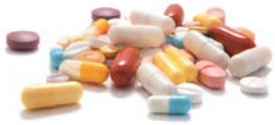


EXPERT
SANTÉ CANADA
MAPAQ

Risk Management
– ICH Q9 –
- FMEA -
Applied to Validation

PBE, Pharma Bio Expert Inc

PBE-Expert Inc – CANADA

Training Company Agreement CPMT #0059104

PBE, Training Company Agreement **CPMT** #0059104

Commission des partenaires du marché du travail
Québec

CERTIFICAT D'AGRÉMENT

Loi favorisant le développement et la reconnaissance des compétences de la main-d'oeuvre

Titulaire : PBE, PHARMA BIO EXPERT INC.

Numéro d'agrément : 0059104

NEQ : 1168916956

Catégorie d'agrément : Organisme formateur

Date de délivrance : 6 février 2018
Date d'échéance : 5 février 2020

CHAMPS PROFESSIONNELS

01 Administration et commerce
03 Alimentation, hôtellerie et tourisme
06 Chimie et biologie

Par : Isabelle Bergeur

Le 7 février 2018

La délivrance du certificat est valide en fonction des documents soumis à la Commission des partenaires du marché du travail.

Ministère du Travail, de l'Emploi et de la Solidarité sociale

EQ-6282 (06-2003)
ENT-0031 (12-2016)

Agenda

1. Definitions & applicable standards
2. History, cost and applications
3. Regulations
4. Reminder of existing tools & methods
5. Risk Management process
6. Risk Assessment approach
7. Characteristics of the process
8. Operation and maintenance
9. Limits and scope
10. Process validation strategy (ies)
    - Goals
    - Principles
    - Tools
    - Methodology of a risk analysis relating to a manufacturing process (FMECA)
11. Conclusion
12. Case Study / Group
    - Purified Water System/ Pure steam generator
    - Cleanroom
    - Sterile filling line (Lyophilizer)
    - Tablet press

Training goals

Training goals

1. The training aims to enable participants to transfer the theory of Risk Management (ICH Q9) to a practical reality in a pharmaceutical context.
2. After a reminder of regulatory requirements (ICH Q9, BP, ISPE):
3. The Risk Management approach will be supported and practiced through several examples worked in groups:
   a. Purified water system.
   b. Pure steam generator.
   c. Cleanroom.
   d. Sterile filling line (Lyophilizer)
   e. Tablet press.

C & Q

C&Q

Name of a person from the departments below

C&Q jointly supported by:

- QA,
- Engineering,
- Automation / IT.

PBE PharmaBio EXPERT cGMP

EXPERT SANTÉ CANADA MAPAQ

PBE EXPERT

Regulatory framework

Regulatory requirements

FDA, Guide to Inspection for Validation of Cleaning Processes, 1993

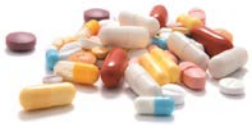
FDA CDRH Guidance for Sterilants & Disinfectants, 1/3/00

ICH Q9, GMP for Pharmaceutical Active Ingredients

ASTM E2500 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment

FMEA : MEC 763, Chapter 7 L'AMDEC. (Oct 2001)

ISPE, vol. 7, Risk Based Manufacture of Pharmaceutical Products (p.89-94), Good Practice Guide_HVAC, Appendice 10 @ 14



Regulatory requirements- ANSM – 04/12-2013, Part 3 - Documentation

Quality risk management (ICHQ9)……...237

8. References

1. ICH Q8 Pharmaceutical development.
2. ISO/IEC Guide 73:2002 – Risk management - Vocabulary– guidelines to be used in the standards.
3. ISO/IEC Guide 51:1999 – Aspects related to security- guidelines to be included in the standards.
4. Process Mapping by the American Productivity & Quality Center, 2002, ISBN 1928593739….

Regulatory requirements-
ANSM – 04/12-2013, Part 3 - Documentation

8. Références

5. IEC 61025 –Fault Tree Analysis (FTA).

6. IEC 60812 - Analysis Techniques for system reliability—Procedures for failure mode and effects analysis (FMEA).

7. Failure Mode and Effect Analysis, FMEA from Theory to Execution, 2nd Edition 2003, D. H. Stamatis, ISBN 0873895983.

Regulatory requirements-
ANSM – 04/12-2013, Part 3 - Documentation

8. Références

8. Guidelines for Failure Modes and Effects Analysis (FMEA) for Medical Devices, 2003 Dyadem Press, ISBN 0849319102.
9. The Basics of FMEA, Robin McDermott, Raymond J. Mikulak, Michael R. Beauregard 1996, ISBN 0527763209.
10. WHO Technical Report Series No 908, 2003, Annexe 7 Application of Hazard Analysis and Critical Control Point (HACCP) methodology to pharmaceuticals.
11. IEC 61882 - Operability and risk Analysis (HAZOP).

Regulatory requirements-
ANSM – 04/12-2013, Part 3 - Documentation

8. Références

ISO 14971:2000 – Application of risk management to medical devices.

ISO 7870:1993 – Control charts.

ISO 7871:1997 – Cumulative sums charts.

ISO 7966:1993 – Control charts for acceptance.

ISO 8258:1991 – Shewhart control charts.

What is Total Quality Control ?; The Japanese Way, Kaoru Ishikawa (Traduit par David J. Liu), 1985, ISBN 0139524339.

Risk analysis: Application

U.S. Food and Drug Administration

FDA 21 Century Risk-Based Quality System Initiative

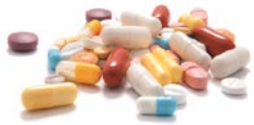
- Define critical product attributes and control of critical processes (Process Capacity) to ensure:
- SAFETY, PURITY, EFFICACY, QUALITY / (ICH)
- Design “Quality” into processes (QBD)
- Science-based risk management
- Real time QA

C-GMP / ICH-Guidelines

Some definitions

FMEA : Failure Mode Effects Analysis

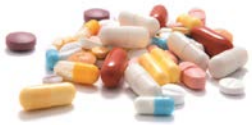
FMECA : Failure Mode Effects and Criticality Analysis



Regulatory requirements ICH Q9

Regulatory requirements

- Risk analysis is a regulatory requirement for validation (EU-GMP annex 15).
- Is a requirement of the quality management system(ICH & FDA):
  - A global approach to Risk Management: ICH Q9
  - A universal approach to Risk Assessment



Pharmaceutical reference regulation

- International reference: WHO & ICH
- European reference: GMP-EU
- USA reference: cGMP & FDA-Guidance

- Five fundamental GMP characteristics for the product

- Identity
- Security
- Purity
- Efficiency
- Quality

Chronology

A globalized notion

2005: Q9. Quality Risk Management

2005: GMP-Eu Vol 4 Part II: Process criticality analysis (active substances)

2004: Risk Management Guidelines based on cGMP

2003: WHO_TRS_90B. Transposition of HACCP to the pharmaceutical field

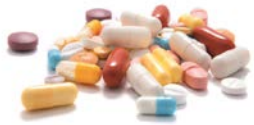
2001: 15 GMP-EU annex. Process criticality analysis, validation and change

2000: ICH/Q7A. Process criticality analysis (active substances)

