PBE PharmaBio EXPERT cGMP

EXPERT
SANTÉ CANADA
MAPAQ

# PROCESS VALIDATION
# ANSM 2015
# FDA 2011

*PBE-Expert Inc – CANADA*

*Training Company Agreement CPMT #0059104*

***Qualified MAPAQ Consultant***

***At the measure 2 of the Levier Program***

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# 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)

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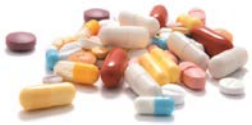

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# Training objectives / PV

1. How can the new requirements be met?
2. How to meet FDA & EMA requirements?
3. How to demonstrate knowledge and comprehension of process based on product and process development studies?
4. When is the process considered validated?
5. What parameters can be used to support process knowledge and comprehension studies?
6. How can "continuous process verification" be achieved?
7. How can statistical analysis be used in the new PV approach?

# Training objectives / PV

1. Update the Validation Master Plan (VMP).
2. Implement the new 3-step process validation approach.
3. Through several practical examples, develop expertise in process knowledge.
4. Highlight the critical parameters of some processes.
5. Focus on the development of PFD, PCP, CQAs, URS & P&ID according to the QBD, ICH Q8 Approach.
6. Develop the control strategy according to the ICH Q9 approach.
7. Run the performance qualification process from commissioning to qualification through a cascading "funnel" process via ICH Q9 (FAT, SAT, IQ, OQ, PQ)
8. Evaluate process capability through statistical analysis of data
9. Ensure continuous verification of process performance on a periodic basis based on the results of the previous point
10. Implement preventive and corrective actions at the process level (step 1)

# Training objectives / PV

1. Understanding of process validation (PV).
2. Reduce the number of routine tests.
3. Ensure product quality.
4. Ensure repeatability of performance.
5. Reduce the number of rejections.
6. Reduce start-up times.
7. Reduce malfunction management times.
8. New approach to PV according to FDA and ANSM.

# HISTORY OF PROCESS VALIDATION GUIDES UPDATES

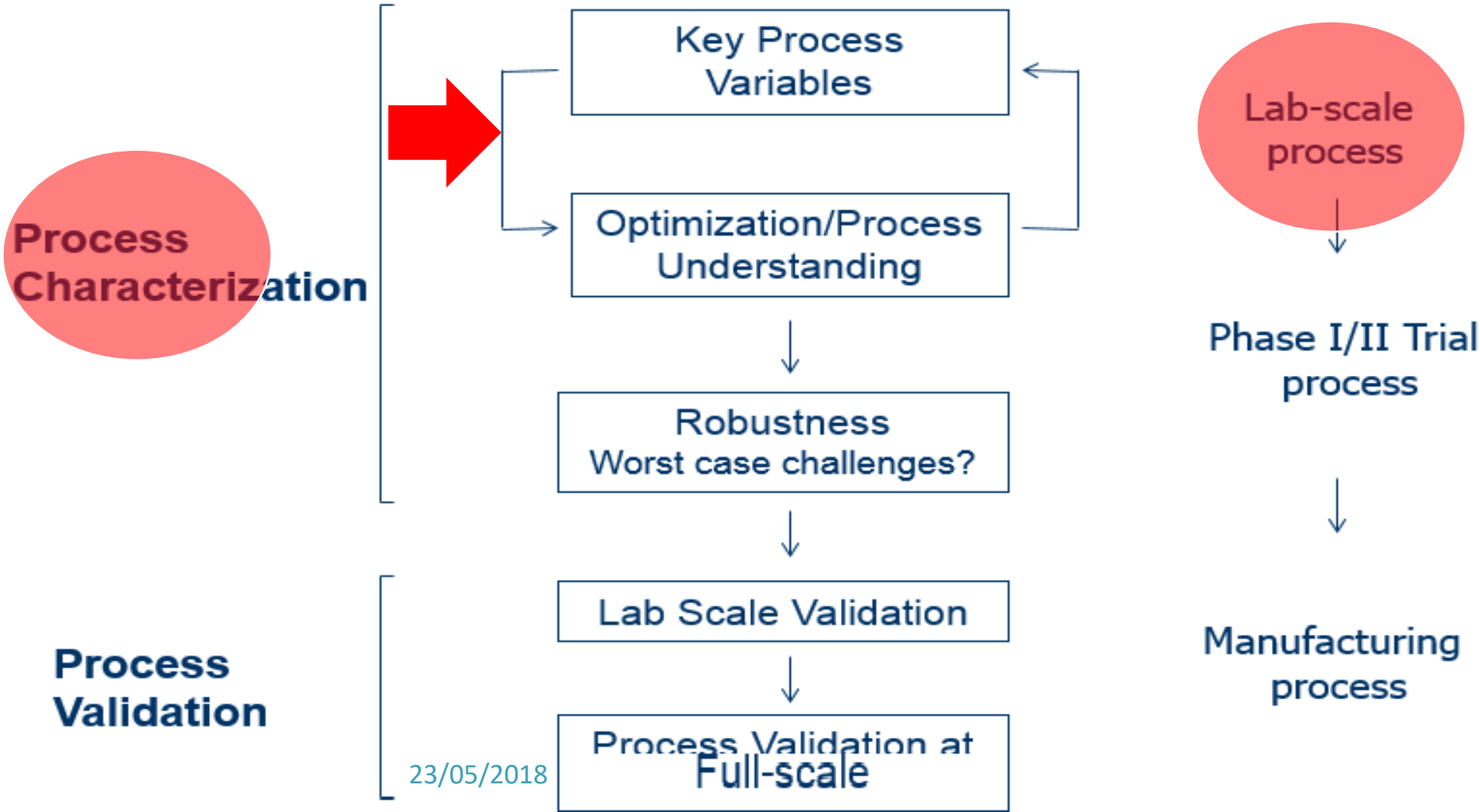
# History of process validation guides updates

