



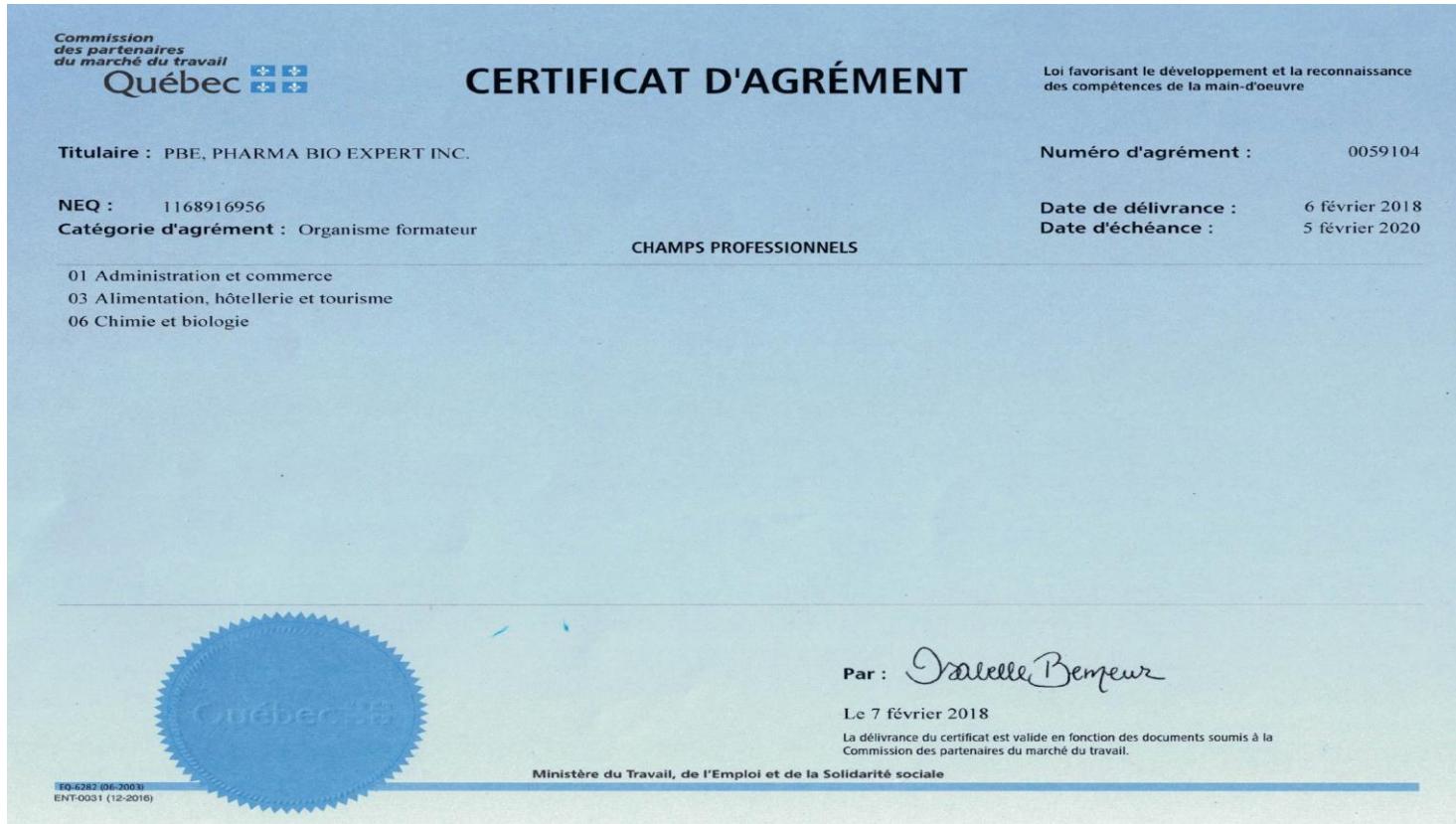
VALIDATION DES PROCÉDÉS ANSM 2015 FDA 2011

PBE-Expert Inc – CANADA
Organisme Formateur Agréé CPMT #0059104
Consultant Qualifié MAPAQ
à la mesure 2 du programme Levier

P B E
EXPERT



PBE, Organisme Formateur Agréé CPMT #0059104



Objectifs de la formation / VDP



- 1. Comment les nouvelles exigences peuvent être atteintes?
- 2. Comment répondre aux exigences de la FDA & de L'EMA?
- 3. Comment démontrer les connaissances et la compréhension des procédés sur la base des études de développement de produit et du procédé?



- 4. Quand maintenant le procédé est considéré validé?
- 5. Quels paramètres peuvent être utilisés pour étayer les études de connaissance et de la compréhension du procédé?
- 6. Comment peut être réalisé la "vérification continu des procédés"?
- 7. Comment l'analyse statistique peut être mise à contribution dans la nouvelle approche de VDP ?