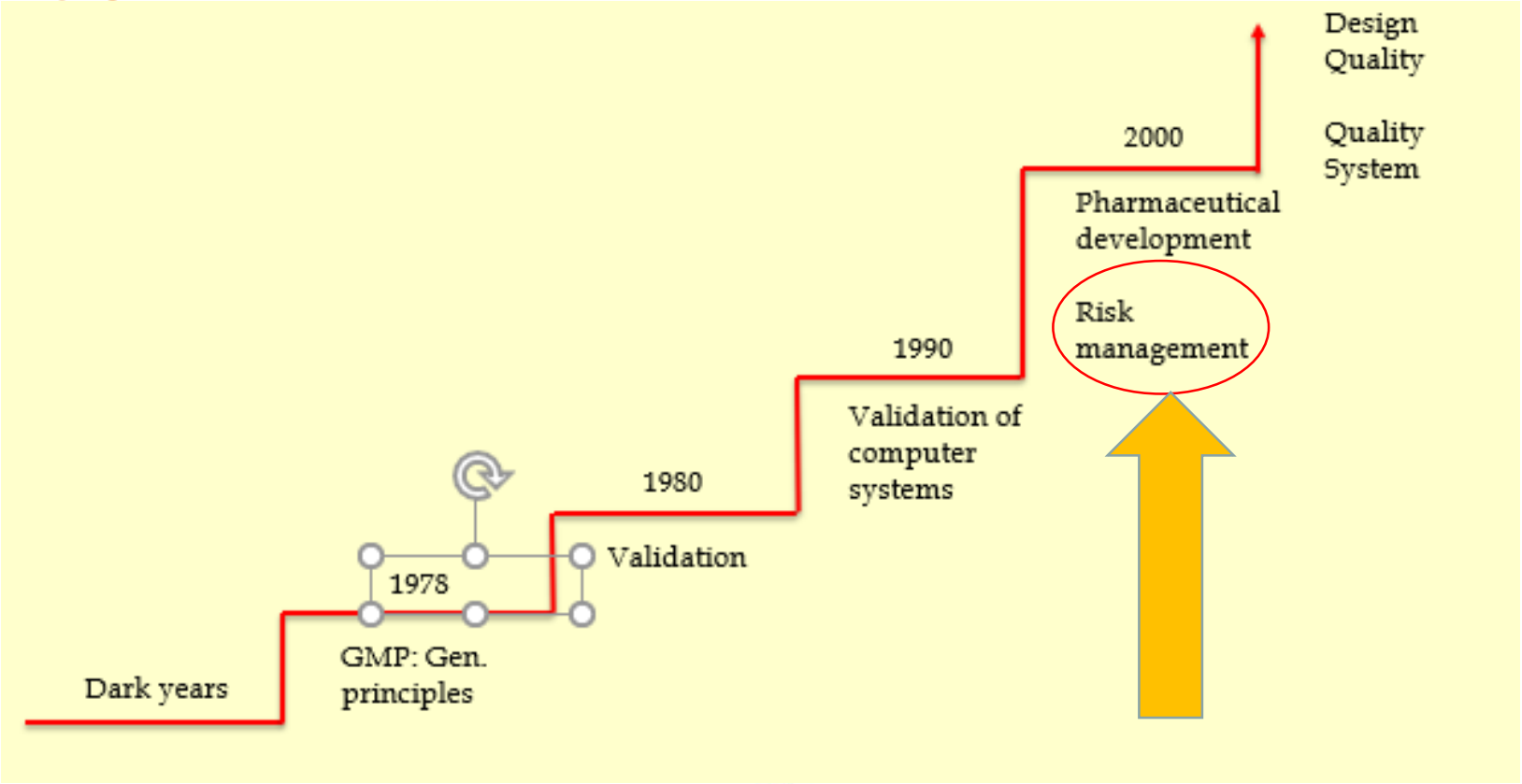
1998-2002 FDA Software Guidance about information systems

FDA - Software Guidance – (draft en 1998 . final january2002)

- " This guidance recommends an integration of software life cycle management and risk management activities"
- Section 2 Risk Management Activities during the Software Life Cycle.
- First concept of Risk Management in the pharmceutical industry related to information systems.



History of GMPs / 30 Years



Scenario and potential opportunities for risk reduction (ANSM-Part 3)

ANNEX 1…Improving scientific approaches to risk

Scénario	Opportunités potentielles
1. Satisfaire aux exigences BPF	Status quo
2. Démontrer un système qualité pharmaceutique efficace, incluant une utilisation efficace des principes de management des risques qualité (exemples : ICH Q9 et ICH Q10).	Augmenter l'utilisation des approches basées sur le risque pour les inspections réglementaires.
3. Démontrer la compréhension du produit et du procédé, incluant une utilisation efficace des principes de management des risques qualité (exemples : ICH Q8 et ICH Q9).	Faciliter les évaluations scientifiques de la qualité pharmaceutique ; permettre des approches innovantes pour la validation du procédé ; mettre en place la libération paramétrique des lots.
4. Démontrer la compréhension du produit et du procédé et l'efficacité du système qualité pharmaceutique, incluant une utilisation efficace des principes de management des risques qualité (exemples : ICH Q8, ICH Q9 et ICHQ10).	Augmenter l'utilisation des approches basées sur le risque pour les inspections réglementaires. Faciliter les évaluations scientifiques de la qualité pharmaceutique ; optimiser les processus de changements post AMM basés sur une approche scientifique et sur le risque, afin de maximiser les bénéfices fournis par l'innovation et l'amélioration continue ; permettre des approches innovantes pour la validation du procédé ; établir la libération paramétrique des lots.

