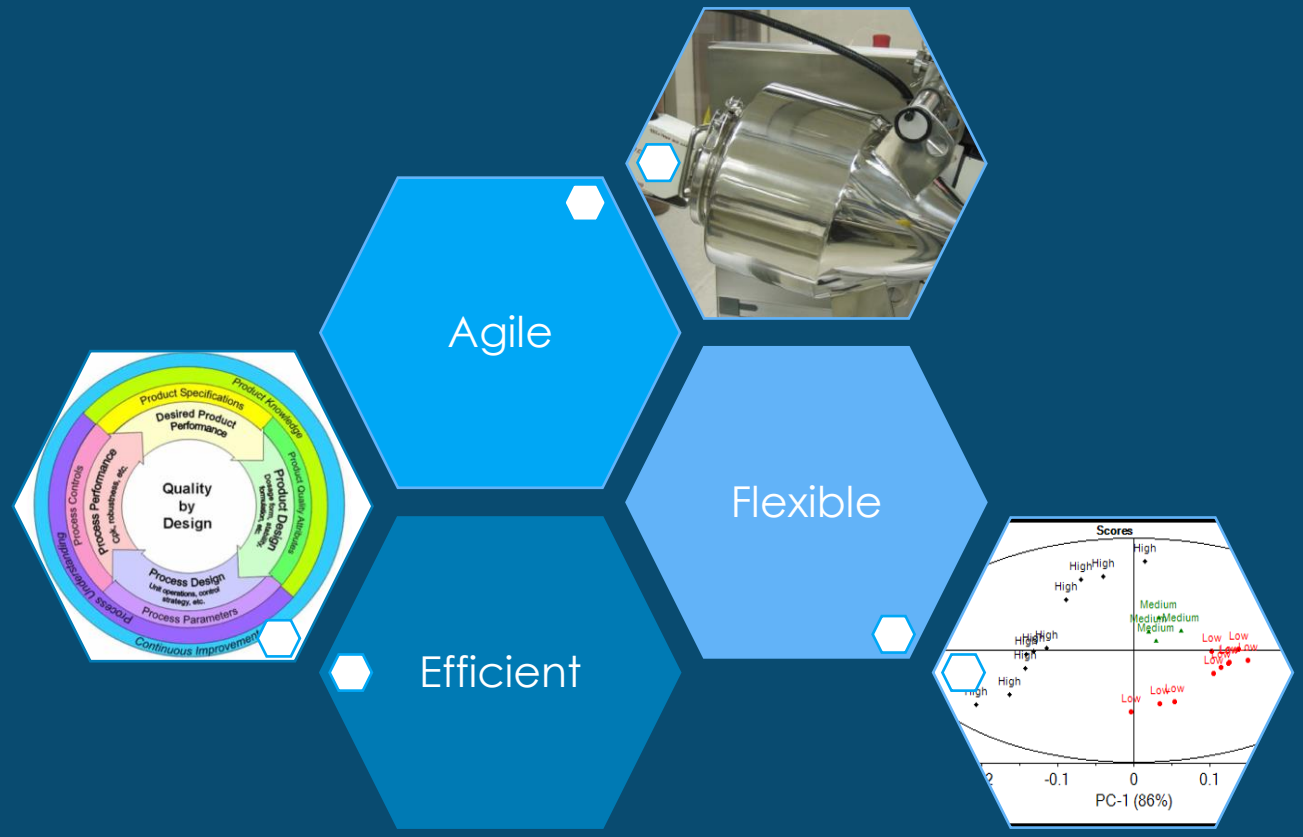
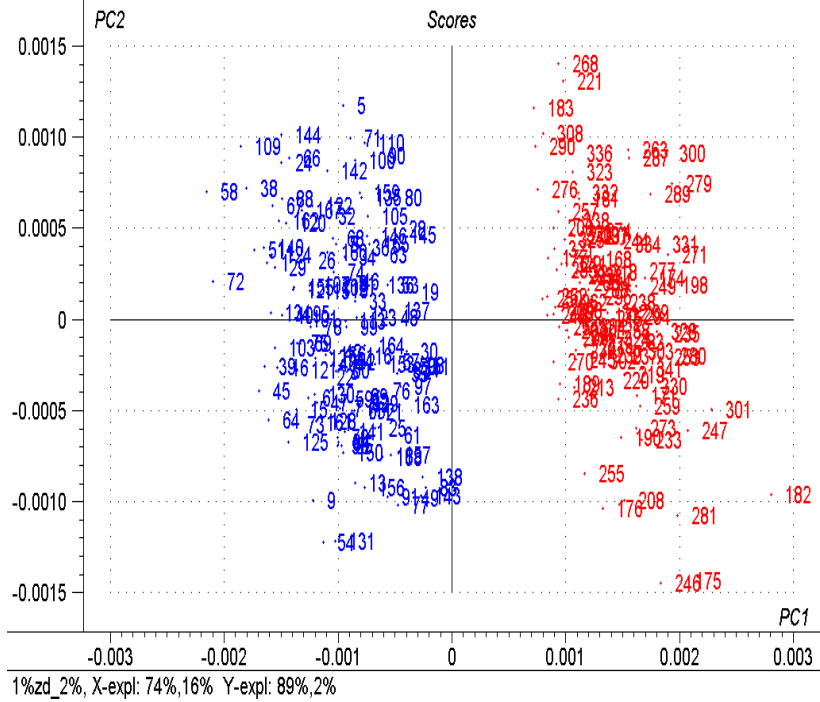
INHALEXPERT

Quality by Design (QbD) approach
Understand and control the manufacturing process to control the drug product



Les plans d'expériences dans le cadre de la démarche QbD
Workshop plans d'experience APEX XIV
Aix en Provence
Pascal Cavaillon
5th to 7th October, 2022