- 2004 – Health Canada guidance
- 2005 – FDA initial presentations
- 2007 – ICH Q10
- 2008 – FDA draft guidance
- 2009 – ICH Q8(R2)
- 2009 – Health Canada revision
- 2011 – FDA guidance issued
- 2012 – EMA draft guidance
- 2014 – EMA Guide

# History of process validation guides updates

| | |
|---|---|
| Draft agreed by CHMP / CVMP Quality Working Party | 2 February 2012 |
| Adoption by CVMP for release for consultation | 8 March 2012 |
| Adoption by CHMP for release for consultation | 15 March 2012 |
| End of consultation (deadline for comments) | 31 October 2012 |
| Agreed by QWP | 8 November 2013 |
| Agreed by BWP | 13 November 2013 |
| Adoption by CHMP | 19 December 2013 |
| Adoption by CVMP | 15 January 2014 |
| Date for coming into effect | 6 months after publication |

# History of process validation guides updates



# Why such an update of FDA & EMA guides?

"Focusing exclusively on qualification efforts without understanding the manufacturing process and associated variations may not lead to adequate assurance of quality."

Poor quality drugs on the market, evidenced by **RECALLS**, complaints and other indicators, from supposedly "validated" processes pointed to a lack of process understanding and adequate process control. This was an impetus (drive) for revising the 1987 Guideline.

# TOP 10 common errors in PV

## Before PV:

1. **In**_____ Protocoles
2. Non-com_____ approach to new requirements (FDA & ANSM)
3. Absence of **CP__, CQ__, SD__, CP__…**
4. Inability to formally **qua**_____ the equipment.
5. Inadequate **rob** _____ studies

# TOP 10 common errors in PV

## DURING PV:

1. Management of **dev**_____ in protocols.
2. Un**qua**_____ staff to perform PV.
3. Insufficient control of **pro**_____, critical equipment and clean utilities.
4. Inadequate monitoring of **val**_____ by contracted production laboratories.

# TOP 10 common errors in PV

## AFTER PV:

1. Validation Reports **Def**_____
2. Lack of monitoring and **ten**_____ in the PV method.
3. Absence of an efficient PV **mai**_____ system.

# Regulatory References

- **Regulatory requirements for Process Validation**

- **Guideline on process validation for finished products - information and data to be provided in regulatory submissions**
- 21 CFR part 820 QSR
- 21 CFR part 211
- ICH Q10: PQS and Lifecycle
- EU Annex 15 and EU PV Guideline March 2012
- FDA process validation guide January 2011
- GHTF Guidance, 2004
- Inspectional observations and expectations

# Regulatory References

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 February 2014

Guideline on process validation for finished products - information and data to be provided in regulatory submissions

# New PV / EMA 2015

# New PV / EMA 2015

- This guideline replaces the previous note for guidance on process validation (CPMP/QWP/848/96, EMEA/CVMP/598/99).
- The guideline is brought into line with ICH Q8, Q9 and Q10 documents and the possibility to use continuous process verification in addition to, or instead of, traditional process validation described in the previous guideline has been added and is encouraged.
- This guideline does not introduce new requirements on medicinal products already authorised and on the market, but clarifies how companies can take advantage of the new possibilities given when applying enhanced process understanding coupled with risk management tools under an efficient quality system as described by ICH Q8, Q9 and Q10.

# New PV / EMA 2015

Process validation should not be viewed as a one-off event.

Process validation incorporates a LIFECYCLE APPROACH linking :

1. Product.
2. PROCESS **KNOWLEDGE** & development.
3. **VALIDATION** of the commercial manufacturing PROCESS.
4. **MAINTENANCE** of the PROCESS in a state of control during routine commercial production.