Regulatory and normative context / ASTM 2500-07

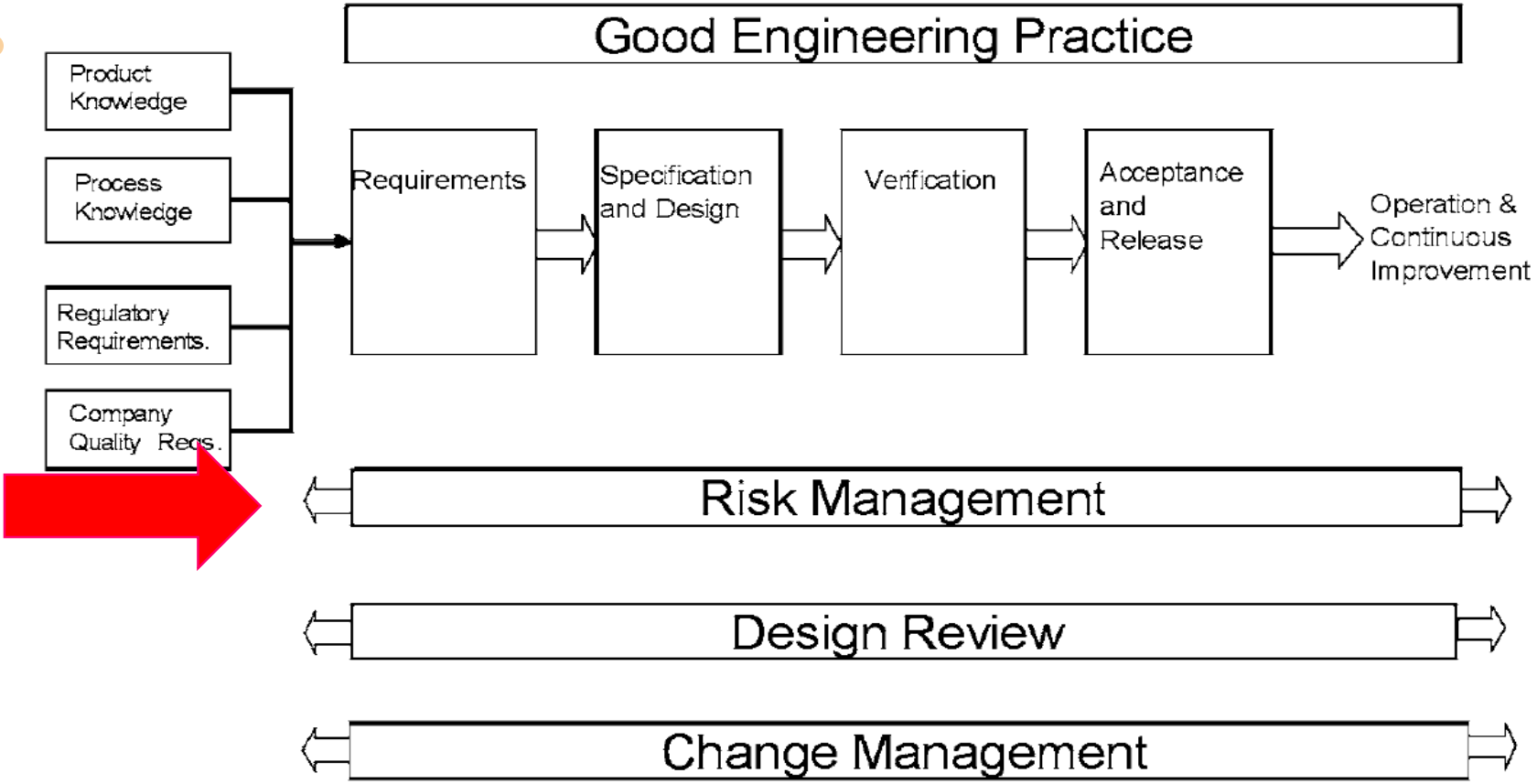
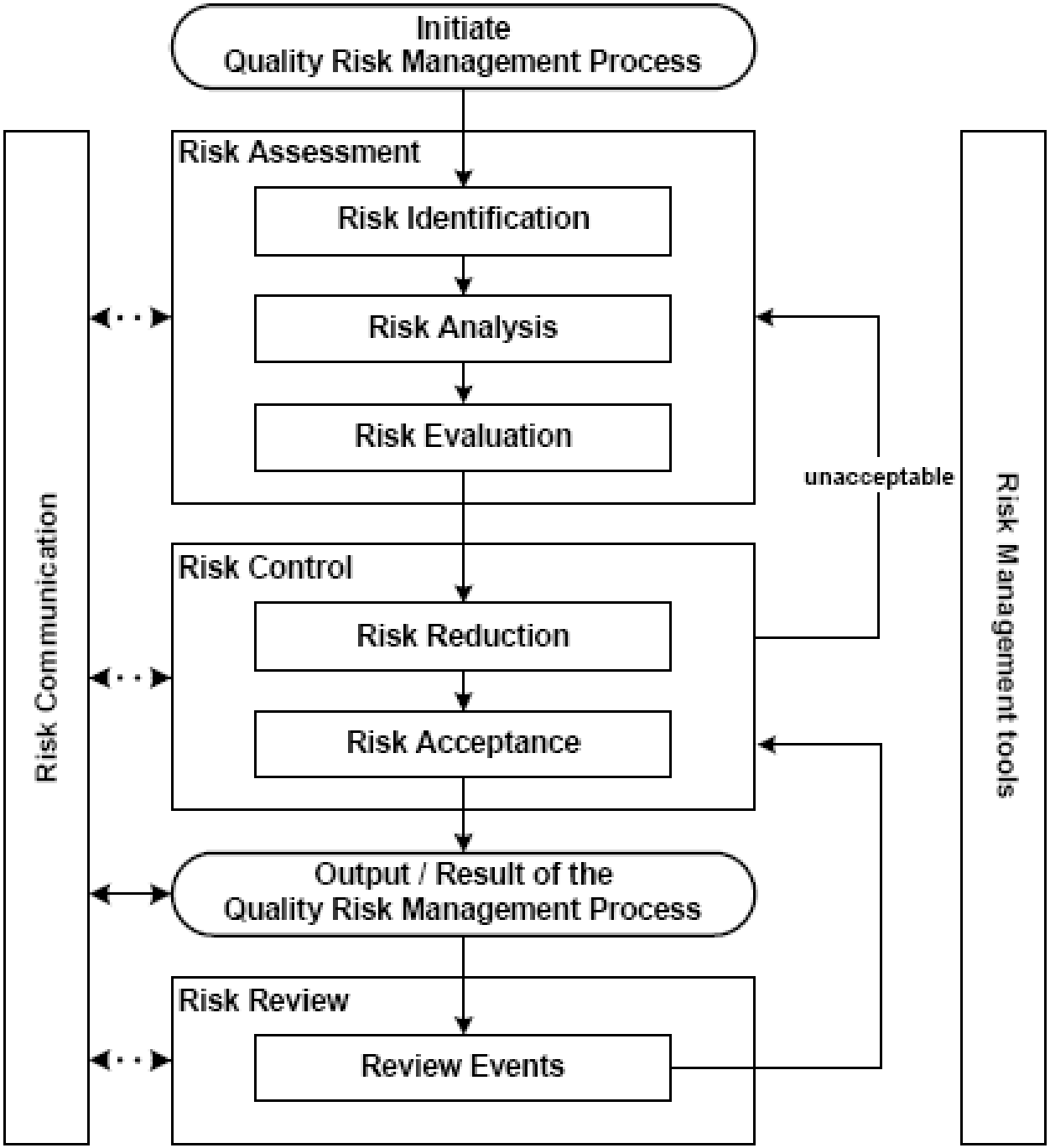


FIG. 1 The Specification, Design, and Verification Process

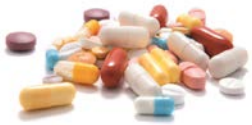
Overview of a classic quality risk management process 00-07



LD.20. QUALITY RISK MANAGEMENT
4- General quality risk management process

- *4.3 Risk assessment*
- *To help define precisely the risk(s) for evaluation purposes, three fundamental questions are often helpful :*
  - ***1.What can go wrong?***

  IDENTIFICATION
  - ***2.What is the PROBABILITY that it goes wrong?***
  - ***3.What are the CONSEQUENCES*** ***(severity) ?***



LD.20. QUALITY RISK MANAGEMENT
4- General quality risk management process

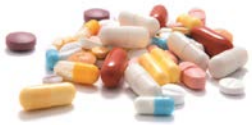
- *Risk identification is the systematic use of information to identify hazards relating to risk or to the description of the problem.*
- *Identifying potential risk addresses the question « What can go wrong ? », including the identification of possible consequences.*

LD.20. QUALITY RISK MANAGEMENT
4- General quality risk management process

- *Risk analysis is the estimation of the risk associated with the identified hazard.*
- *It is the qualitative or quantitative process of linking the probability of occurrence of damage and its severity.*
- *With some risk management tools, the ability to detect damage (DECTABILITY) also takes into account the risk estimate.*

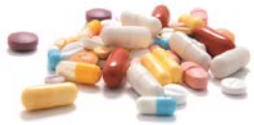
LD.20. QUALITY RISK MANAGEMENT
4- General quality risk management process

- *Risk assessment compares the identified and analyzed risk against given risk criteria.*
- *Risk assessment takes into account the importance of data collected for each of the three questions.*
  1. *What can go wrong?*
  2. *What is the probability that it goes wrong?*
  3. *What are the consequences (severity) ?*
- *Exemple 1 : PW*
- *Exemple 2 : GVP*
- *Exemple 3 : CIP*



LD.20. QUALITY RISK MANAGEMENT
4- General quality risk management process

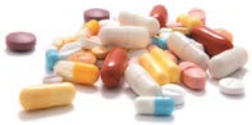
- *The potential risk cans be expressed using qualitative adjectives such as*
  - « *high* »,
  - « *medium* »
  - « *low* »,
- *Which are defined as precisely as possible.*