CONTENT

Regulatory input and situation in pharma industry

QbD objective, associated tools and drivers

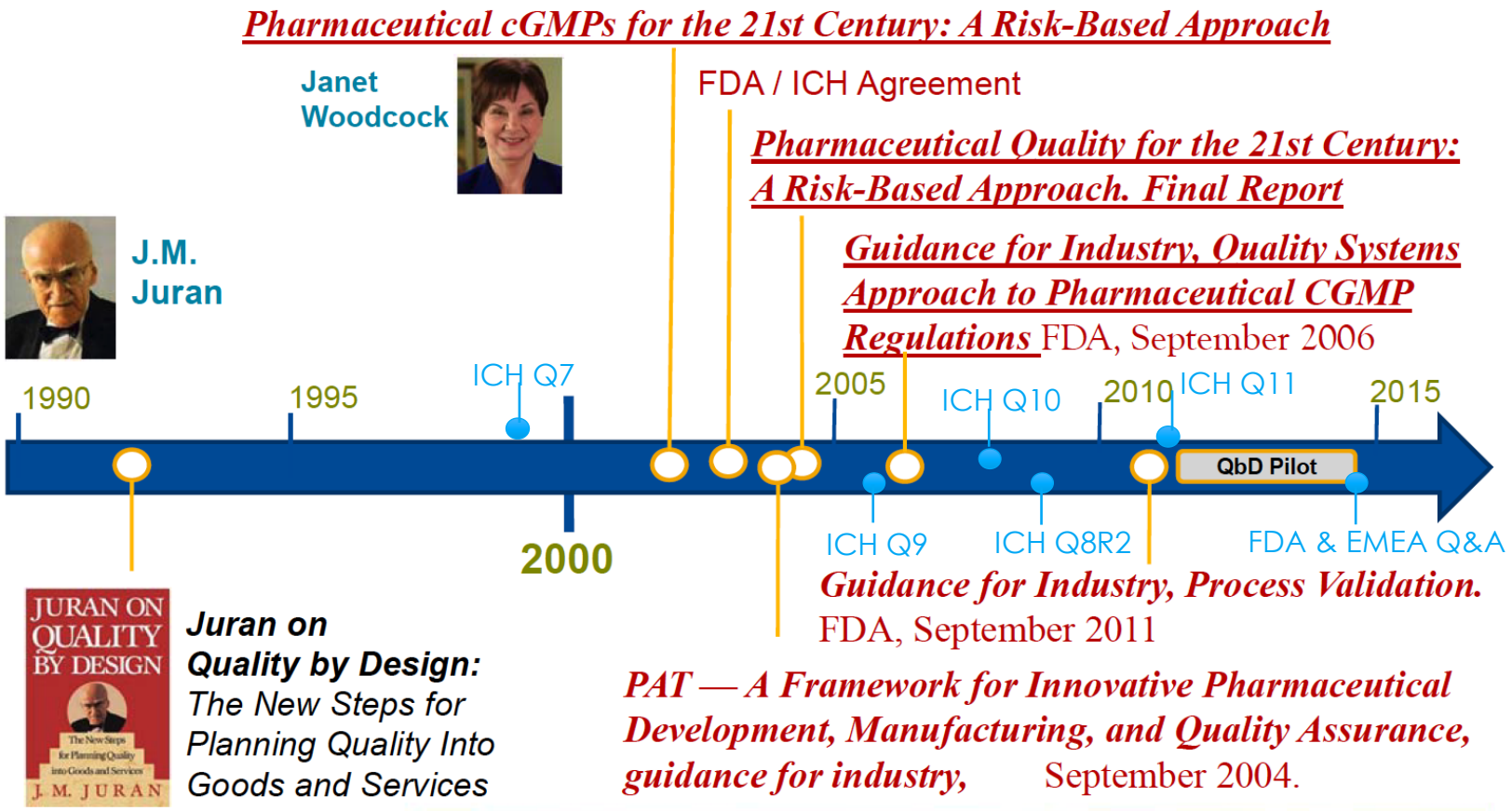
Critical sources of variability, risks analysis, DOE, knowledge and "Control Strategy"

COLBERT, 3RD AUGUST 1664 … A FIRST IDEA OF QUALITY!

"Si nos fabriques imposent, à force de soin, la Qualité supérieure de nos produits, les étrangers trouveront avantage à se fournir chez nous et leur argent affluera dans le royaume"

QBD RELEVANT PUBLICATIONS

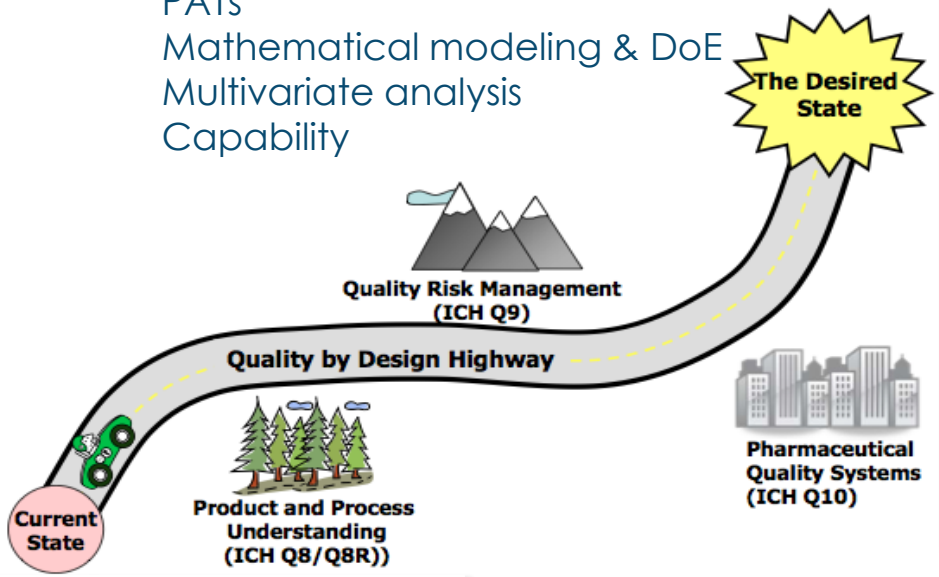
FDA and ICH initiatives since the 2000s



Very low use of this approach, associated principles, tools, mathematical models and statistics compared to other industries

THE VISION: QBD TO ACHIEVE THE DESIRED STATE

ICH Q7 to ICH Q12
PATs
Mathematical modeling & DoE
Multivariate analysis
Capability



"The Desired State: a maximally **efficient, agile, flexible pharmaceutical manufacturing sector** that reliably produces **high-quality drug products** without extensive regulatory oversight "

(Janet Woodcock, MD - FDA Deputy Commissioner for Operations - 05 Oct 2005)

Sigma level	Cost of Poor Quality
2σ	25 – 35%
3σ	20 – 25%
4σ	12 – 18%
5σ	4 – 8%
6σ	1 – 3%

2000s Mfg

Targeted Quality to patients

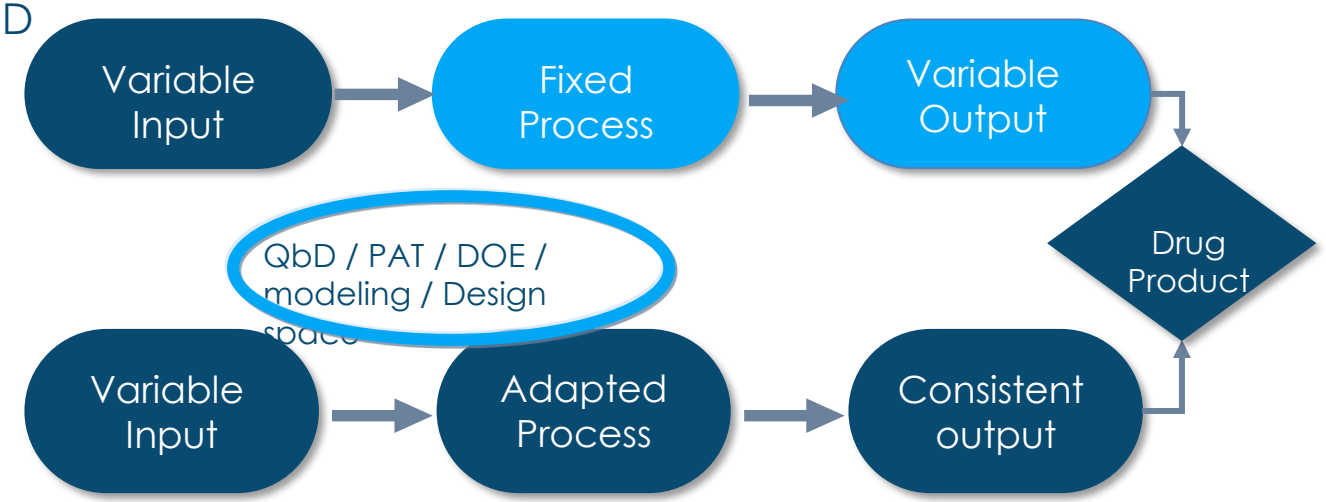
PWC and FDA in 2002

FOR FDA AND EMA, A PROCESS IS GENERALLY CONSIDERED WELL UNDERSTOOD WHEN:

1. All critical sources of variability are **identified and explained** (Level 1),
2. Variability is **managed** by the process (Level 2),
3. DP CQAs can be **accurately and reliably predicted** over the ranges of acceptance criteria established for API CQAs, CMAs, CDAs, QCPPs, CQAs and manufacturing environmental and other conditions (Level 3)

(Guidance for Industry PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance – FDA - Pharmaceutical CGMPs - September 2004.)