# Objectives of PV in GMP / EMA / ANSM - 2013

# PROCESS VALIDATION ANSM 02/27/2014

# PROCESS VALIDATION ACCORDING TO HEALTH CANADA GUIDELINES -01 & -029

# VALIDATION ACCORDING TO FDA (2011 Guide)

# CASE STUDY
# WHO
# Synthesis

# NEW APPROACH TO PROCESS VALIDATION

# New PV/ EMA 2015

| ICH Q8 | ICH Q9 | ICH Q10 | ICH Q11 | ICH Q12 |
|---|---|---|---|---|
| | | | | |
| | | | | |

# QBD (quality by design) def.?

Labeled Use
Safety and Efficacy

DEFINE Quality
Target Product Profile

DESIGN Formulation
and Process

IDENTIFY Critical Material Attributes
and Critical Process Parameters

CONTROL Materials
and Process

ICH-Q9

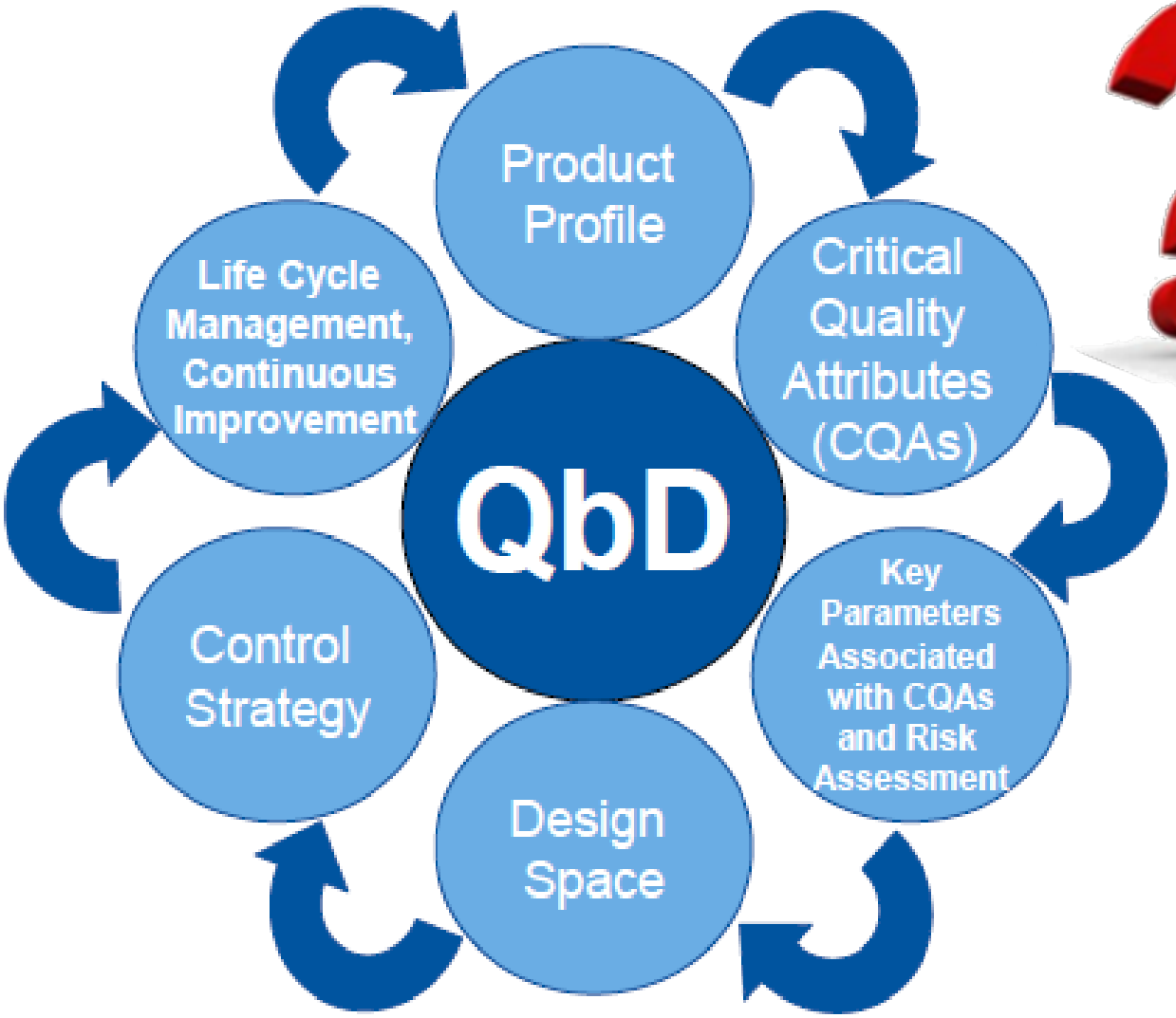
URS

CONTROL

DESIGN

TARGET → DESIGN → IMPLEMENTATION

# NEW PV / EMA 2015




ICH Q8(R2) Pharmaceutical Development; ICH Q9 Quality Risk Management

# QUIZ ICH Q6 @ Q11 - GR.1

| TERM | EXPLANATION | SOURCE |
|---|---|---|
| Acceptance criteria | Numerical limits, ranges, or other suitable measures for acceptance which the drug substance or drug product or materials at other stages of their manufacture should meet to conform to the specification for analytical procedures. | |
| Action limits | An action limit is an internal (in-house) value used to assess the consistency of the process at less critical steps. These limits are the responsibility of the manufacturer. | |
| Batch Release (BR) | The process by which the product is tested and results reviewed to ensure product quality under cGMP regulations and guidelines. | |
| Capability of a Process (Ppk) | Ability of a process to realise a product that will fulfil the requirements of that product. The concept of process capability can also be defined in statistical terms via the process performance index Ppk or the process capability index Cpk (ISO 9000:2005). | |
| Control Strategy | A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. | |
| Critical | Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification. | |

# QUIZ ICH Q6 @ Q11 - GR.2

| TERM | EXPLANATION | SOURCE |
|---|---|---|
| Critical Material Attribute (CMA) | A material attribute, whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. | |
| Critical Process Parameter (CPP) | A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality | |
| Critical Quality Attribute (CQA) | A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. | |
| Design Space | The multidimensional combination and interaction of input variables (eg, 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. | |
| Detect-ability | The ability to discover or determine the existence, presence, or fact of a hazard. Detect-ability is a component of a Failure Modes Effects Analysis (FMEA). | |