LD.20. QUALITY RISK MANAGEMENT
4- General quality risk management process

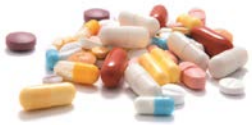
- *Risk reduction = MITIGATION…*

- *Risk acceptance is a decision taken to accept a risk.*



LD.20. QUALITY RISK MANAGEMENT
4- General quality risk management process

- *4.5 Communication relating to risk*



LD.20. QUALITY RISK MANAGEMENT
5 Risk management methodology

- *Quality risk management uses documented, exhaustive and reproductible methods to carry out the steps of the quality risk management process on:*
  - *the current knowledge base*
  - *on the evaluation probability*
  - *of occurrence of the severity and, sometimes*
  - *the detectability of risk.*

LD.20. QUALITY RISK MANAGEMENT

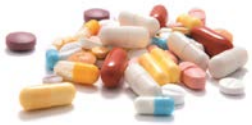
6- Integrating quality risk management into industry and regulatory activities

- *Examples of operations for the industry and competent authorities (cf. Annex II) :*
  - *Quality management.*
- *Examples for industrial activities(cf. Annex II) :*
  - *Development*
  - *Premises, equipment and infrastructures*
  - *Equipment management*
  - *Production*
  - *Control Laboratories and stability tests*
  - *Packaging and labeling.*
- *Examples of operations for competent authorites (cf. Annex II) :*
  - *Inspection and evaluation activities.*

Origin of risk analysis?

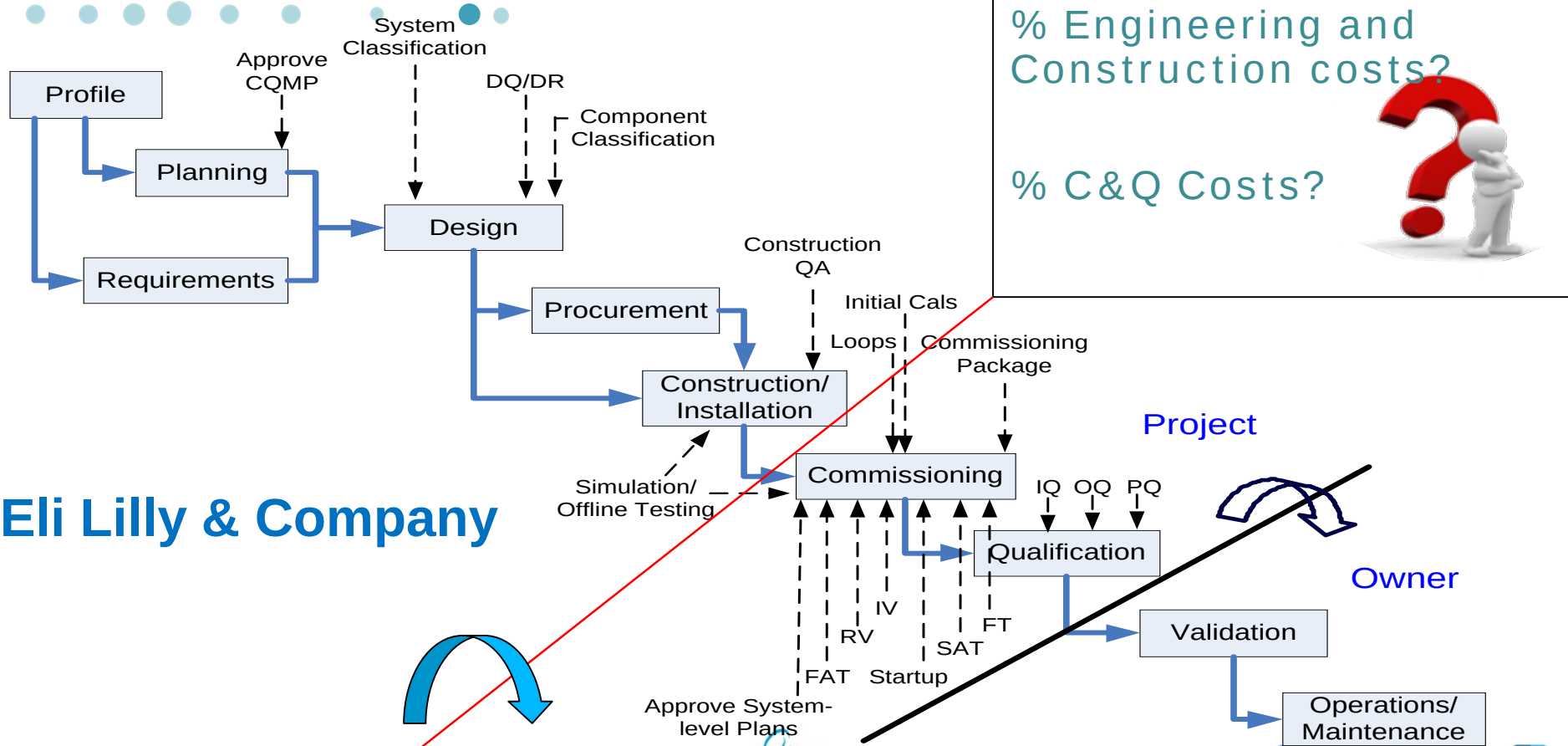
Current state of risk management at multinationals

- Eli Lilly & Company
- Abbott Laboratories
- Pfizer



Fundamental C&Q Delivery Strategy

~ for Global Facilities Delivery (GFD) Capital Projects



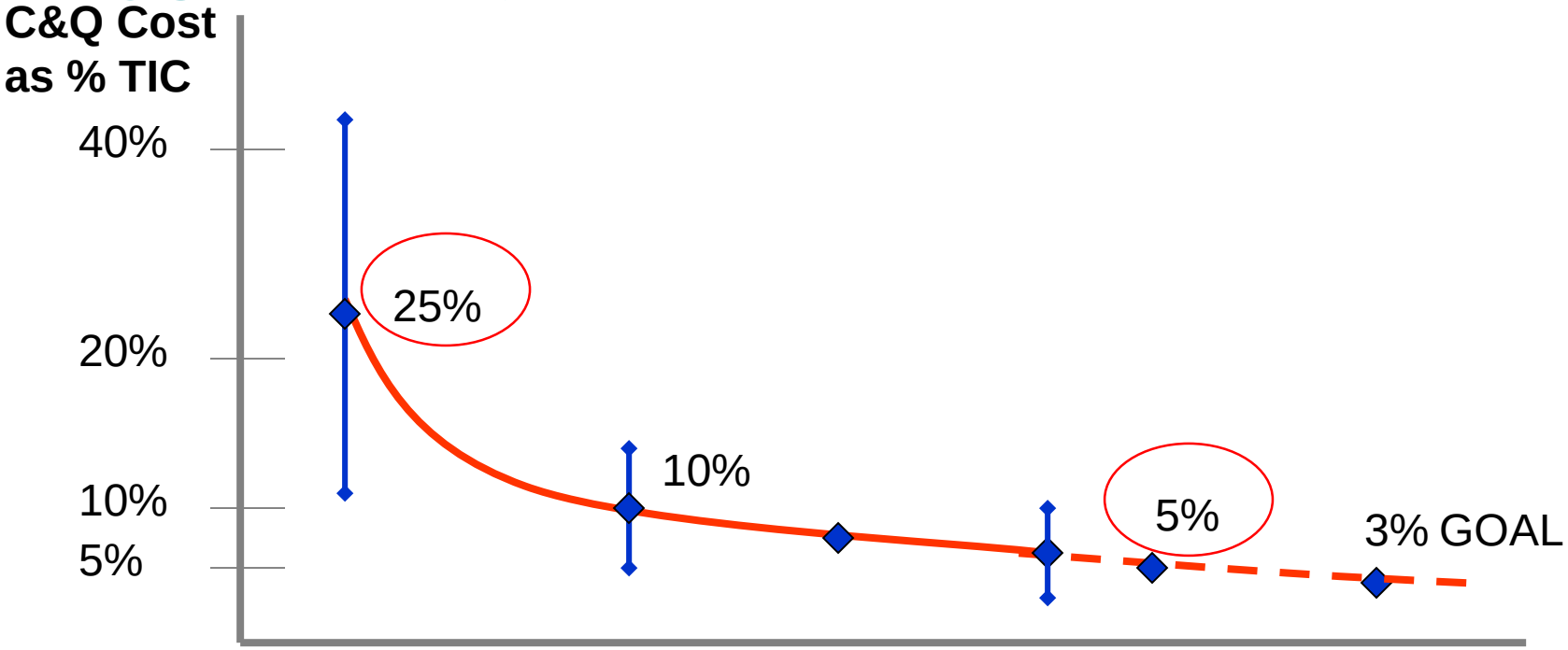
% Engineering and Construction costs?