Before QbD



Control the Inputs (X's).....Monitor the Output (Y's)

The ability to predict reflects a high degree of process understanding

QBD SCOPE

- Chemical, physical, biological or microbiological reaction
- (Bio) pharma industry including chemistry, veterinary and dentistry
- Drug Substance and Drug Product
- Development and Production

QBD OBJECTIVE: UNDERSTAND AND CONTROL MANUFACTURING PROCESS

PROCESS UNDERSTANDING

- Understanding leads to control
- Understand the links between input CQAs and output CQAs by unit operation
- Understand the links between output CQAs and DP CQAs

➔

PROCESS CONTROL

The API and each unit operation should be under control ➔ control of the entire manufacturing process

➔

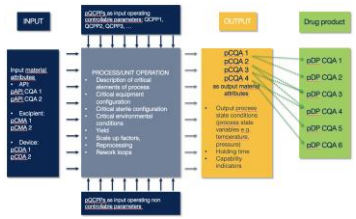
PRODUCT CONTROL

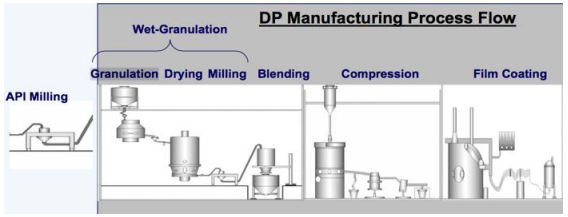
- To control all DP CQAs
- To control variability
- To reduce risks

➔

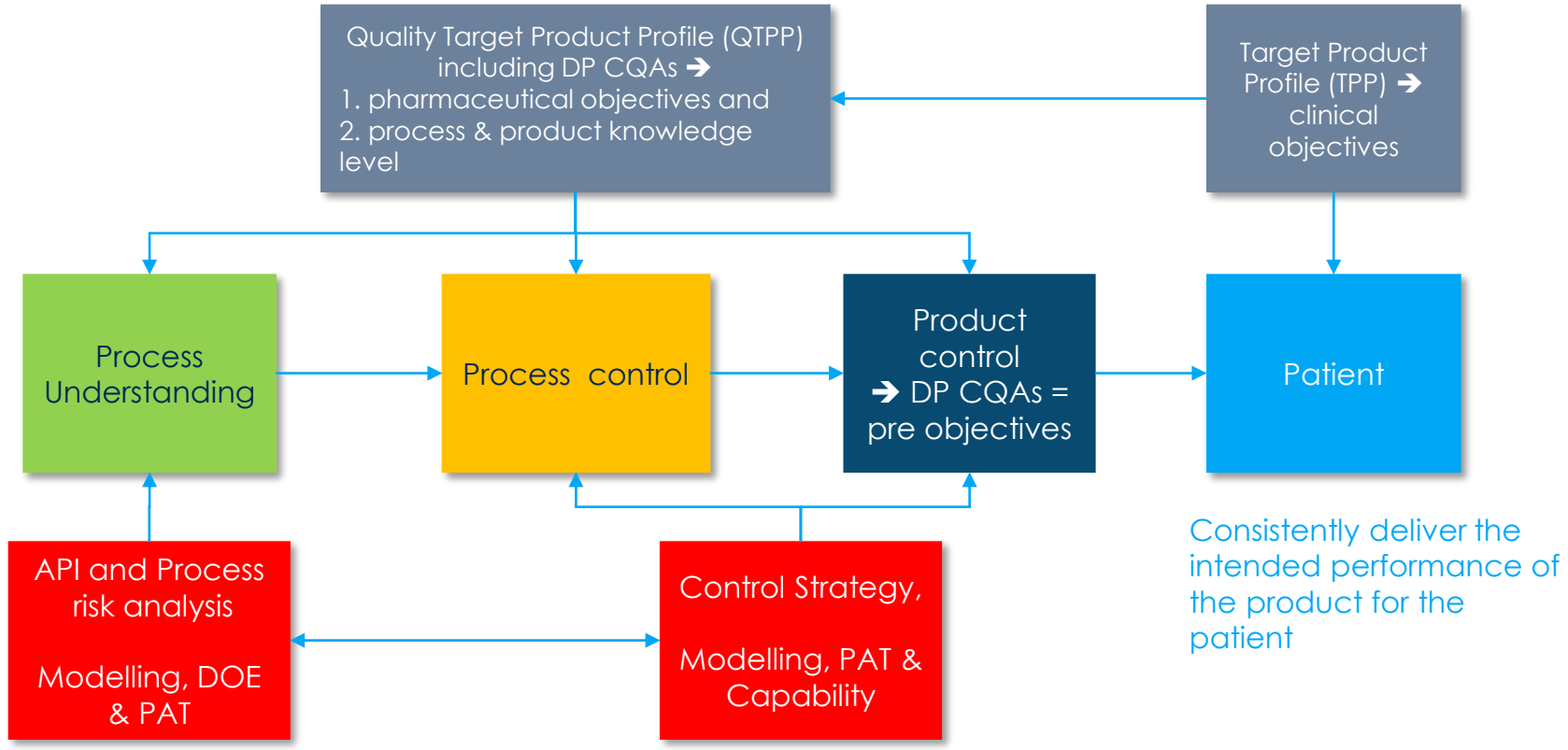
BENEFIT FOR THE PATIENT

- Higher level of assurance of product Quality linked to:
  - ➔ Safety
  - ➔ Efficacy
- Reducing risk