Objectifs de la formation / VDP

-
- 1. Mettre à jour le plan directeur de validation (VMP).
- 2. Mettre en place la nouvelle approche de validation de procédé selon les 3 étapes.
- 3. À travers plusieurs exemples pratiques, développer de l'expertise dans la connaissance des procédés.
- 4. Mettre en évidence les paramètres critiques de quelques procédés.
- 5. Mettre l'accent sur le développement des PFD, PCP, CQAs, URS & P&ID selon l'Approche QbD, ICH Q8.
- 6. Développer la stratégie de contrôle selon l'approche ICH Q9.
- 7. Dérouler le processus de qualification des performances depuis le commissioning à la qualification selon un processus « entonnoir » en cascade via ICH Q9 (FAT, SAT, IQ, OQ, PQ)
- 8. Évaluer la capabilité du procédé via l'analyse statistique des données
- 9. Assurer une vérification continue des performances du procédé sur une base périodique selon les résultats du point précédent
- 10. Mettre en place des actions préventives et correctives au niveau du procédé (étape 1)



Objectifs de la formation / VDP



1. Compréhension de la validation de procédés (VDP).
2. Réduire le nombre des tests de routine.
3. Assurer la qualité du produit.
4. Assurer répétabilité des performances.
5. Diminuer le nombre de rejets.
6. Diminuer les temps de démarrage.
7. Réduire les temps de gestion des dysfonctionnements.
8. Nouvelle approche de VDP selon FDA et ANSM.





HISTORIQUE DES MISES À JOUR DES GUIDES DE VALIDATION DE PROCÉDÉS

• • • • •



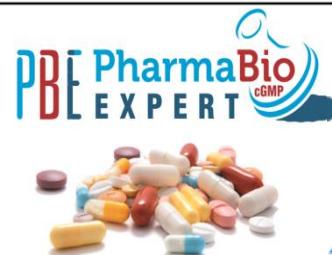
Historique des mises à jour des guides de validation de procédés

- • • • • • • • • •
 - 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
- • • • • • • • • •

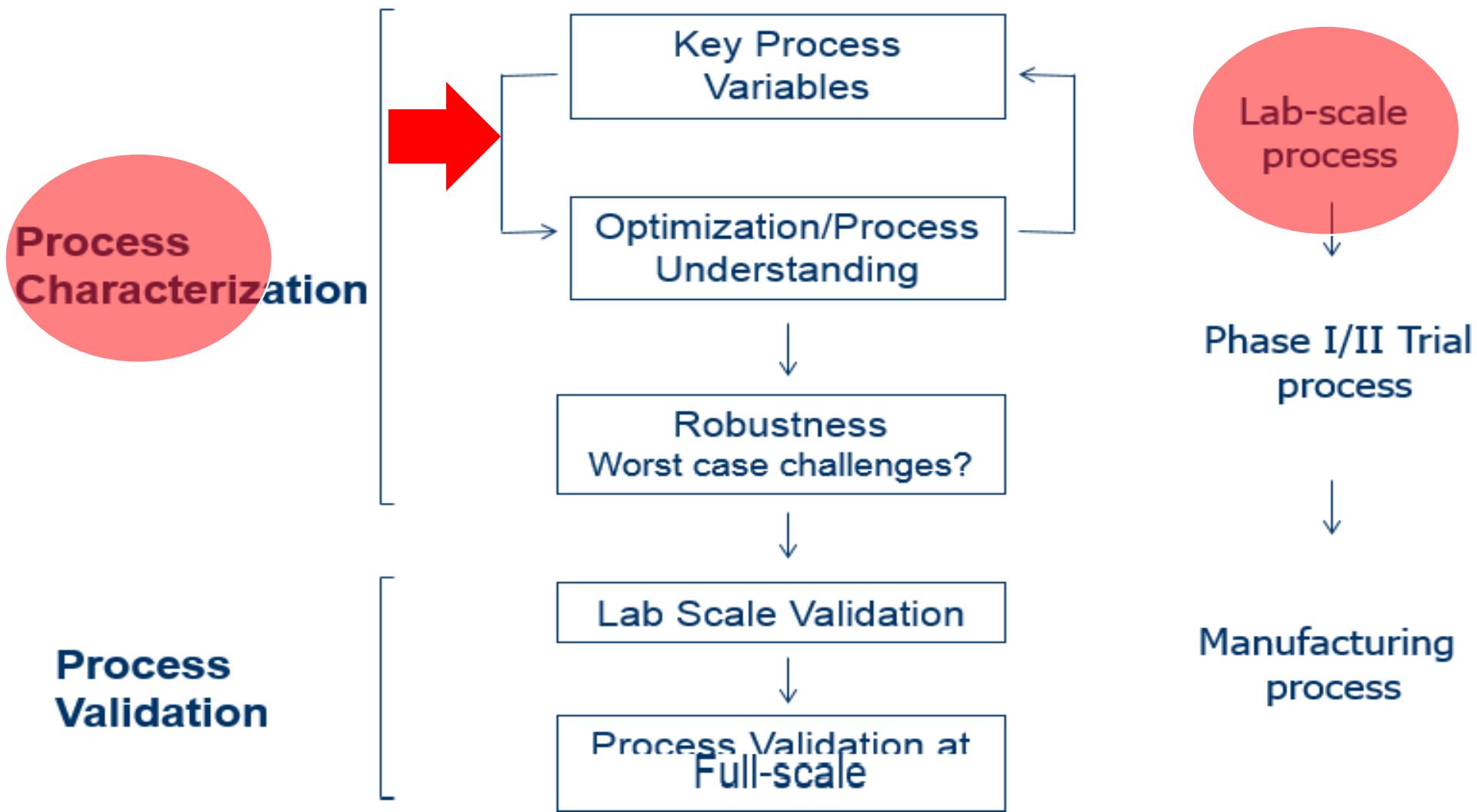


Historique des mises à jour des guides de validation de procédés

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



Historique des mises à jour des guides de validation de procédés



Pourquoi une telle mise à jour des guides FDA & EMA?