% C&Q Costs?

Eli Lilly & Company

Eli Lilly & Company

Historical evolution of C & Q costs



No C&Q prog
1998- 2001

Part. C&Q prog
2001-2003

Full C&Q prog
2002- pres.

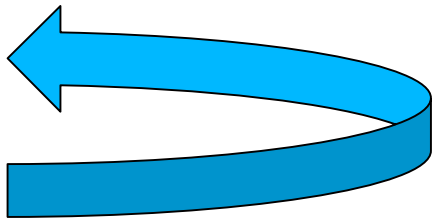
Eli Lilly & Company

Commissioning and Qualification Approach

Lilly C&Q Work Breakdown Structure

Lilly budgets/tracks C&Q expenses via 4 primary WBS categories:

1. Planning & Design
2. Commissioning
3. Qualification
4. Administration



New C&Q Cost Data spec recently approved to provide guidance

Lilly C&Q Work Breakdown Structure

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1. Planning & Design
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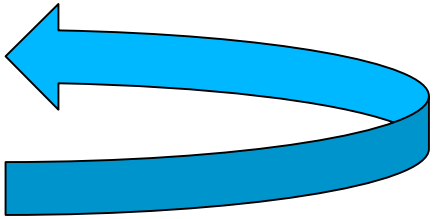
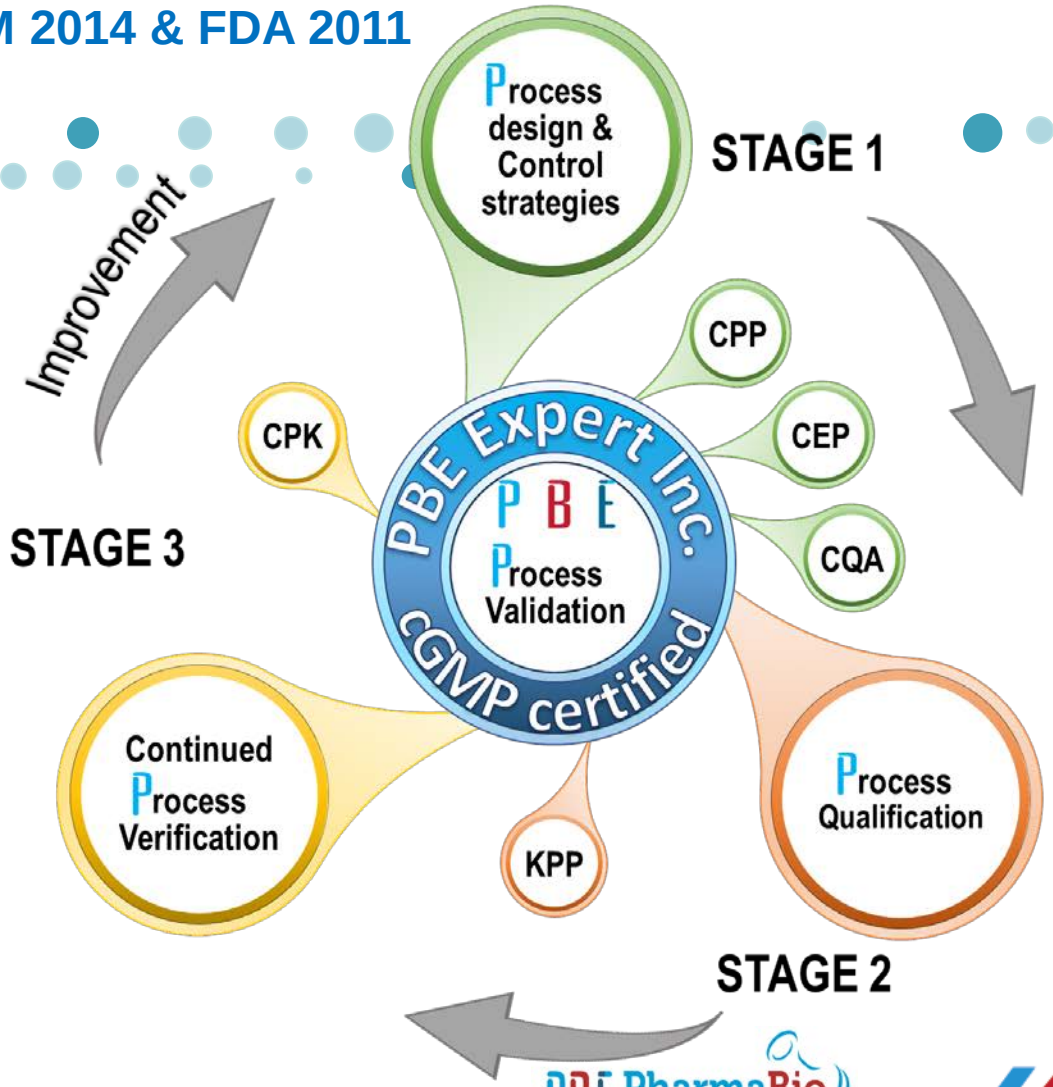
3. Qualification
4. Administration