# QUIZ ICH Q6 @ Q11 - GR.3

| TERM | EXPLANATION | SOURCE |
|---|---|---|
| Failure Modes Effects Analysis (FMEA) | One of the first systematic techniques for failure analysis. It was developed by reliability engineers in the 1950s to study problems that might arise from malfunctions of military systems. A FMEA is often the first step of a system reliability study. It involves reviewing as many components, assemblies, and subsystems as possible to identify failure modes, and their causes and effects. For each component, the failure modes and their resulting effects on the rest of the system are recorded in a specific FMEA worksheet. There are numerous variations of such worksheets. | |
| Impurity | Any component present in the drug substance or drug product that is not the desired product, a product-related substance, or an excipient (including added buffer components). It may be either process- or product-related. | |
| In-Process Control (IPC) | Checks performed during production in order to monitor and if necessary to adjust the process and/or to ensure that the intermediate or API conforms to its specifications. | |
| In-process tests | Tests which may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal battery of tests which are conducted prior to release. | |
| Intermediate | For biotechnological/ biological products, a material produced during a manufacturing process that is not the drug substance or the drug product but for which manufacture is critical to the successful production of the drug substance or the drug product. | |

# QUIZ ICH Q6 @ Q11 - GR.4

| TERM | EXPLANATION | SOURCE |
|---|---|---|
| Key Process Attribute (KPA) | It is important not to confuse a KPA, which is a measure of process consistency with measures of quality such as CQAs. ***N.B.*** *at the time of writing, the European Medicines Agency (EMA) draft guidance on Process Validation is out for consultation, referring to KPAs as 'performance indicators*'. | |
| Key Process Parameter (KPP) | An adjustable parameter (variable) of the process that, when maintained within a narrow range, ensures optimum process performance. A key process parameter does not meaningfully affect critical product quality attributes. this category of parameter is not recognized by the FDA or the EMA for use in formal submissions and reports, though they do not oppose its use internally. The agencies see all parameters that may have an impact on CQAs as Critical and hence CPPs | |
| Knowledge Management | Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components. | |
| Performance Indicators | Measurable values used to quantify quality objectives to reflect the performance of an organisation, process or system, also known as —performance metrics in some regions. | |
| Pharmaceutical Quality System (PQS) | Management system to direct and control a pharmaceutical company with regard to quality. | |

# QUIZ ICH Q6 @ Q11 - GR.5

| TERM | EXPLANATION | SOURCE |
|---|---|---|
| Potency | Potency is the measure of the biological activity using a suitably quantitative biological assay (also called potency assay or bioassay), based on the attribute of the product which is linked to the relevant biological properties. | |
| Process Analytical Technology (PAT) | A system for designing, analyzing, and controlling manufacturing through timely measurements (ie, during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. | |
| Process Control | See In-Process Control. | |
| Process Robustness | Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality. | |
| Process-related impurities | Impurities that are derived from the manufacturing process. They may be derived from cell substrates, culture (eg, inducers, antibiotics, or media components), or from downstream processing (eg, processing reagents or column leachables). | |

# QUIZ ICH Q6 @ Q11 - GR.6

| TERM | EXPLANATION | SOURCE |
|---|---|---|
| Product lifecycle | All phases in the life of a product from the initial development through marketing until the product's discontinuation. | |
| Product-related impurities | Product-related impurities are molecular variants of the desired product arising from processing or during storage (eg, certain degradation products) which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety. | |
| Proven Acceptable Range | A characterized range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria. | |
| Quality | The degree to which a set of inherent properties of a product, system or process fulfils requirements. | |
| Quality Attribute (QA) | A molecular or product characteristic that is selected for its ability to help indicate the quality of the product. Collectively, the quality attributes define the adventitious agent safety, purity, potency, identity, and stability of the product. Specifications measure a selected subset of the quality attributes. | |

# QUIZ ICH Q6 @ Q11 - GR.7

| TERM | EXPLANATION | SOURCE |
|---|---|---|
| Quality by Design | A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. | |
| Quality Control (QC) | Checking or testing, that specifications are met. | |
| Quality Target Product Profile (QTPP) | A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. | |
| Quality risk management | A systematic process for the assessment, control, communication, and review of risks to the quality of the drug product across the product lifecycle. | |
| Raw material & Reference standards/ materials | Raw material is a collective name for substances or components used in the manufacture of the drug substance or drug product. | |

# QUIZ ICH Q6 @ Q11 - GR.8

| TERM | EXPLANATION | SOURCE |
|---|---|---|
| Risk | The combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51). | |
| Statistical Process Control (**SPC**) | Statistical process control (SPC) is a method of quality control which uses statistical methods. SPC is applied in order to monitor and control a process. Monitoring and controlling the process ensures that it operates at its full potential. At its full potential, the process can make as much conforming product as possible with a minimum (if not an elimination) of waste (rework or Scrap). SPC can be applied to any process where the "conforming product" (product meeting specifications) output can be measured. Key tools used in SPC include control charts; a focus on continuous improvement; and the design of experiments. An example of a process where SPC is applied is manufacturing lines. | |
| Specification - Release | The combination of physical, chemical, biological and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release. | |
| Risk evaluation | The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk. | |

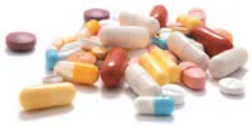
# QUIZ ICH Q6 @ Q11 - GR.9

| TERM | EXPLANATION | SOURCE |
|---|---|---|
| Risk analysis | The estimation of the risk associated with the identified hazards. | |
| Specification | A specification is a list of tests, references to analytical procedures, and appropriate acceptance criteria with numerical limits, ranges, or other criteria for the tests described, which establishes the set of criteria to which a drug substance or drug product or materials at other stages of their manufacture should conform to be considered acceptable for its intended use. | |
| Severity | A measure of the possible consequences of a hazard, which is a component of a Failure Modes Effects Analysis (FMEA). | |
| Risk assessment | A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. | |

