing process
- Control strategy
  - Product and process understanding and quality risk management
  - Real time release testing (RRT)

# ..elements in ICHQ8

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- Continuous Process Verification
- Process signature
- Design Space
- Formal Experimental Design

# Summary ICH Q8

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- Quality work, is based on scientific understanding, gained experience and increased knowledge during the pharmaceutical development phases.
  - Built in Quality by Design
- The documented development work is the ground for the CTD (Common Technical Documentation)-files

# Q11 Development and Manufacture of Drug Substances (chemical entities and biotechnological/biological entities)

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- Highlights
  - Process understanding
  - Similarities and differences in drug substance development of chemical vs biotechnological substances
  - Guidance for setting specifications for Chemical substances(Q6A) and Biotech Substances (Q6B)
  - Guidance to information to be included in Section 2 in the CTD

# Pharmaceutical Quality System

## ICHQ10

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- **Objectives**

- Achieve Product Realisation
- Establish and Maintain a State of Control by using quality system in the product Life Cycle
- Facilitate Continual Improvement

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Thank you !!