QBD TOOLS

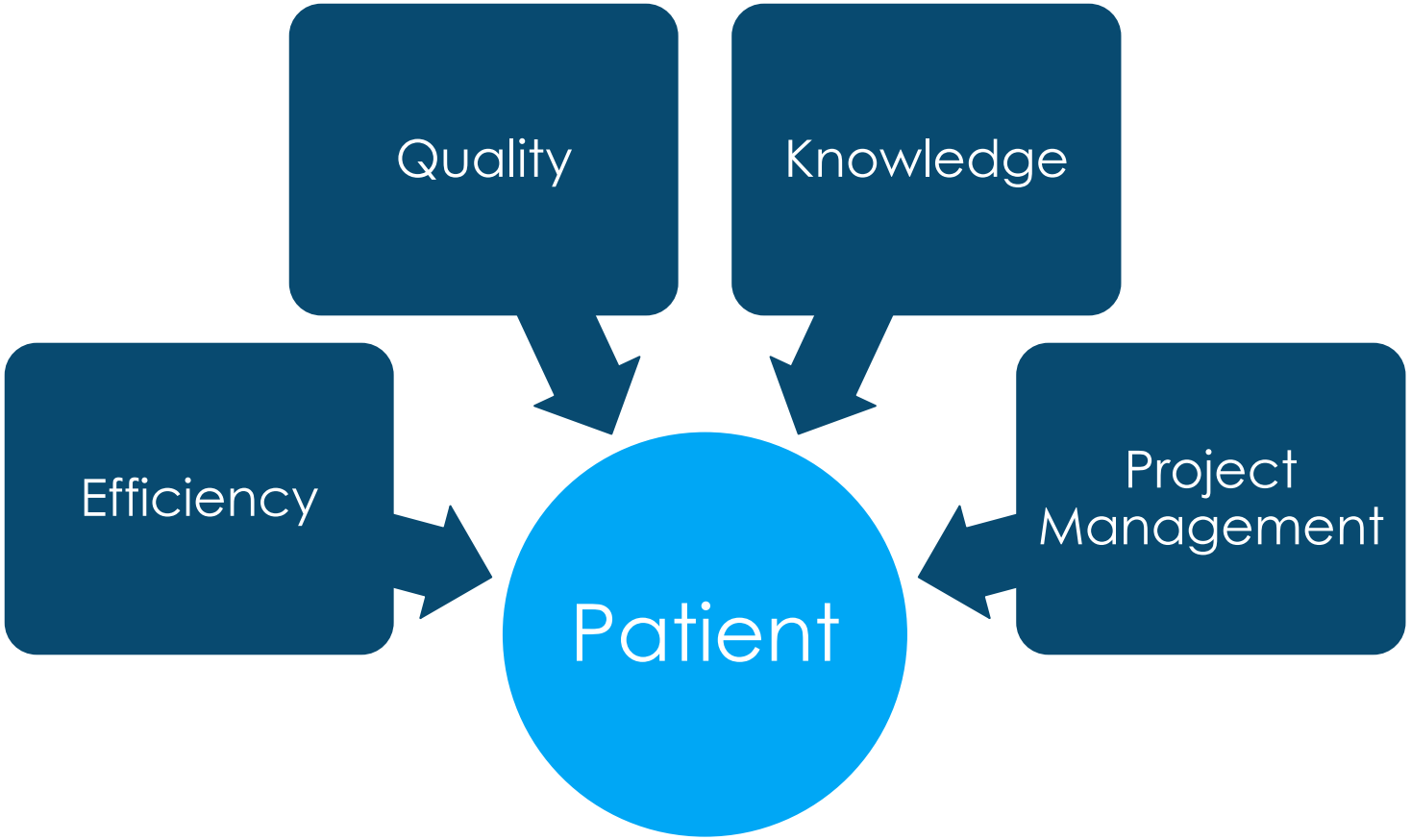


Consistently deliver the intended performance of the product for the patient

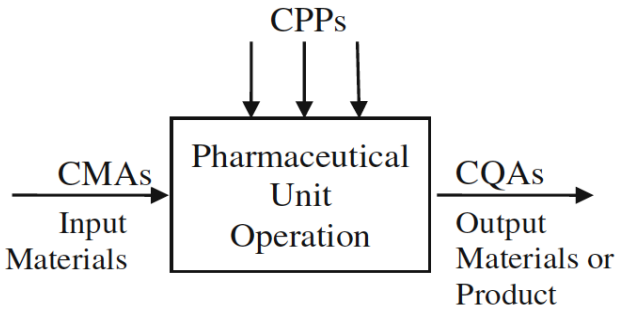
The impact of raw and starting materials, process parameters and intermediate product on product quality i.e. DP CQAs is well **understood**

And the sources of process and product **variability** are **well-known** and **controlled**

KEY DRIVERS AND BENEFIT

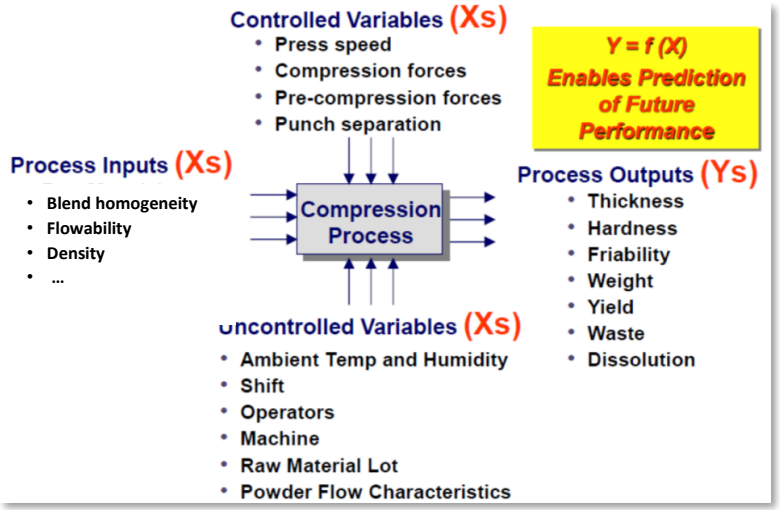


REPRESENTATION OF A UNIT OPERATION AND THE MANUFACTURING PROCESS

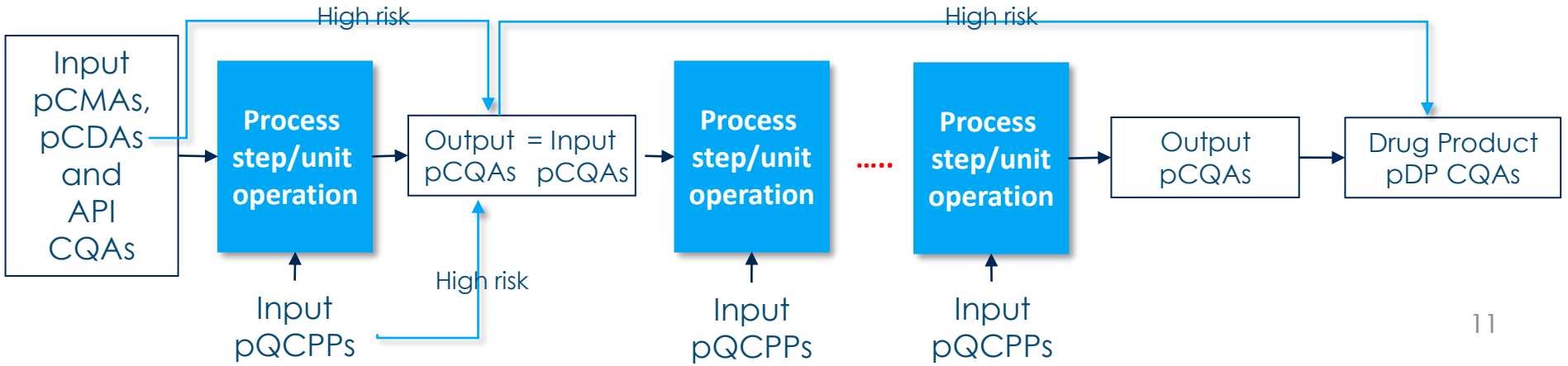


$$CQAs = f(CPP_1, CPP_2, CPP_3 \ldots CMA_1, CMA_2, CMA_3 \ldots)$$

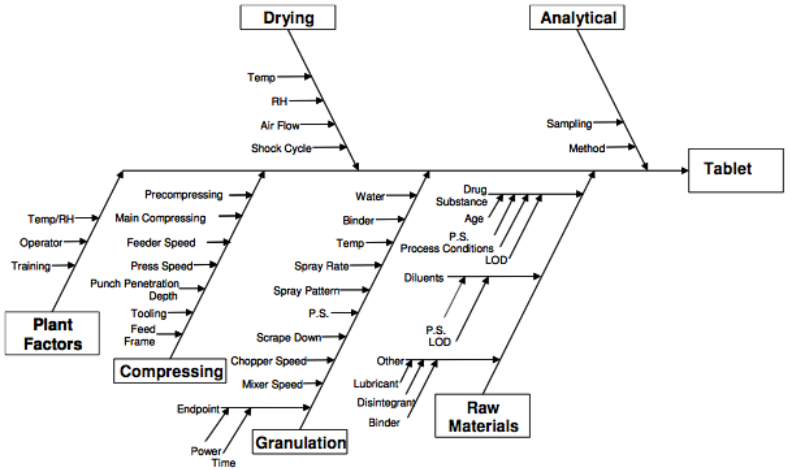
Understanding Pharmaceutical Quality by Design - The AAPS Journal, Vol. 16, No. 4, July 2014 - Lawrence X. Yu, Gregory Amidon, Mansoor A. Khan, Stephen W. Hoag, James Polli, G. K. Raju, and Janet Woodcock



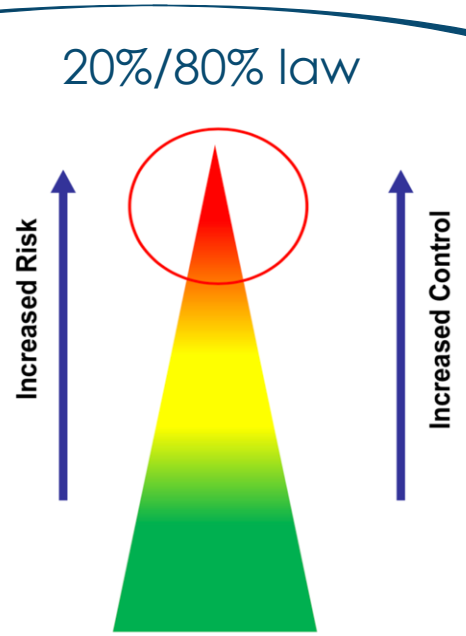
How to identify the X?