# PROCESS VALIDATION PREREQUISITES

# PROCESS VALIDATION PREREQUISITES

C & Q



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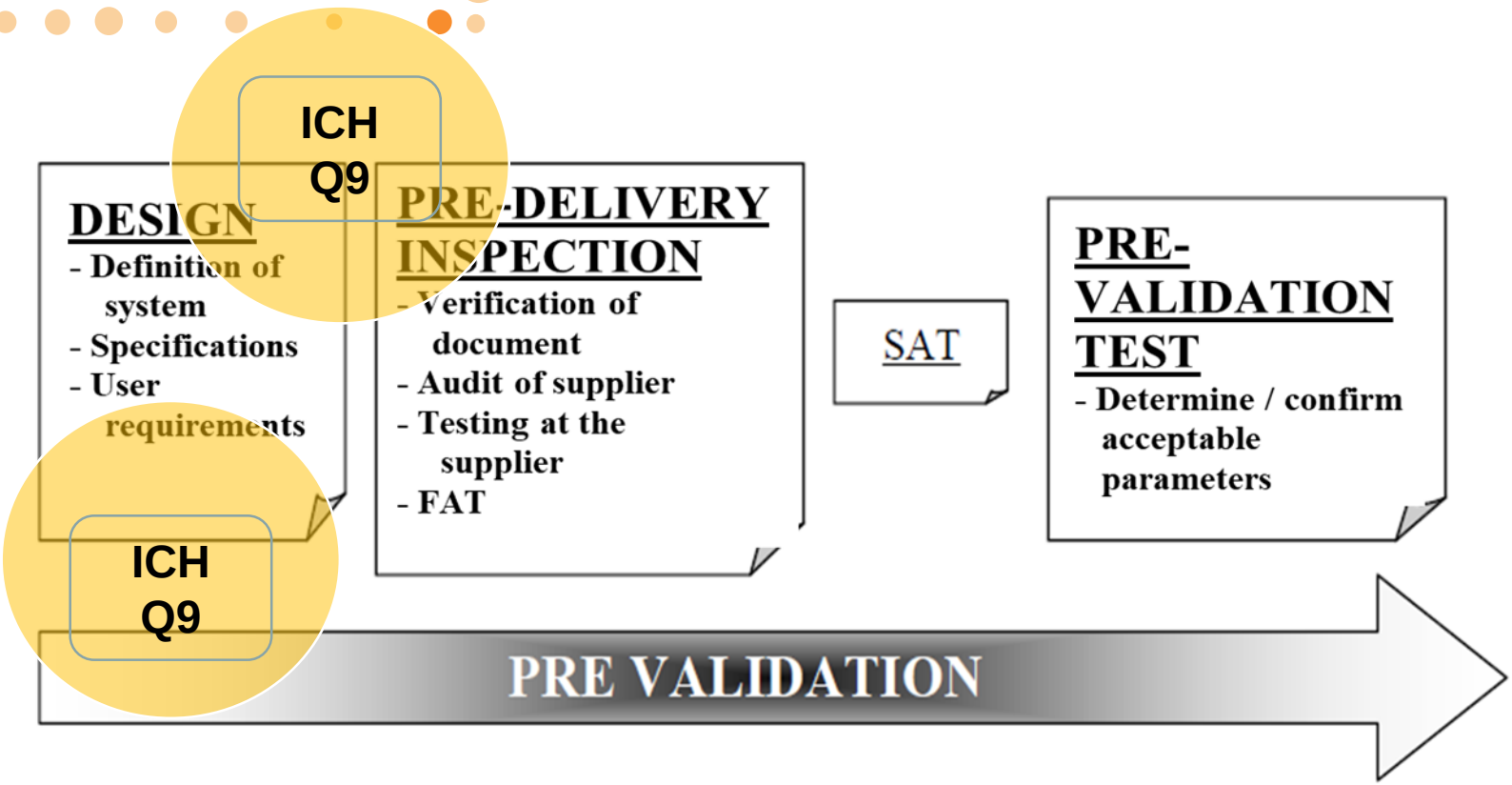
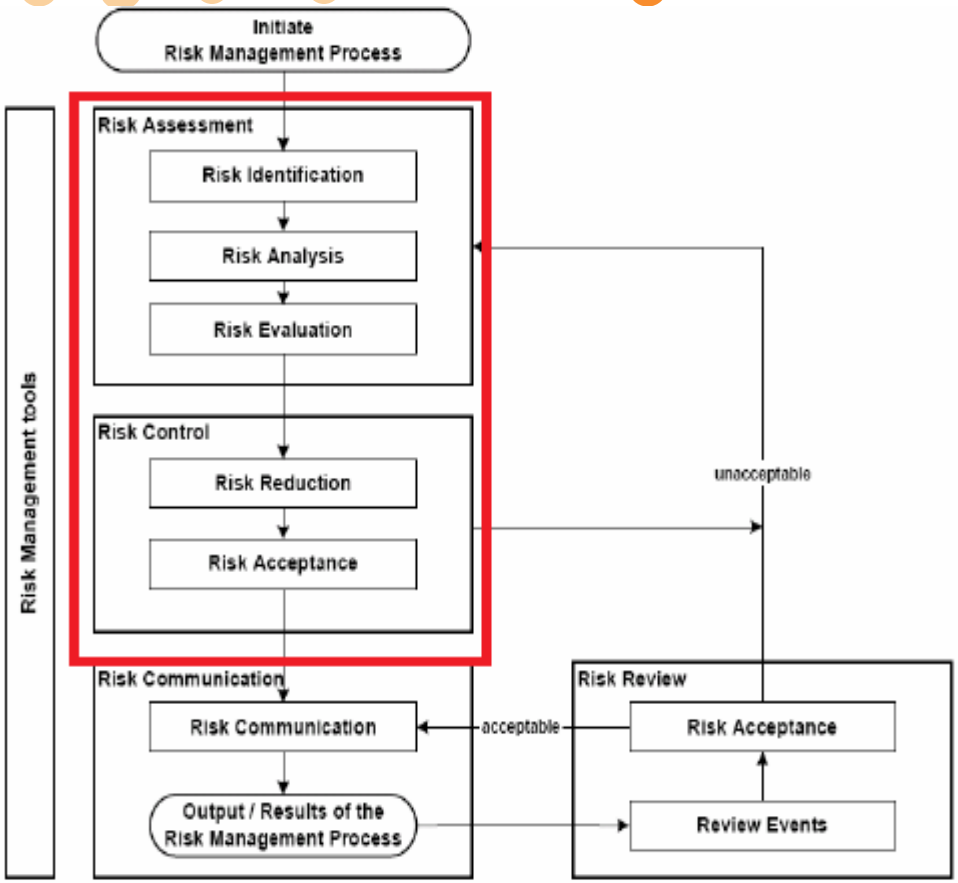
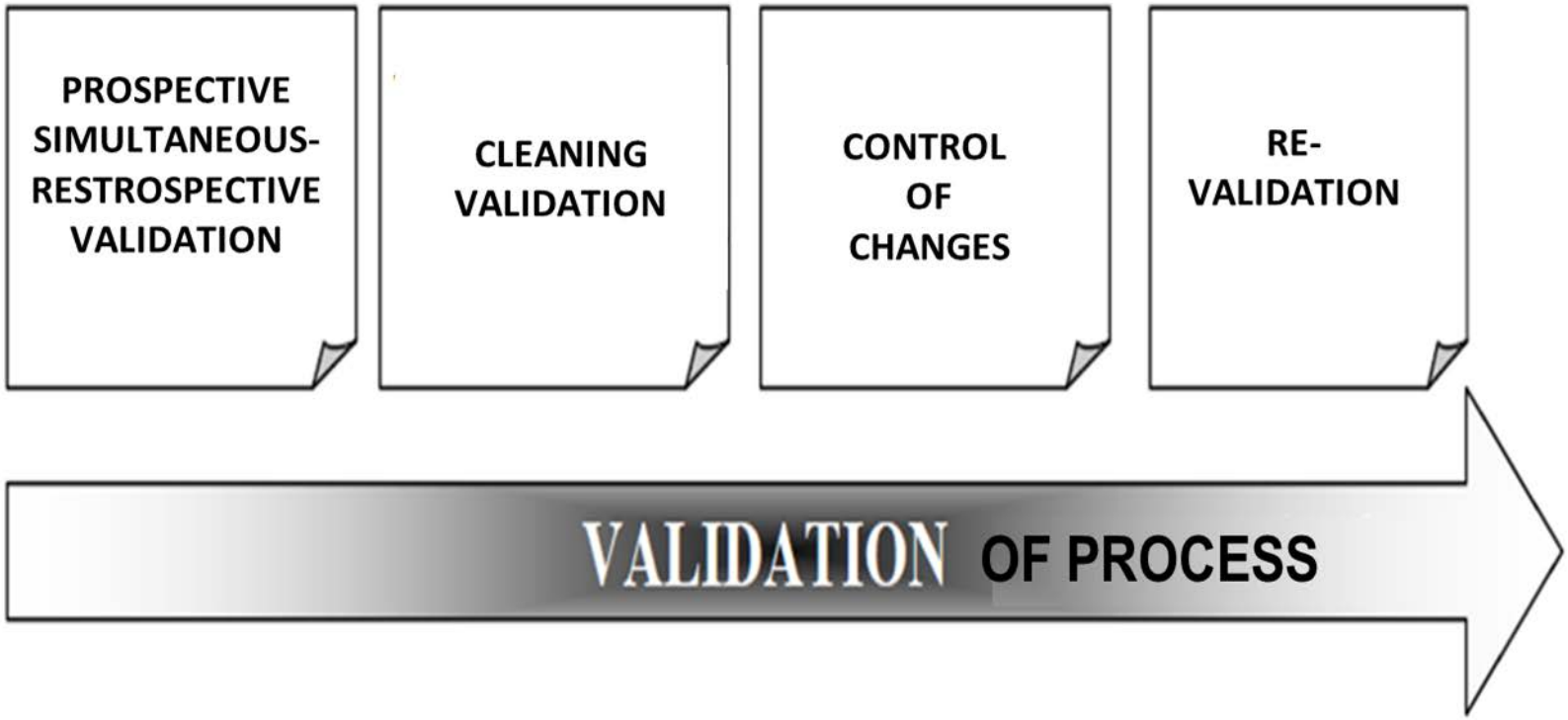