New C&Q Cost Data spec recently approved to provide guidance

NEW PROCESS VALIDATION REQUIREMENTS/ ANSM 2014 & FDA 2011



Q8

Q9

Q10

Q11

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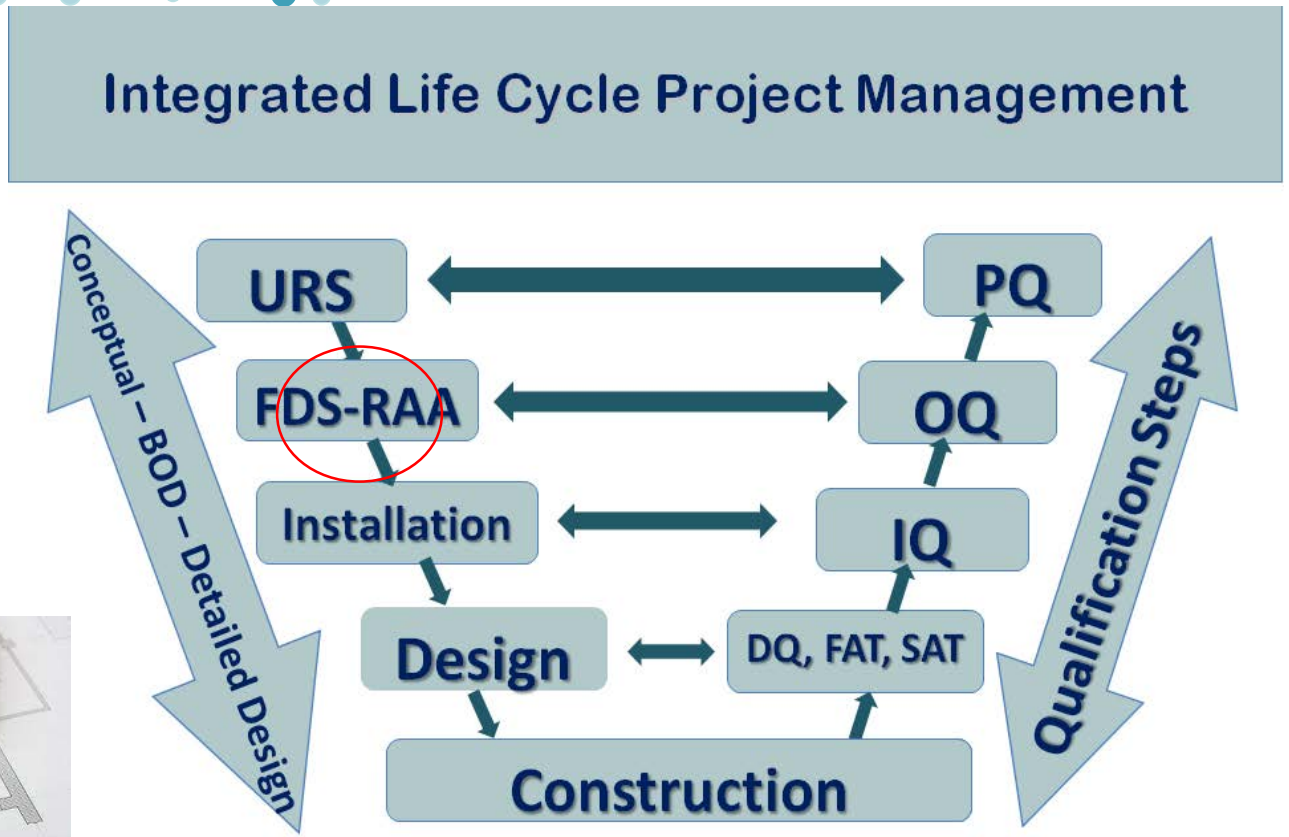
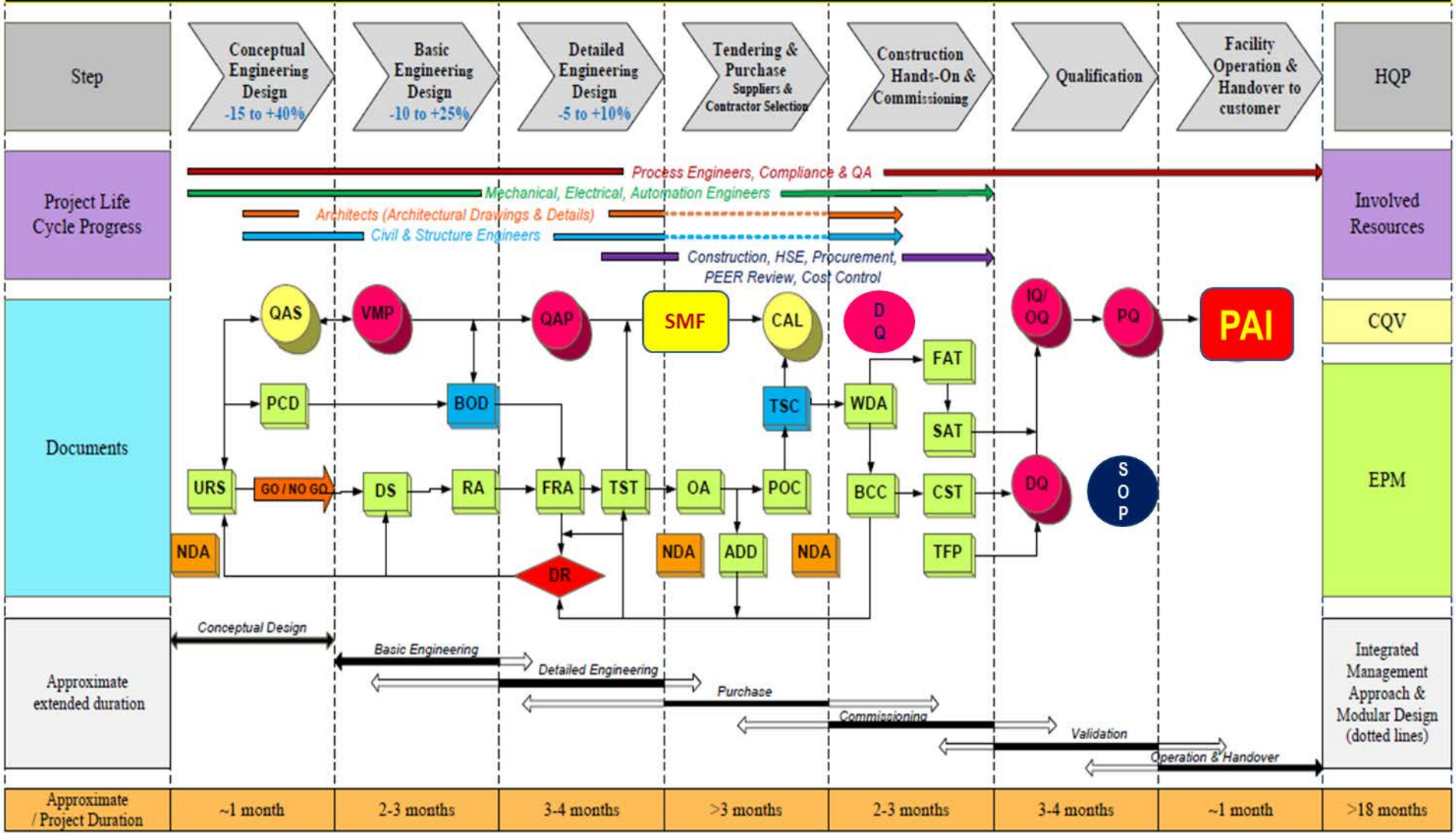
Risk management
V-Model



PROJECT LIFE CYCLE FLOW DIAGRAM



ADD	Addenda
BCC	Benchmark & Change Control management
BOD	Basis Of Design
CAL	Construction Authorization & Licenses, MENVIQ
CQV	Commissioning, Quality Assurance & Validation Team
CST	Commissioning & Startup, SOP, Training, …
DQ & DR	Design Qualification & Design Review