IDENTIFICATION OF CRITICAL SOURCES OF VARIABILITY = HIGH RISK TO IMPACT



It is **unrealistic** that a formulation scientist **investigates all the identified pQAs and pPPs** during the formulation optimization studies.



1. **Criticality** continuum
2. **Focus on the vital few**

Identification of pCQAs and pQCPPs. Focus on the vital few factors that impact the most

The **role of the scientist** is to identify and explain through **FMECA and DOE**

QBD PROCESS

Input	Objectives phase	Design phase	Experimental phase	Validation phas
Prior Knowledge	Define QTPP and objectives → DP CQAs	• API CQAs study • Formulation and process strategy • IPO matrix • Perform API CQAs, and process risks analysis → Development plan	Perform all development studies including DOE, stability, PAT … QbD report → Validation protocol	Risks control Define Control Strategy → QbD dossier

Identification → Explanation → Control and justification

Critical sources of variability

Specific knowledge and Capability

Risks and COPQ

DETERMINING THE FUNCTIONAL RELATIONSHIPS THAT LINK CMAS, CQAS AND QCPPS TO DP CQAS

Unit operation = IPO matrix of blending

Inputs of unit operation

- API CQA1
- CMA1
- CMA2
- Critical Materiai Attributes
- QCPP1
- QPP2
- QCPP3
- Quality Critical Process Parameters

Outputs of unit operation

Critical Quality Attributes

- CQA1
- CQA2
- CQA3

Using prior knowledge, models, DOE, and risk assessment processes, relationships between input and output are analyzed :

CQA1 = function (API CQA1, CMA1)
CQA2 = function (QCPP1, QCPP3)
CQA3 = function (CMA1, CMA2, QCPP1)

Intermediate output CQAs of tableting

Critical Quality Attributes

- CQA1
- CQA2
- CQA3

Using prior knowledge, models, DOE and risk assessment processes, pCMAs, pCDAs, pAPI CQAs and pQCPPs which could have an impact upon DP CQAs are analyzed.