“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 des erreurs courantes en VDP



AVANT VDP:

1. Protocoles **ina**_____
2. Approche non **con**_____ aux nouvelles exigences
(FDA & ANSM)
3. Absence des **CP**__, **CQ**__, **SD**__, **CP**__...
4. Incapacité à **qua**_____ formellement l'équipement.
5. Études de **rob**_____ déficientes



TOP 10 des erreurs courantes en VDP



DURANT VDP:

1. Gestion des dév_____ dans les protocoles.
2. Personnel non qua_____ pour exécuter la VDP.
3. Maitrise insuffisante du pro_____, des équipements critiques et des utilités propres.
4. Surveillance inadéquate de la val_____ effectuée par des laboratoires de production en sous-traitance.



TOP 10 des erreurs courantes en VDP



APRÈS VDP:



1. Rapports de validation déf_____.
2. Absence de suivi et des ten_____ dans la méthode VDP.
3. Absence de système de mai_____ performants de la VDP.



Références Réglementaires

- **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



Références Réglementaires



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**



Nouvelle VDP / EMA 2015

• • • • • • • • • • • •	
4. General considerations	4
5. Process validation	4
5.1. Traditional process validation	4
5.2. Continuous process verification	5
5.3. Hybrid approach	6
5.4. Design space verification	7
6. Scale-up	7
7. Post approval change control	7
8. Standard vs. non-standard methods of manufacture	8
Definitions	8
References	10
Annex I: Process validation scheme	12
Annex II: Standard/non-standard processes	14



Nouvelle VDP / 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.



Nouvelle VDP / 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.





Objectifs de la VDP dans les BPF / EMA / ANSM - 2013



VALIDATION DES PROCÉDÉS ANSM 27/02/2014





VALIDATION DES PROCÉDÉS SELON SANTÉ CANADA GUIDES - 01 & -029



VALIDATION DES PROCÉDÉS SELON FDA (Guide 2011)