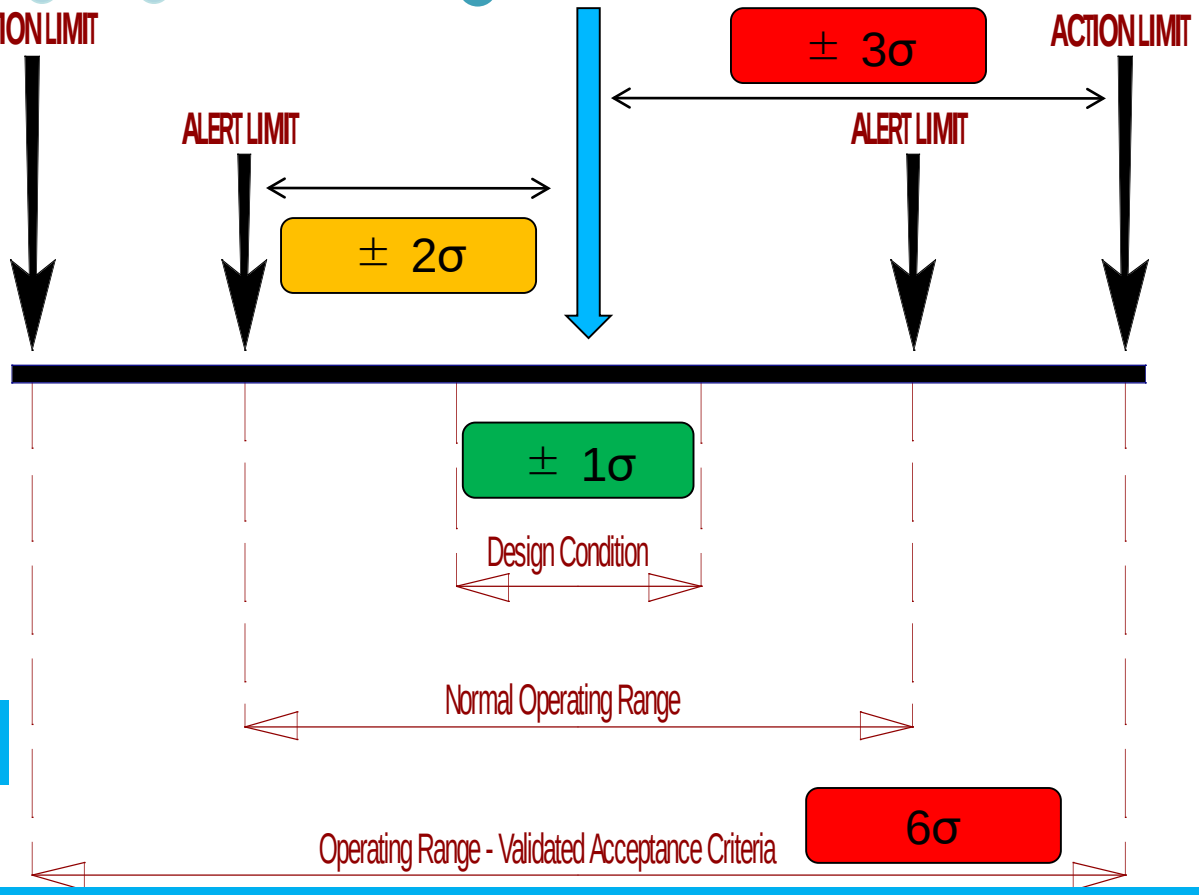
EPM	Engineering, regulatory compliance & Project Management Team
DS	Design Specifications
FAT	Factory Acceptance Tests
FRA	Functional Risk Analysis
HCP	Handover to Customer of Project equipment Files
HQP	High Qualified People
NDA	Non Disclosure Agreement

OA	Offers Analysis & Approvals
PCD	Preliminary Conceptual Design
POC	Purchase Orders & Contracts
QAP/S	Quality Assurance Plan / Sheet (FAQ)
RA	Risk Assessment & Analysis
SAT	Site Acceptance Tests
TFP	Technical & Functional Program/Plan

TSC	Technical Specifications for Construction
TST	Technical Specifications for Tender (Plans & devis)
URS	User Requirements Specifications
VMP	Validation Master Plan
WDA	Workshop Drawings & Plans Approvals

C / O / V ranges
OOS vs Actions / ICH Q9

- Design conditions (±1*Sigma)
- Normal operating ranges set to achievable limits
- Alert Points (±2*Sigma)
- Action Points (±3*Sigma)
- OOS results recorded
- CAPA / GAPA / RAPA



Sigma = standard dev./1,128

BPF/ANSM/04-12-2013 &p59,15. Class ***C*** and ***D*** monitoring should be conducted in accordance with the principles of quality risk management. The requirements and the ***alert and action thresholds*** depend on the nature of the operations carried out, but the recommended cleaning times must be respected.

Validation activities

1. Equipment design specifications
2. ZAC
3. List of reagents and cell cultures
4. Equipment preparation

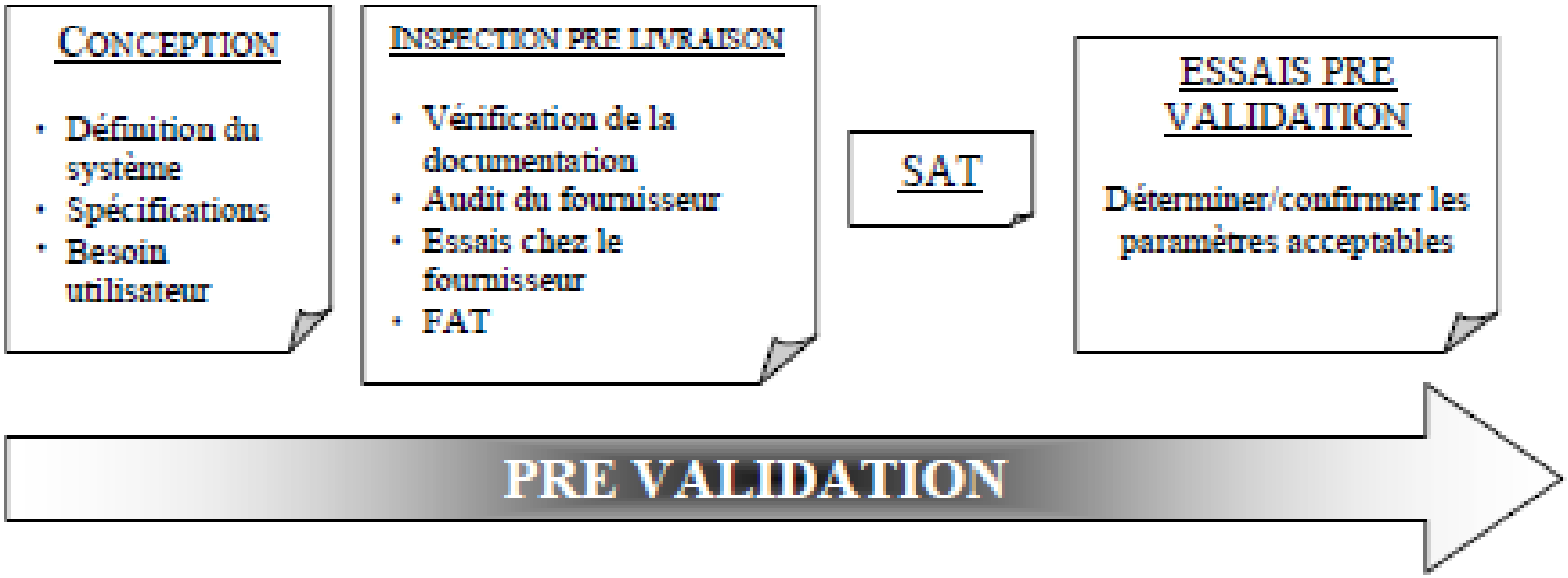
Cleaning/CIP, Passivation, Sterilization/SIP

5. Preparation of reagents
6. Production process (PFD, P&ID, …)
   - sampling, controlled conditions…
   - Methodology, Analytical Tests & Methods