Tablets

DP CQAs

- DP CQA1
- DP CQA2
- DP CQA3

Input process variables

1. PSD ➔ API CQA1
2. PSD ➔ CMA1
3. Density ➔ CMA2
4. Mixing speed ➔ QCPP1
5. Mxing time ➔ QCPP2

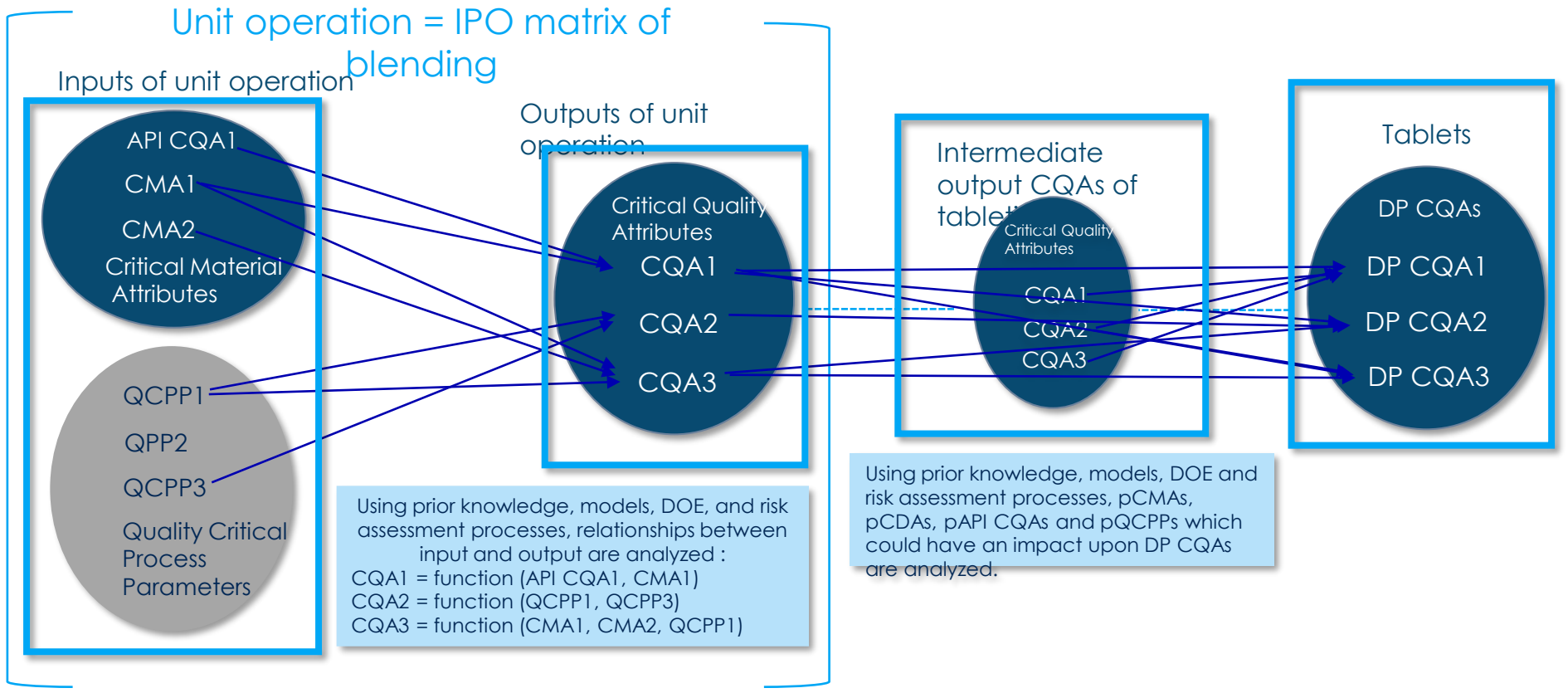
Output CQA 1
Blend uniformity

Output CQA 2
Flow properties

Intermediate CQA 1
Mass uniformity

DP CQA 1:
Content uniformity

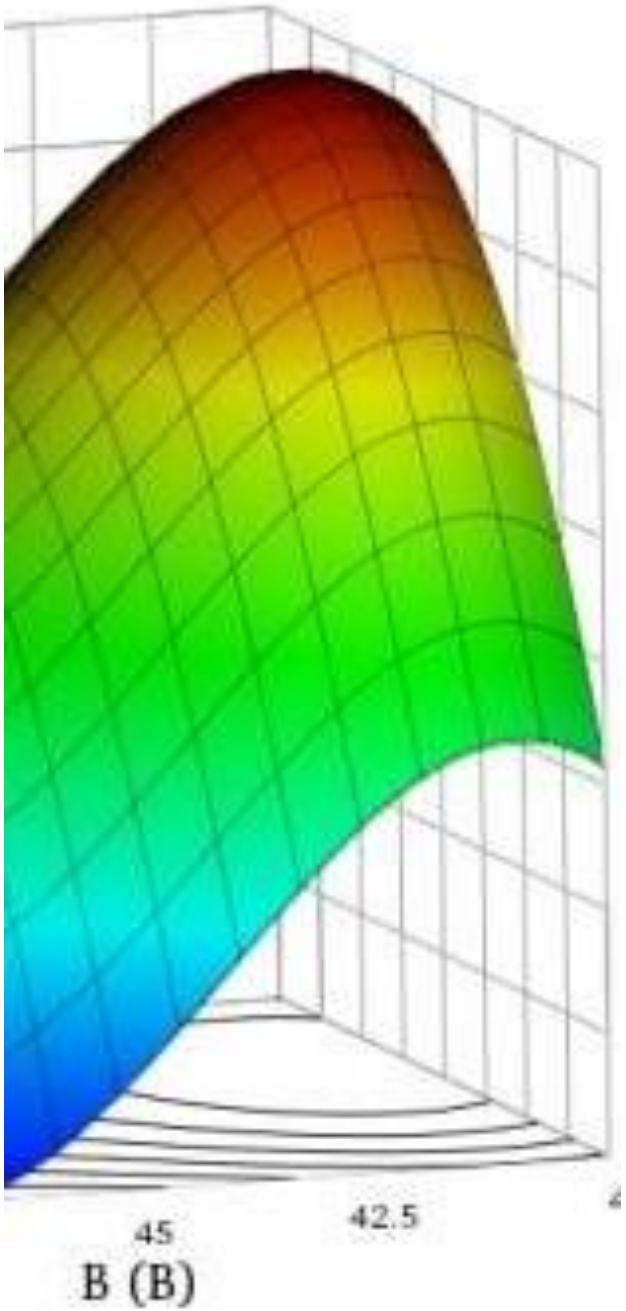
DETERMINING THE FUNCTIONAL RELATIONSHIPS THAT LINK CMAS, CQAS AND QCPPS TO DP CQAS



Risks analysis = Identification of critical sources of variability ➔ Input to DOE

DOE: A structured, organized method for determining the relationship between factors affecting a process and the output of that process.(ICH Q8) = Explanation of critical sources of variability

Control Strategy = Control of critical sources of variability ➔ Output of DOE



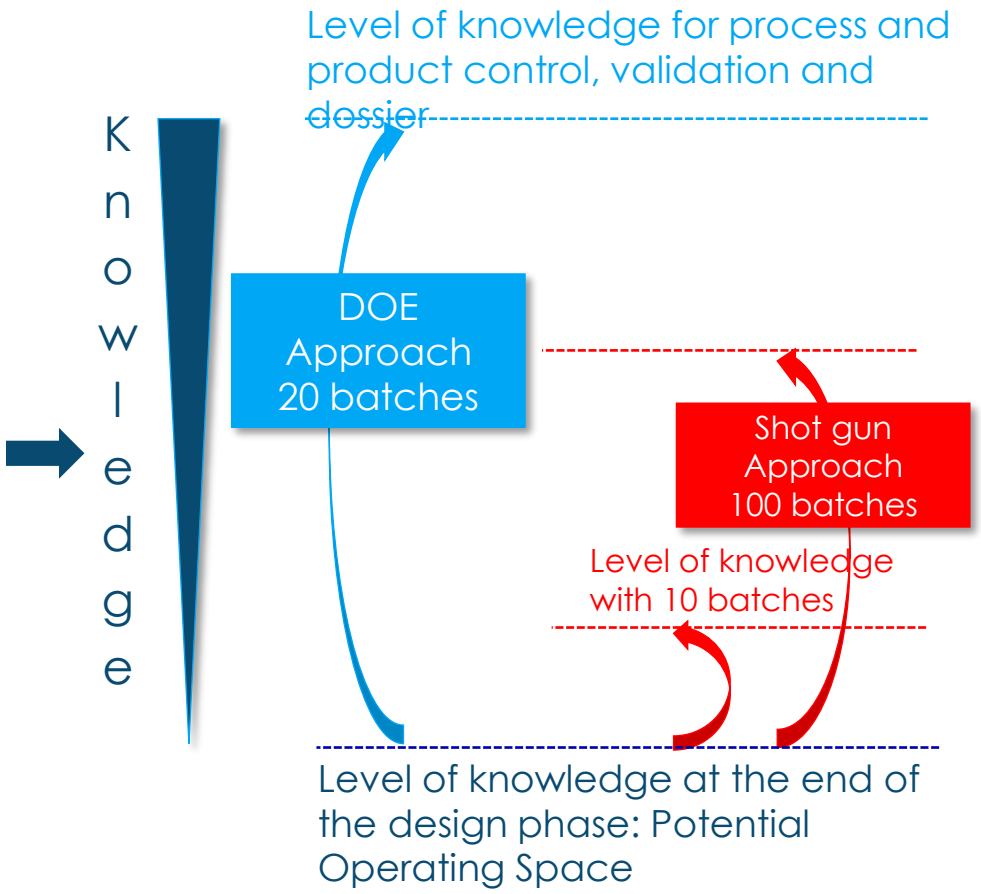
DOE AND KNOWLEDGE

DOE:

- To determine and demonstrate **critical factors**
- **To measure effect and level of criticity**
- To determine **relationship between factors** affecting a process and the **response** of that process i.e. CQAs and DP CQAs
- To provide **justification** for establishing **ranges (Proven Acceptable Range - PAR)**
- To establish **design space**.

DOE enables **maximum information / knowledge** i.e. right level of information to demonstrate the control of the manufacturing process, with **minimum experimental trials**

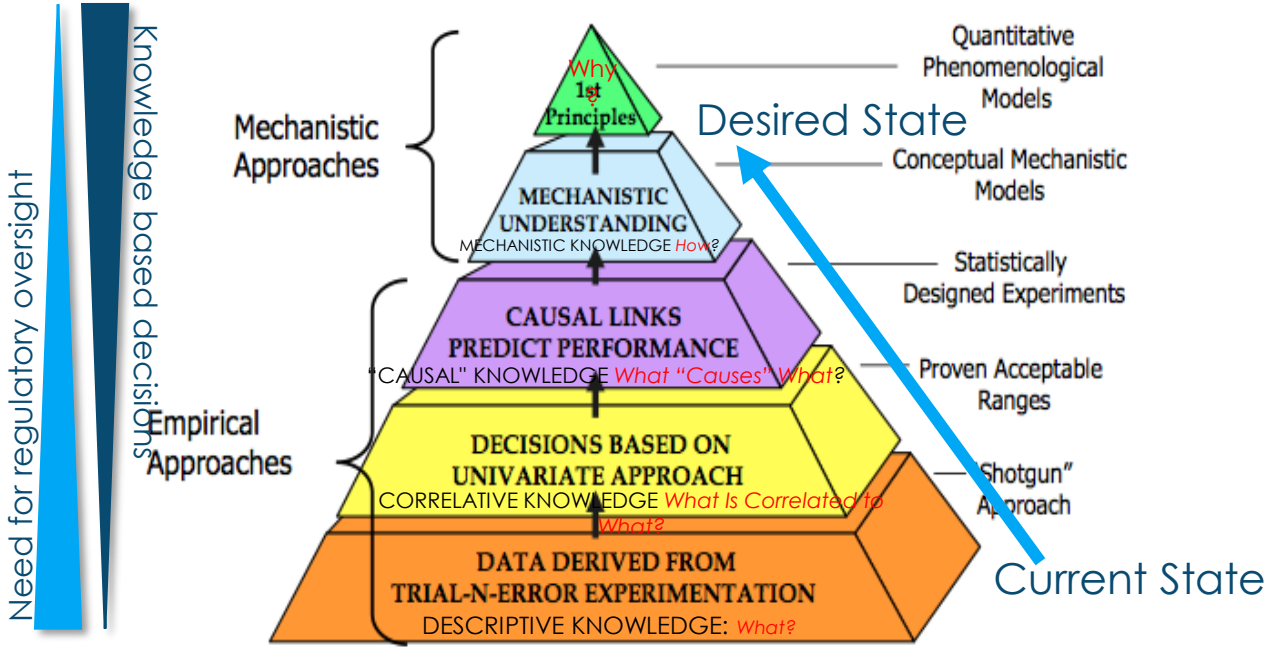
Traditional **one-factor-at-a-time** experiments do not address interactions among product and process variables (Guidance for Industry PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance – FDA - Pharmaceutical CGMPs - September 2004.)