ÉTUDE DE CAS WHO - OMS Synthèse





NOUVELLE APPROCHE DE LA VALIDATION DES PROCÉDÉS



Nouvelle VDP / EMA 2015



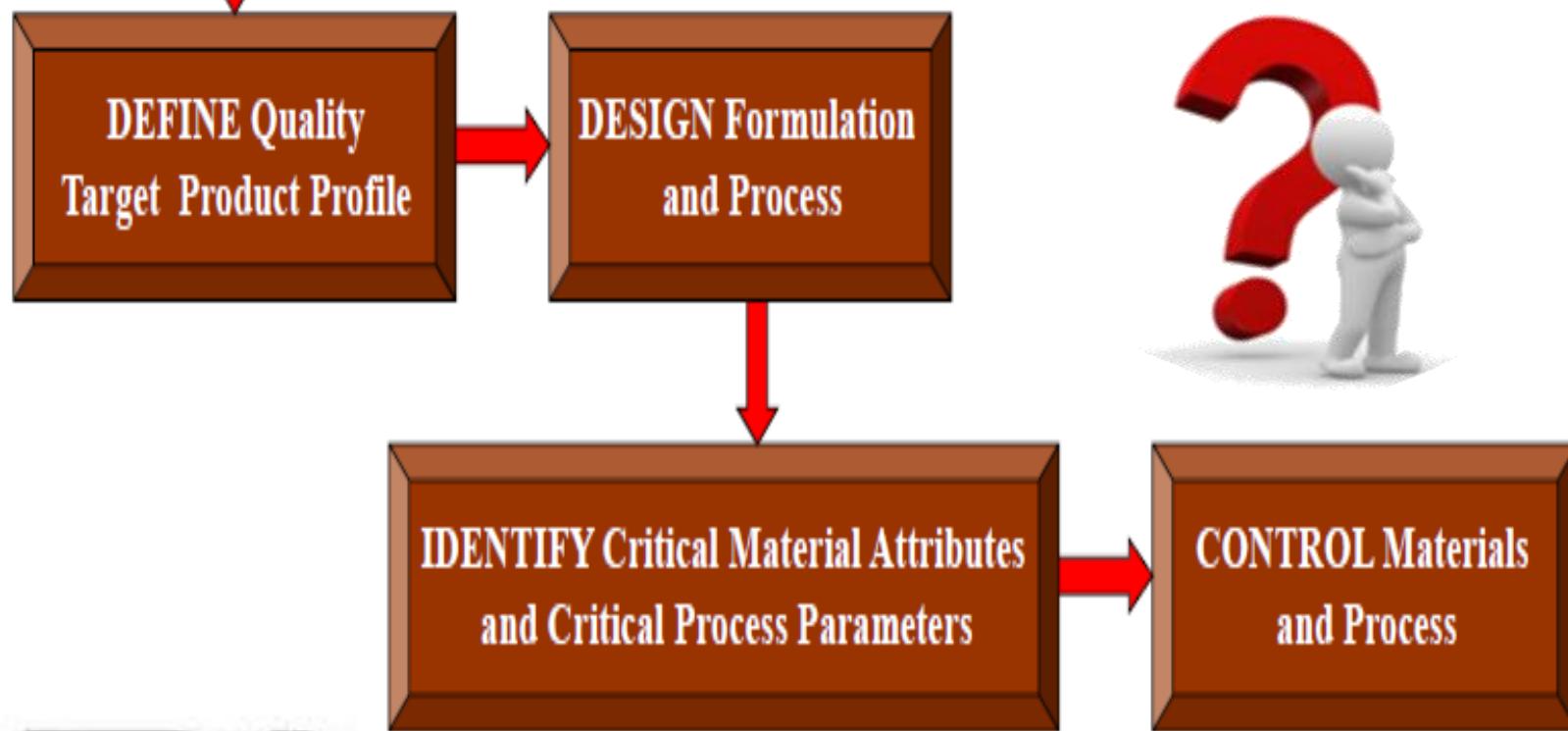
ICH Q8	ICH Q9	ICH Q10	ICH Q11	ICH Q12



Labeled Use
Safety and Efficacy

ICH-Q9

Définition de QBD ?



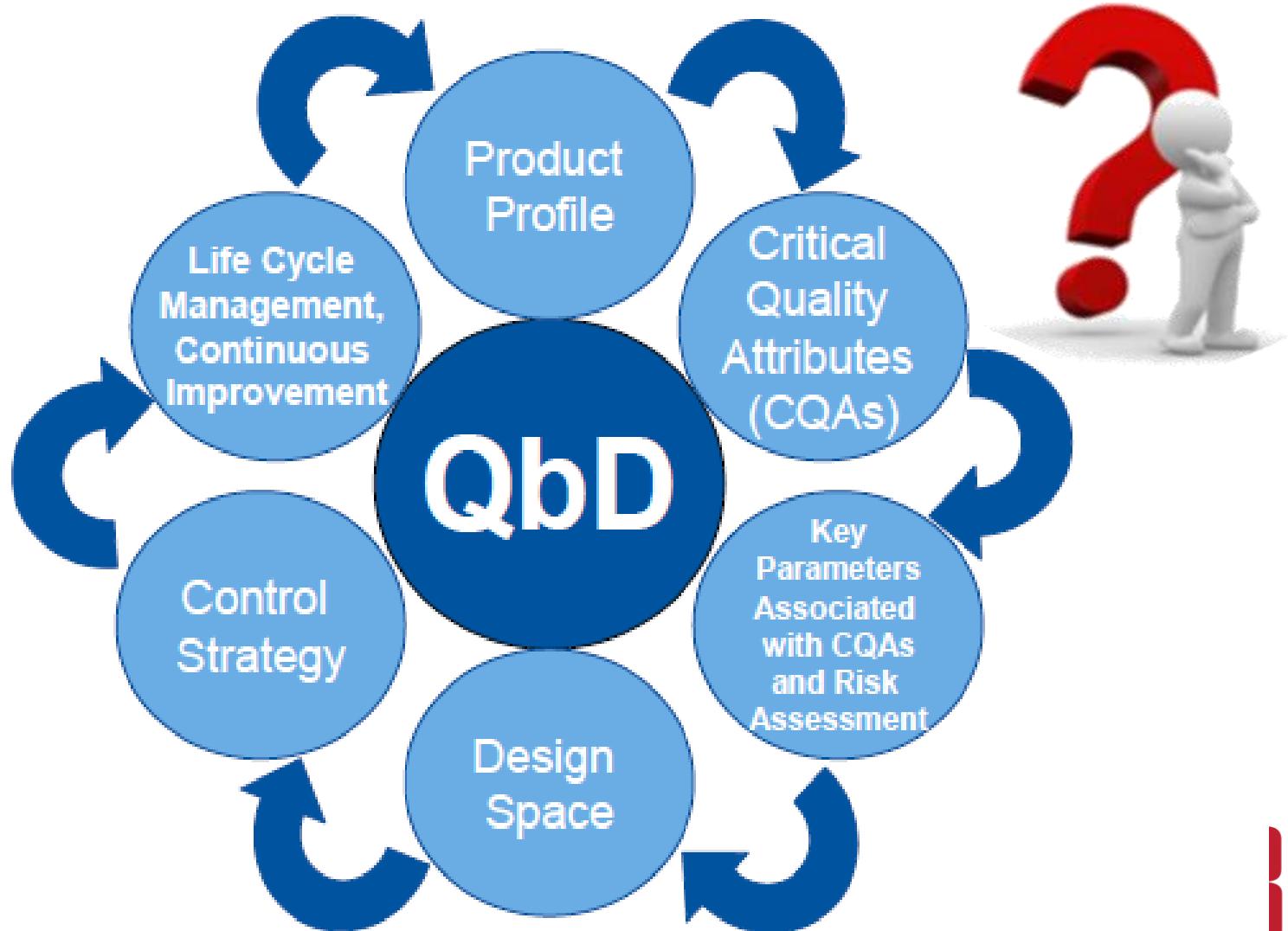
URS

CONTROL

DESIGN

TARGET —————> DESIGN —————> IMPLEMENTATION **X P E R T**

Nouvelle VDP / EMA 2015



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).	