Pharmaceutical Risk Management

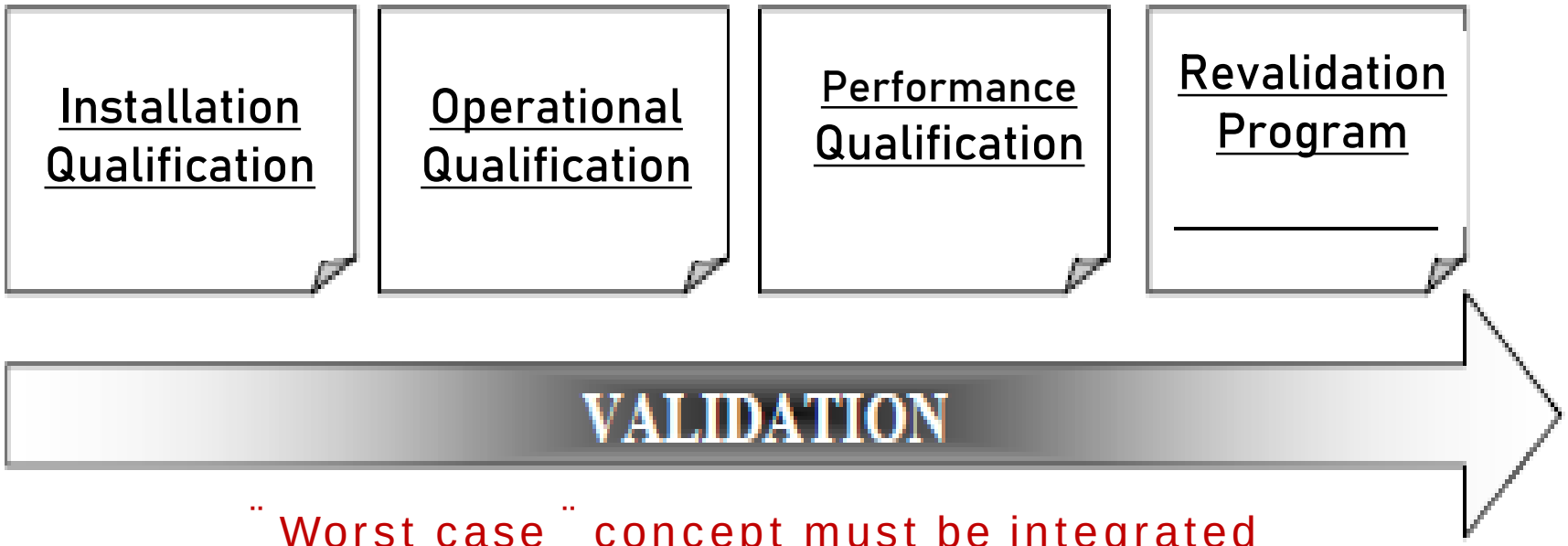
Approach to risk analysis

1- Criticality analysis determines which qualification tests to perform during validation



Approach to risk analysis

Any equipment defined as critical will have to pass all the qualification tests (IQ, OQ, PQ):



¨ Worst case ¨ concept must be integrated

CASE STUDY 1 – Process Validation Strategy

Process Validation Strategy

RISK ANALYSIS WORKSHOP
GRANULATION

RISK ANALYSIS WORKSHOP CLEAN UTILITIES

RISK ANALYSIS WORKSHOP – CLEAN UTILITIES

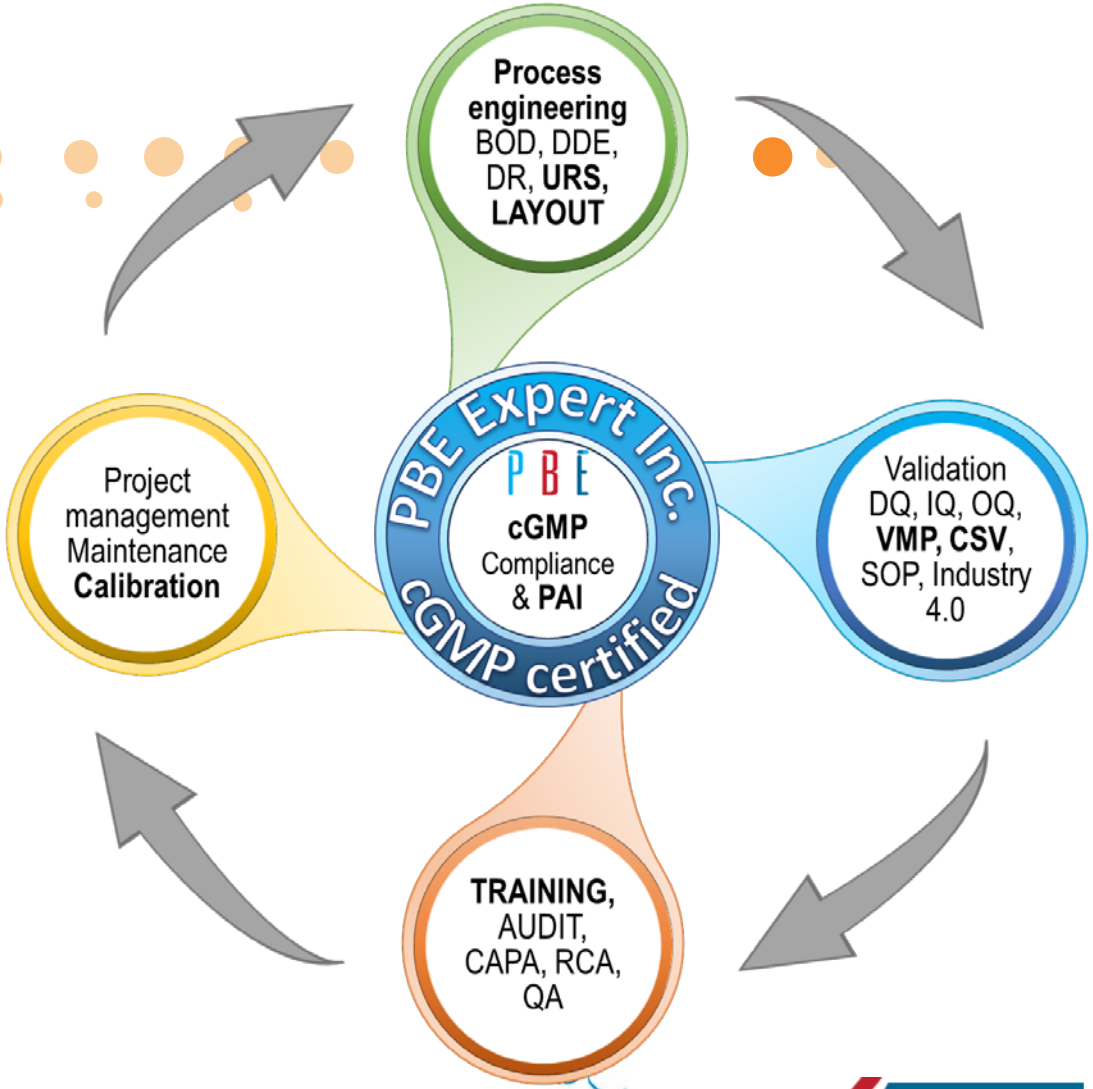
CLEAN UTILITY	GROUPE N.
1- PW	GROUP 1
2- PURE STEAM	GROUP 2
3- CIP	GROUP 3
4- CLEAN COMPRESSED AIR	GROUP 4
5- WFI	GROUP 5

RISK ANALYSIS WORKSHOP
LYOPHILIZER

RISK ANALYSIS WORKSHOP EXTREME ENVIRONMENTS LAYOUTS

RISK ANALYSIS WORKSHOP
EXTREME ENVIRONMENTS LAYOUT

PRODUCTION	GROUP N.
1- MONO-PRODUCT OSD / FL / FP / FSP	GROUP 1
2- MULTI-PRODUCTD OSD - RH < 15%	GROUP 2
3- MONO-PRODUC OSD – HP5	GROUP 3
4- MULTI-PRODUCTS OSD – HP5	GROUP 4
5- STERILE INJECTABLES	GROUP 5
6- STERILE INJECTABLE UNIT HP5	GROUP 6



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