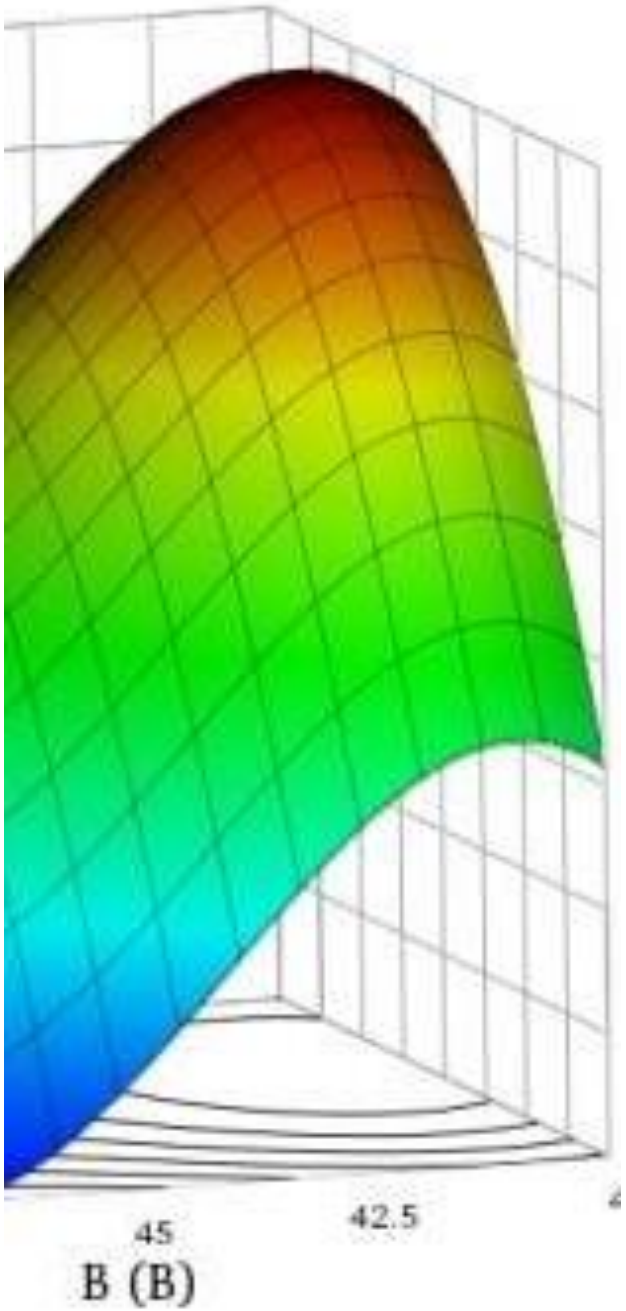


SPECIFIC KNOWLEDGE TO BE DEVELOPED FOR AUTHORITIES AND PRODUCTION AND FOR FUTURE PROJECTS

It is the knowledge gained and submitted to the authorities, and not the volume of data collected, that forms the basis for science- and risk-based submissions and regulatory evaluations. (ICH Q8 R2)

Knowledge management: systematic approach to acquiring, analysing, storing, and disseminating information related to products, manufacturing processes and components





DESIGN SPACE

A Design Space:

- May be constructed for a **single unit operation, multiple unit operations, or for the entire process.**
- With a purpose that quality is no more assured by achieving a target value**, but a range of values, called Design Space,** space in which the production parameters **can vary without affecting the quality of the final product**

➔ Regulatory flexibility

- Working within the design space is not considered as a change. (Glossary ICH Q8)

➔ Manufacturing flexibility

Under QbD, establishing a Design Space or using Real Time Release Testing is not necessarily expected (ICH Q8 - Q&A volume 4 EMA/CHMP/ICH/265145/2009)

DOE ALLOWS JUSTIFYING CONTROL STRATEGY

Every product MUST have a control strategy

A control strategy should **evolve** as knowledge increases.

- The elements of the control strategy should describe and justify **how controls** of **pAPI CQAs, pCMAs, pCDAs and pCQAs contribute** to the final product quality i.e. **pDP CQAs**
- It can include facility and equipment operating conditions, IPC, specifications, and the associated methods and frequency of monitoring and control,…

Control Strategy that assures process performance and product quality

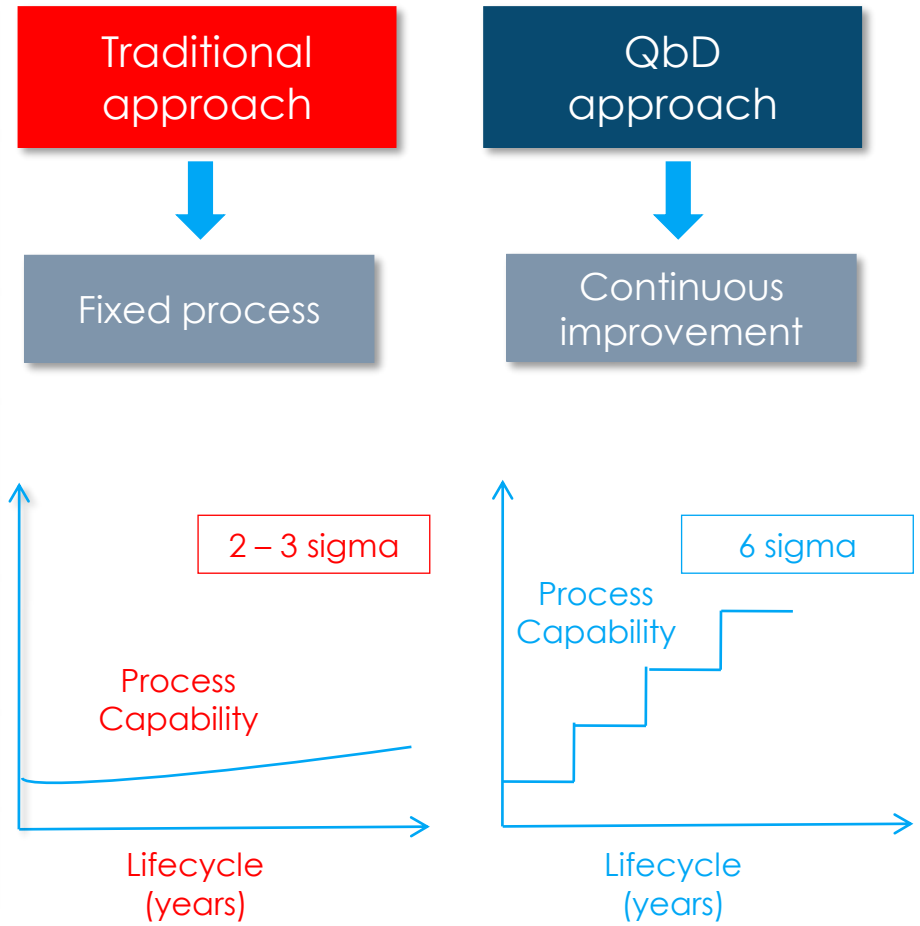
CONCLUSION

- More the drug product is a complex pharmaceutical form ➔ more risks we have ➔ More critical sources of variability i.e. CQAs and QCPPs we have in the manufacturing process
- More we have variability for those CQAs and QCPPs