E X P E R T

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)	<p>It is important not to confuse a KPA, which is a measure of process consistency with measures of quality such as CQAs. <i>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'.</i></p>	
Key Process Parameter (KPP)	<p>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</p>	
Knowledge Management	<p>Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components.</p>	
Performance Indicators	<p>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.</p>	
Pharmaceutical Quality System (PQS)	<p>Management system to direct and control a pharmaceutical company with regard to quality.</p>	

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 (Q TPP)	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.	



PRÉALABLES À LA VALIDATION DES PROCÉDÉS



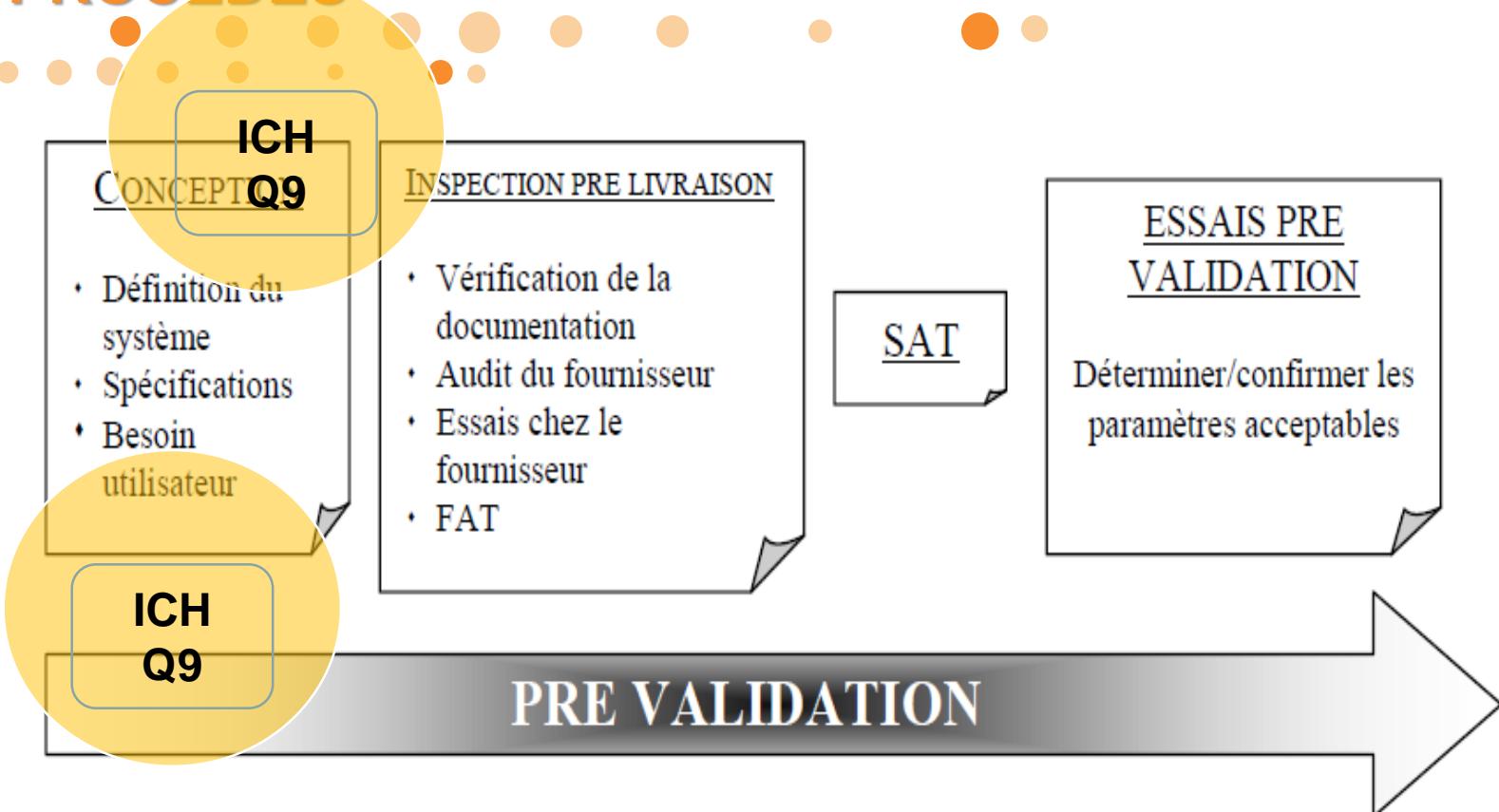
PRÉALABLES À LA VALIDATION DES PROCÉDÉS



C & Q



PRÉALABLES À LA VALIDATION DES PROCÉDÉS

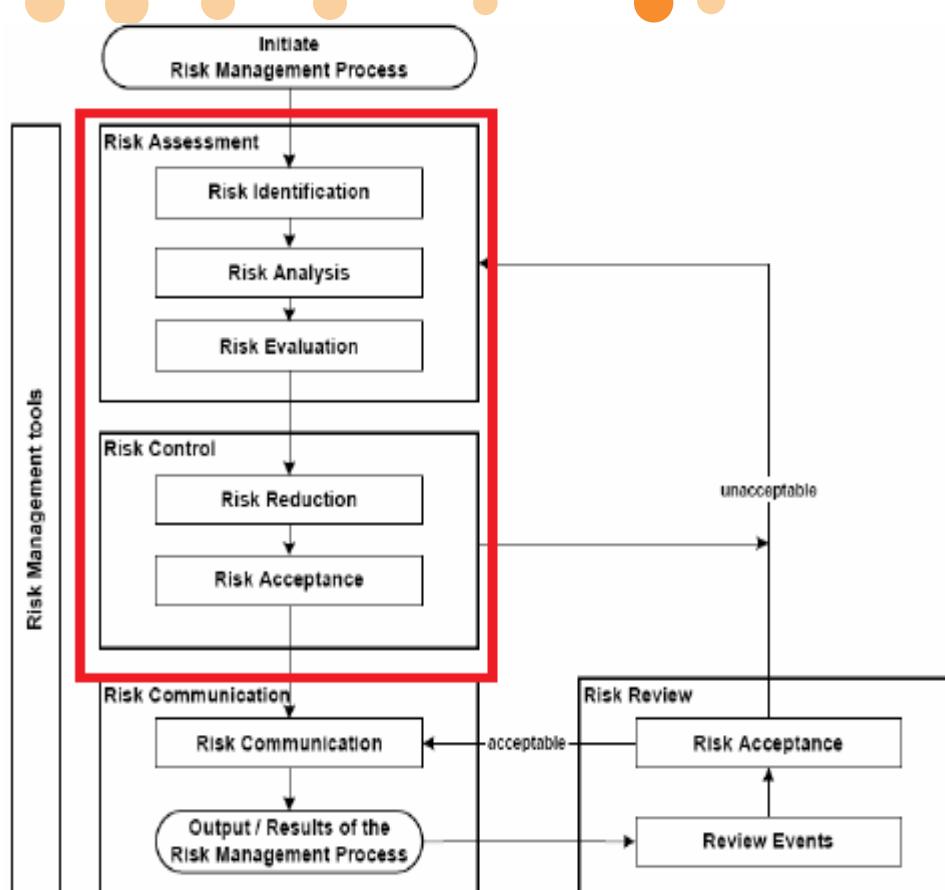


P B E
E X P E R T

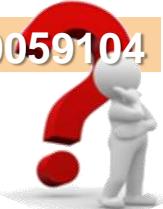
PRÉALABLES À LA VALIDATION DES PROCÉDÉS



ICH
Q9



PRÉALABLES À LA VALIDATION DES PROCÉDÉS



VALIDATION
PROSPECTIVE
SIMULTANÉE -
RÉTROSPECTIVE

VALIDATION
DE
NETTOYAGE

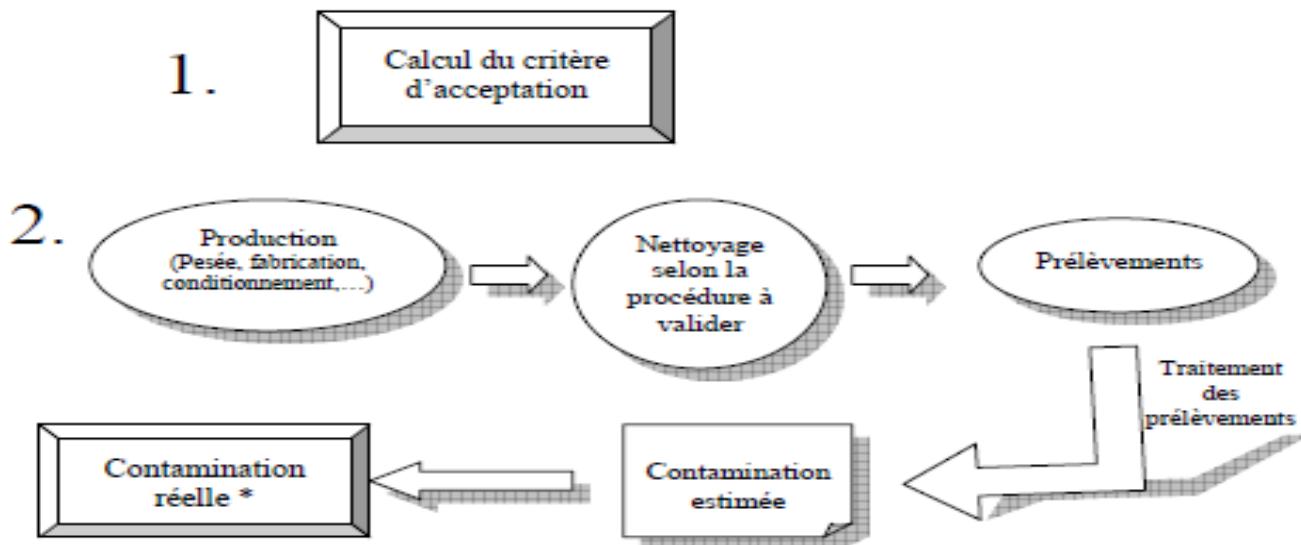
MAÎTRISE
DES
CHANGE-
MENTS

REVALI-
DATION

VALIDATION DE PROCÉDÉ



PRÉALABLES À LA VALIDATION DES PROCÉDÉS



3. Contamination résiduelle < Critère d'acceptation

3 fois consécutives

→ Méthode validée



P B E
EXPERT



Usine Validée est ce Obligatoirement Conforme BPF ?