# PROCESS VALIDATION PREREQUISITES

**ICH Q9**



# PROCESS VALIDATION PREREQUISITES



# PROCESS VALIDATION PREREQUISTES

1. Calculation of the acceptance criterion

2. Production (weighing, manufacturing, packaging, ...) → Cleaning according to the procedure to be validated → Sample → Sample treartment → Estimated contamination → Real contamination

3. Residual contamination < Acceptance criteria

3 consecutive times

→ Validated method

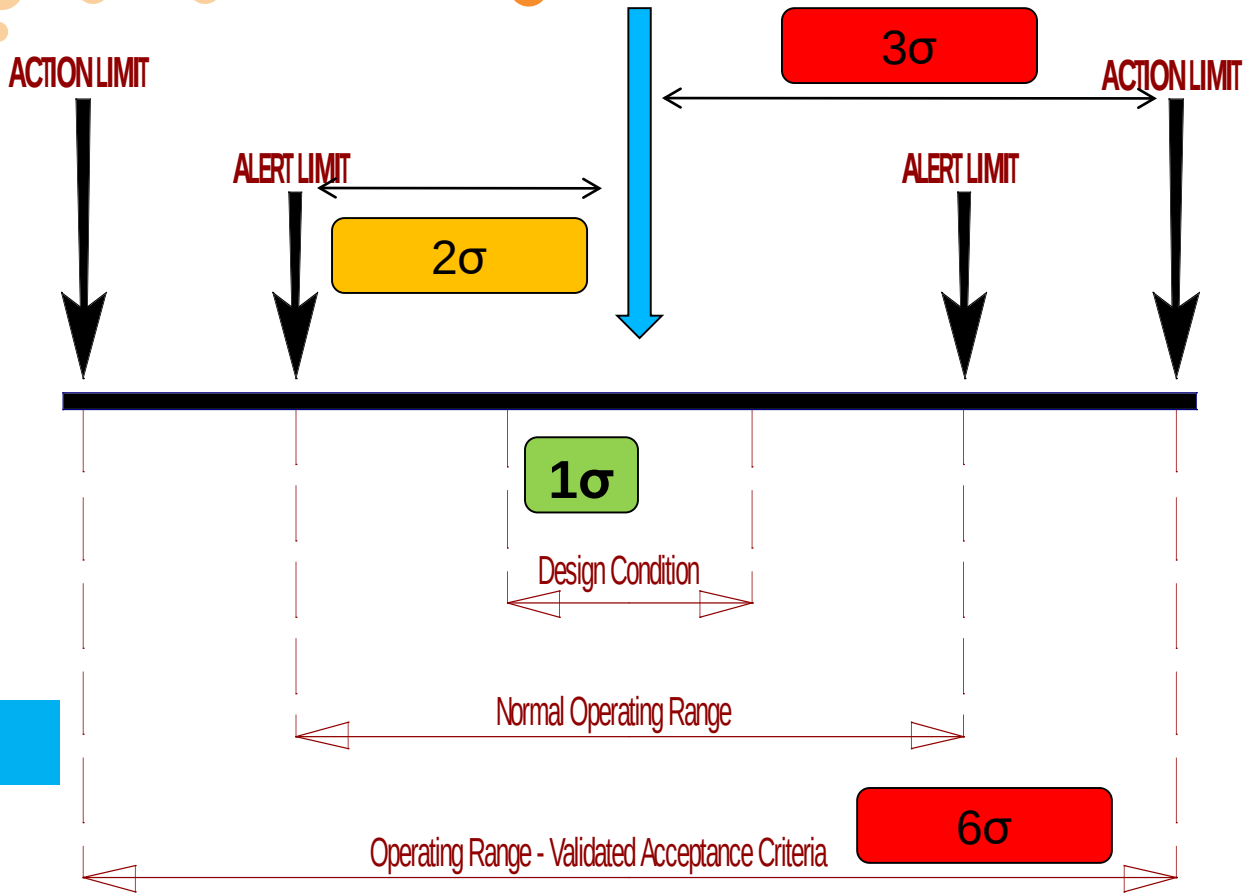
# Validated Factory, is it necessarily cGMP compliant?

# CPP & DIRECT/INDIRECT IMPACT

# CPP ~ PV / C&Q - 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*

***Sigma = std dev/1,128***




BPF/ANSM/04-12-2013 &p59,15. **C** and **D** class oversight should be conducted in accordance with quality risk management. Requirements and **alert/action thresholds** depend on the nature of operations but recommended purification time must be respected.