➔ More we need mathematical modelling and DOE

CONCLUSION: A FOCUS INVESTMENT DURING THE DEVELOPMENT WITH THE BENEFIT AT THE MANUFACTURING

Traditional approach	QbD approach
To start from scratch	To search and integrate prior knowledge i.e. publication, expert,…
To address problems	To assess, anticipate and address risks
To perform one shot experiment	To perform Design Of Experiments (DOE)
To study low risk and high risk factors	To study high risk factors
End-product testing	PAT and Real-time Release testing and Control Strategy
Process capability ➔ 3 sigma level	Higher process capability ➔ 6 sigma level
Registration oversight 2 to 3 Y	Regulatory oversight: Between 6 month to 1Y



REVOLUTION ➔ CULTURE CHANGE ➔ TOP MANAGEMENT

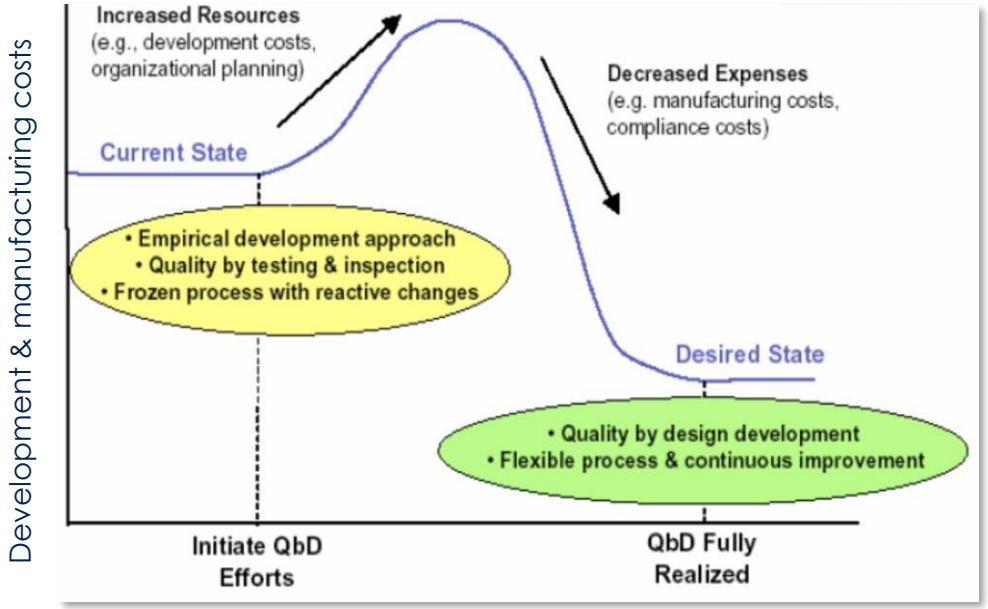
Culture challenges: "To be successful, the program needs from the top management team:

- Support, governance, and cultural experience
- Make QbD a priority
- Act as role models through their own behaviour"

(Mc Kinsey)

Implementation challenges

- Collaboration between functions
- Experience with new concepts
- Workload and resource limitations



QbD implementation progress

THANK YOU FOR YOUR QUESTIONS

INHALEXPERT

PASCAL CAVAILLON

BENEFITS OF QBD

To increase efficiency

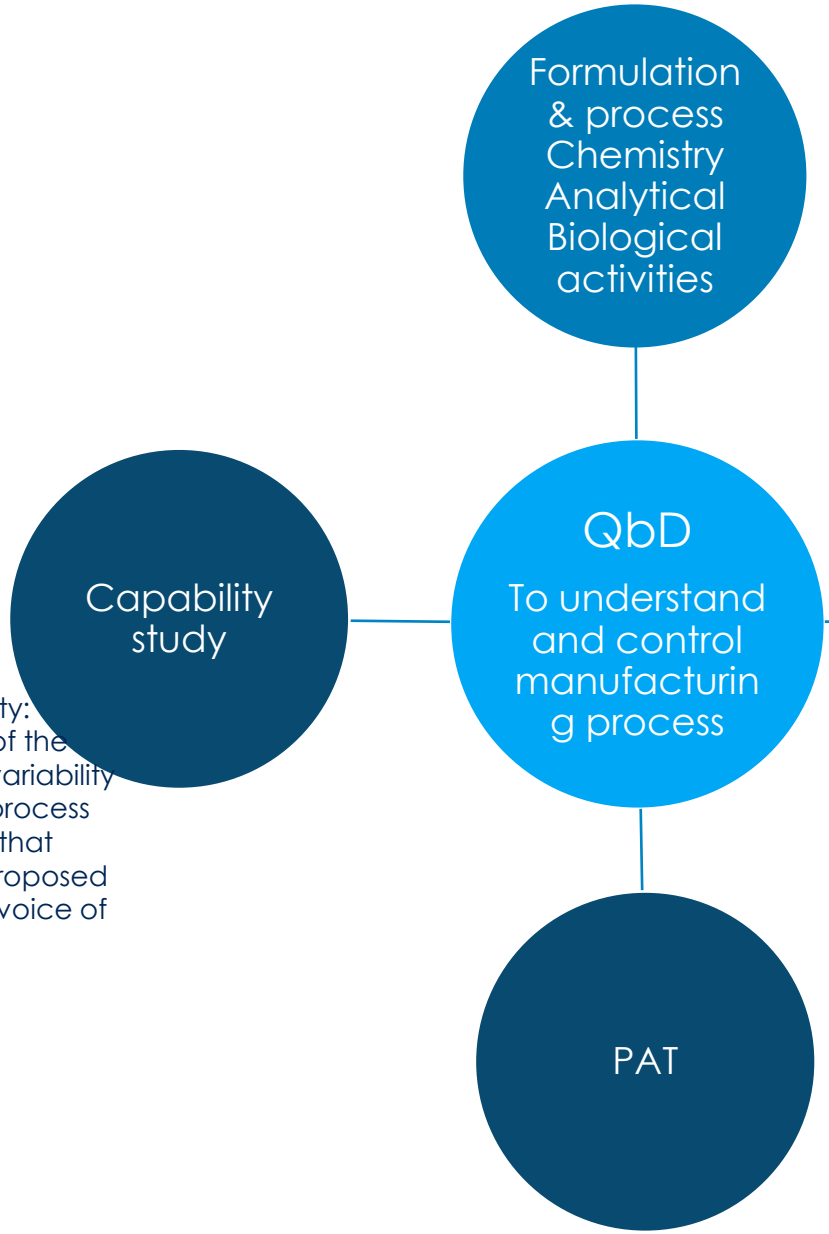
- Reducing manufacturing cost, cost of poor quality (COPQ) and cycle time including (Partial) Real Time Release
- Reducing regulatory oversight for the dossier ➔ to bring much-needed therapies to market quicker.

To increase Quality

- Reducing risks ➔ Reducing manufacturing and quality issues
- Complying with FDA and EMA requirements and guidelines (Validation of finished product - ICH Q7 to ICH Q13)
- Enhancing post approval change management
- Guaranteeing a state of control of the commercial manufacturing ➔ Continuous process improvement

Sponsors who implement QbD early can **save money** through increased product/process knowledge, less re-work, less product deviation, less product out-of specification, fewer rejects and improved quality.

INTEGRATION OF ALL THOSE COMPLEMENTARY ACTIVITIES



Process capability:
1. To measure of the process output variability ➔ voice of the process
2. To compare that variability with proposed specification ➔ voice of the customer

- To propose multivariate mathematical approaches to identify, explain and predict CQAs and DP CQAs

- Process analyzers provide more representative, non destructive measurements in real time that contain information related to biological, physical, and chemical attributes of the materials being processed.
- At-line, on-line, off-line or in-line including process signature and end-point

CONCLUSION: VARIABILITY DRIVES RISK, QUALITY, COST AND CUSTOMER SATISFACTION