CPP & IMPACT DIRECT / INDIRECT



CPP ~ VDP / C&Q - ICH Q9

- Design conditions ($\pm 1 \text{ *Sigma}$)

- Normal operating ranges set to achievable limits

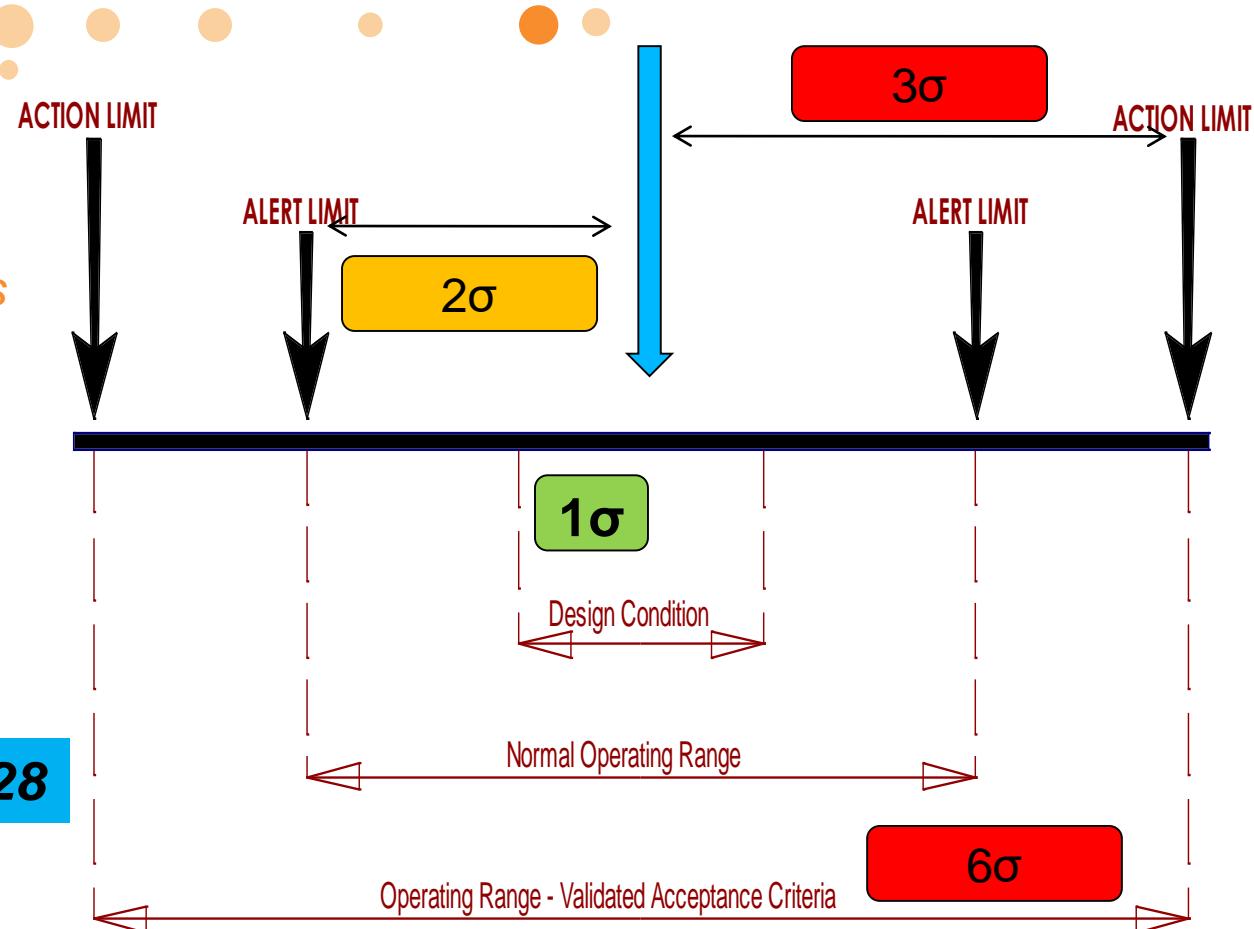
- Alert Points ($\pm 2 \text{ *Sigma}$)

- Action Points ($\pm 3 \text{ *Sigma}$)

- OOS results recorded

- CAPA

Sigma = écart type/1,128



BPF/ANSM/04-12-2013 &p59,15. La surveillance des classes **C** et **D** en activité doit être réalisée conformément aux principes de gestion des risques qualité. Les exigences et les **seuils d'alerte et d'action** sont fonction de la nature des opérations réalisées, mais les temps d'épuration recommandés