# PROCESS VALIDATION according to FDA 2011

# New PV / FDA Process

Following **QBD** principles



Following **QBD** principles

# New PV / FDA Process


# LIFE CYCLE APPROACH - PROCESS VALIDATION

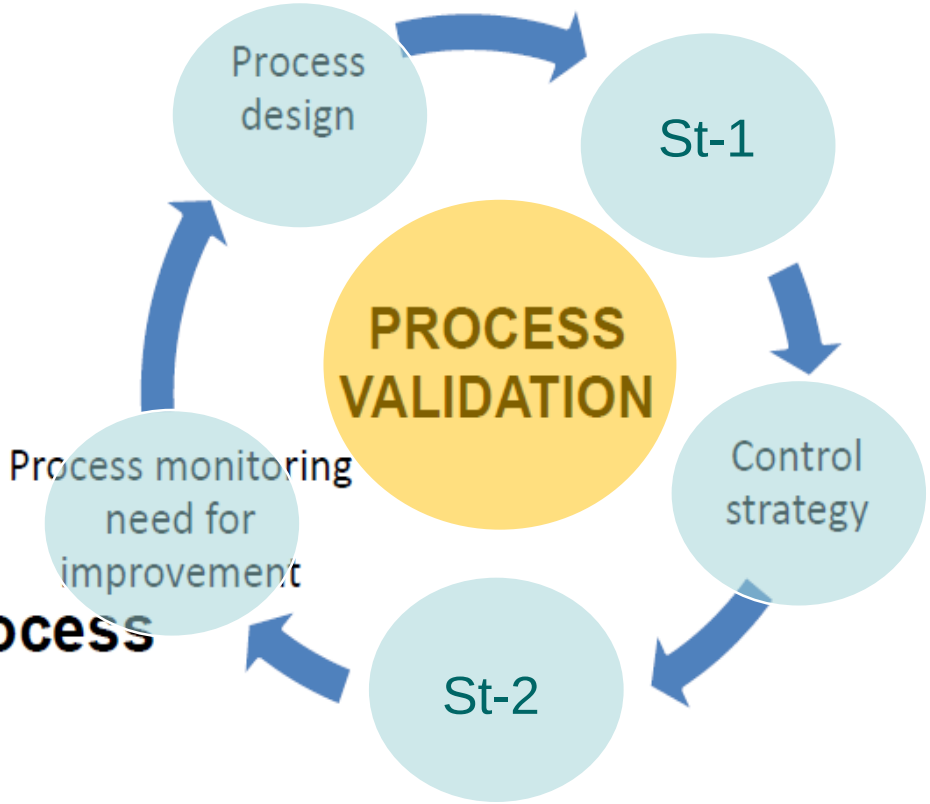
Q8

Q9

Q10

Q11

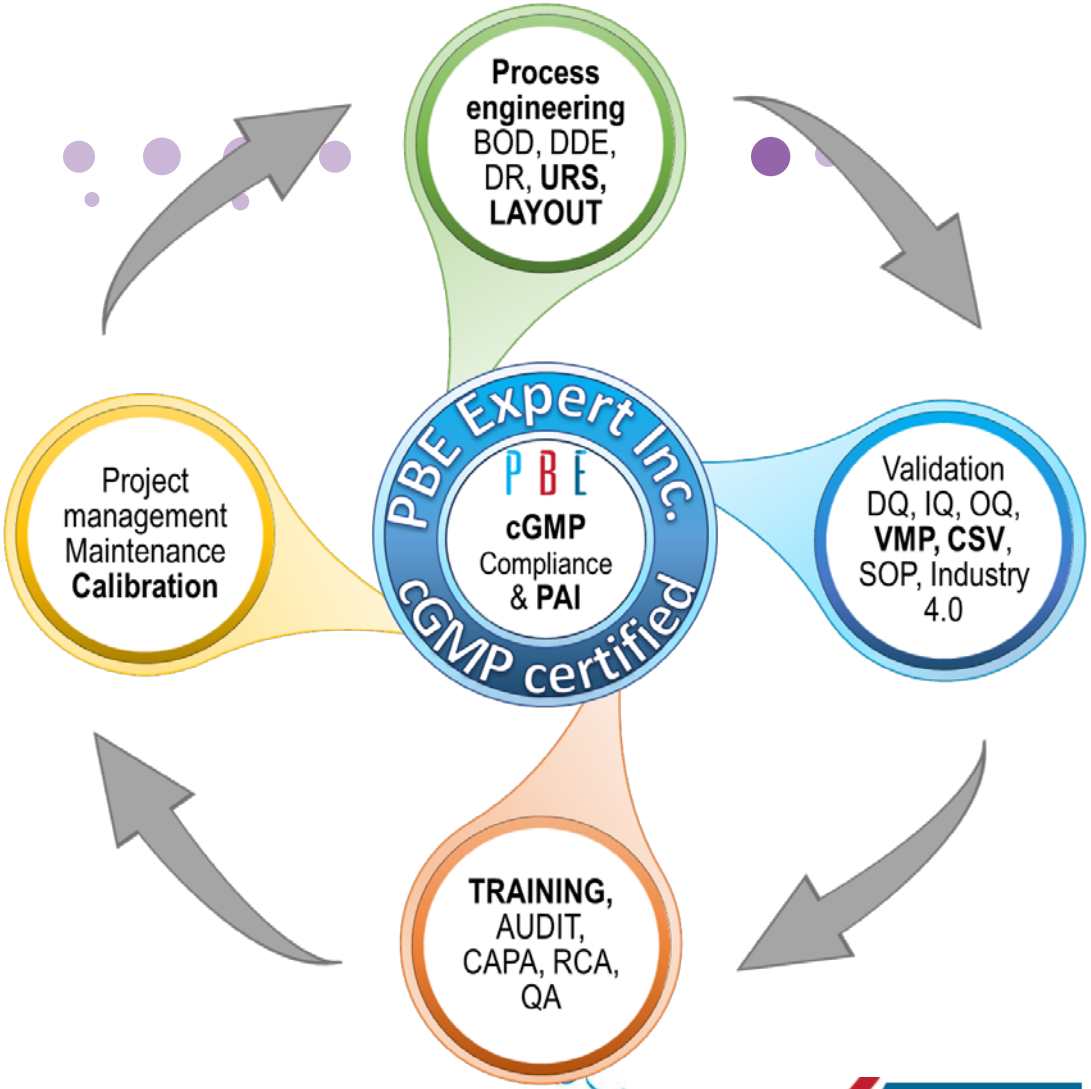
**Stage 1 process design**




**Stage 3 continued process verification**

**Stage 2 process qualification**

# CASE STUDIES

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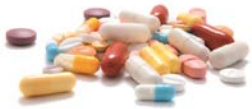


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