VALIDATION DES PROCÉDÉS selon FDA 2011



Nouveau Processus de VDP / FDA

Selon principe du QBD



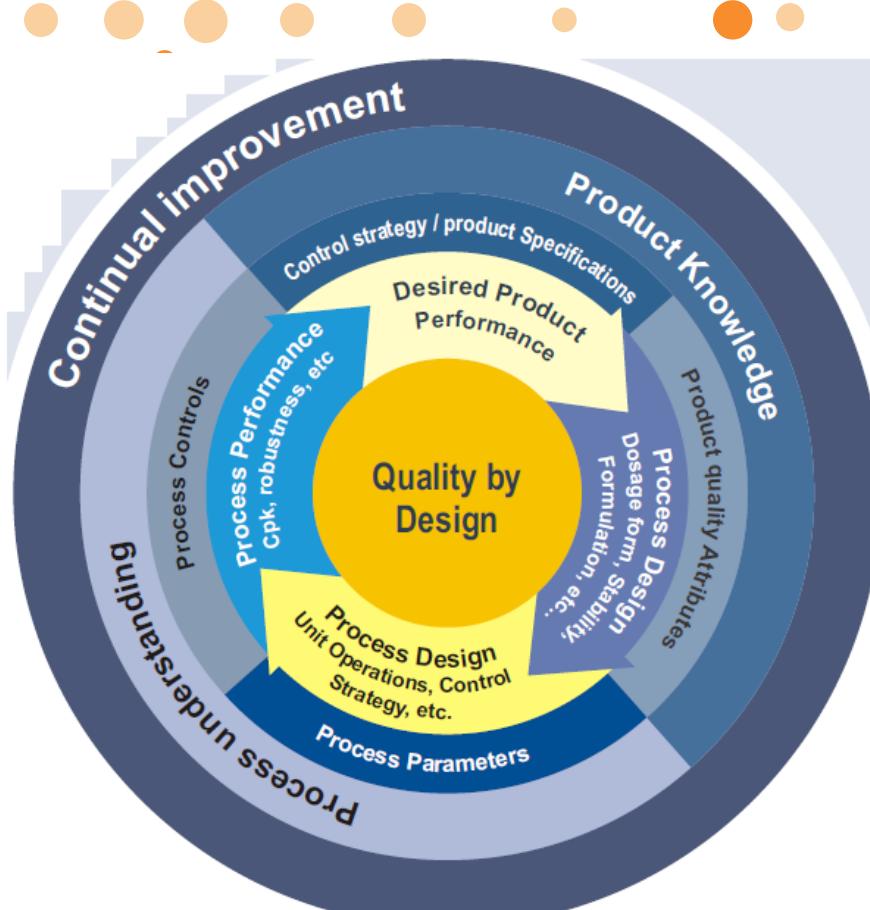
Selon principe du QBD



EXPERT
SANTÉ CANADA
MAPAQ

P B E
E X P E R T

Nouveau Processus de VDP / FDA



EXPERT
SANTÉ CANADA
MAPAQ

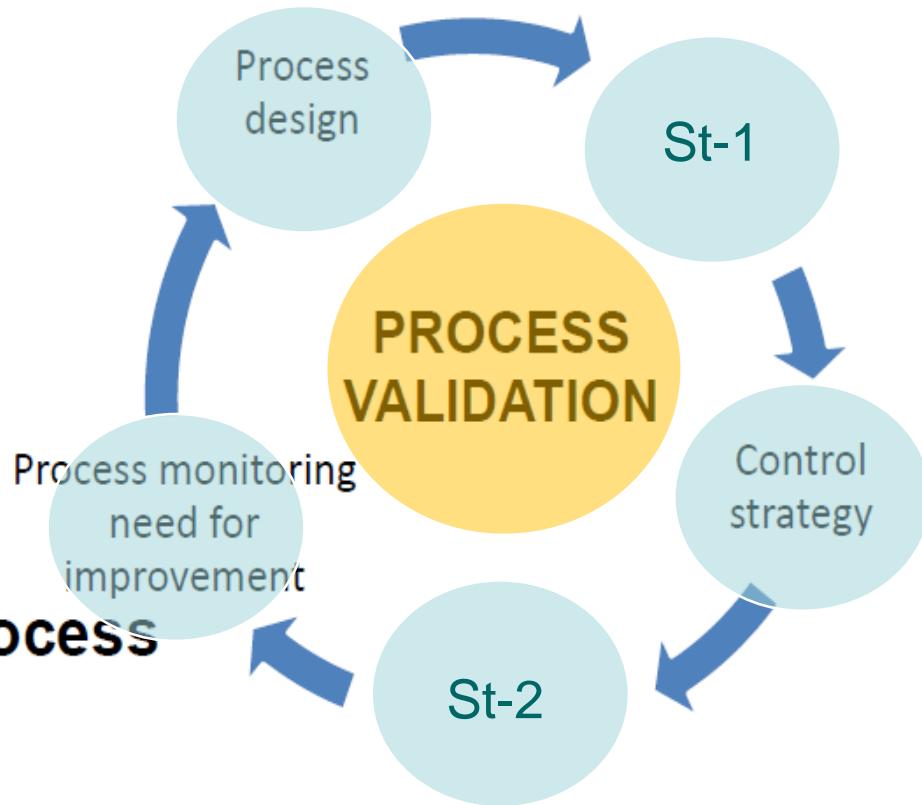
P B E
EXPERT

Q8

LIFE CYCLE APPROACH VALIDATION DE PROCÉDÉS



Stage 1 process design





ÉTUDES DE CAS





PBE Expert Inc. Votre
partenaire en conformité



PBE Expert Inc
(Canada) 1.514-616-2692
1.450-600-0790
(Maroc) 212-622-629-224
(Algérie) 213-540-961-234
(Tunisie) 216- 96-751-330
www.pbe-expert.com
pbe@pbe-expert.com
Laval, Canada



P B E
E X P E R T