Making Implementation of Quality by Design in the Generic Industry a Successful Business Advantage

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Outline

- Is there a business case for the Generic Industry to apply QbD principles?
- How to implement QbD from a practical point of view
  - How can QbD help prioritise development activities?
  - QbD Roadmap
  - QRM tools
  - DoE
  - PAT
  - Templates
- Result of a successful implementation
  - Process Validation
  - Development activities, QbR, ANDAs
  - Industry Progress

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Is QbD a realistic opportunity for the Generic Industry?

- Innovator - Generic culture
- West – East differences
- Generic medicine supposed to be cheap with the same quality
- How can QbD be possible in the short development framework?
- Technology and innovation costs versus labour costs
- PAT is still premature in e.g. India. Can QbD be implemented without or with limited PAT?

A pharmacy in Mumbai.
Photograph: Kuni Takahashi/Getty Images

Figure: Bikash Chatterjee, Pharmatech Associates

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The driver behind QbD in Generics

- The Generic market is expanding - >75% of prescriptions in US are being filed with generic products
- Crucial need to develop more efficient, reliable and versatile manufacturing methods
- Extensive manufacturing expertise in the industry
  - Generic companies often manufacture 100-500 different products
  - Product and process understanding is critical for efficiency
- Many elements of QbD have been in use by the industry for many years but without being as systematic and science driven
- Generic industry is used to be more risk oriented

So why not use this advantage to start implementing QbD?

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The expected benefits of QbD within the Generics

1. More robust processes & shorter development time!
   - QRM and DoE will enable the industry to concentrate on what is really important rather than trying at everything with not much consequence
   - PAT will reduce off-line testing and hence save much time too in development
2. QbD will improve the image of generic products, resulting in better sales
   - QbD unfortunately seems like an ' innovator-only' forte, but focusing on designing quality into the products should help the patient making the right product choice
3. Compliance: The generic industry will have to do it now. They can stall it for awhile, but sooner rather than later they have to do it.
   - The DMF/ANDA approval and review procedure is changing
   - QbR will based on QbD

Quotes from a "generic friend"

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Why does Generics quiver at the idea of QbD?

- The Generic Industry has begun to implement QbD later than the innovators
- Now the generics are catching up and trying to learn and implement faster which is not always possible
- The expectation that QbD will take too much time
  - ⇨ It will not be possible to be First-to-File
  - ⇨ How to establish a QTPP and start QbD when there is no RLD yet?
- No post-approval concrete promise, what are the industry getting in return for QbD submissions?

Quotes from a "generic friend"

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QbD, a business or compliance driver?

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Example:
Dr Reddy – QbD is a Business driver (from the Web)

- Supply chain excellence
- High throughput and productivity
- Good quality production processes

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Practical implementation of QbD

- **Systematic approach – be fast and effective**
  - Corporate policy/guide (senior management support)
  - Corporate QbD roadmap
  - Prioritisation
    - ⇨ Quality Risk Management
  - Activities with clear scope and short time frame (DMAIC)
  - Common Tools
    - ⇨ Process Map
    - ⇨ Risk Assessment tools including scales
    - ⇨ DoE and other PAT tools
  - Templates, SOPs, Reporting & documentation
- **Supportive Pharmaceutical Quality System**
  - Updated to reflect an effective and systematic QbD approach
- **Cross functional teams**
- **Knowledge sharing**
  - Prior knowledge, best practises, lessons learned

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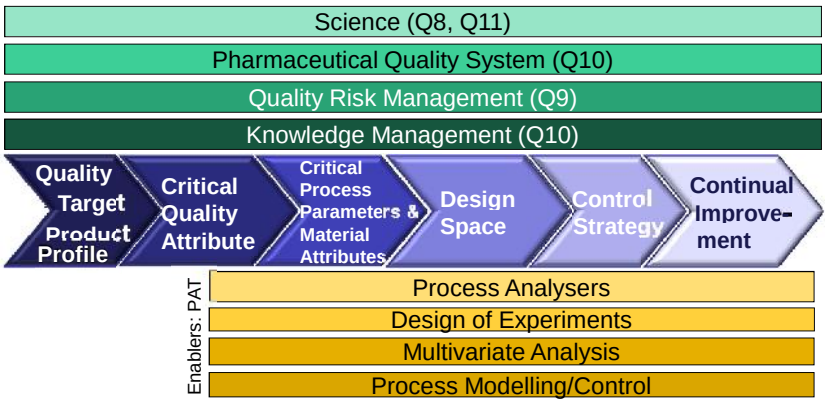
QbD Roadmap – based on ICH Q8



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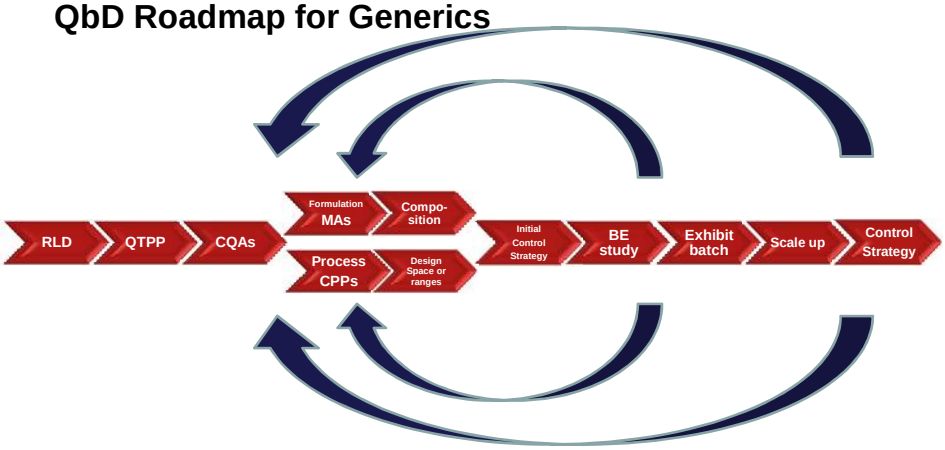
QbD Roadmap for Generics



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Drug product development, approach – from CQA to Control Strategy

1. Use risk assessment to identify all possible drug substance and excipient attributes/amounts that could impact the performance of the product
2. Determine levels or ranges of these attributes.
3. Use appropriate DOE to design experiments.
4. Conduct actual experiments.
5. Analyse the experimental data to determine if an input material attribute is critical.
6. Define a Control Strategy for critical material attributes (acceptable ranges)

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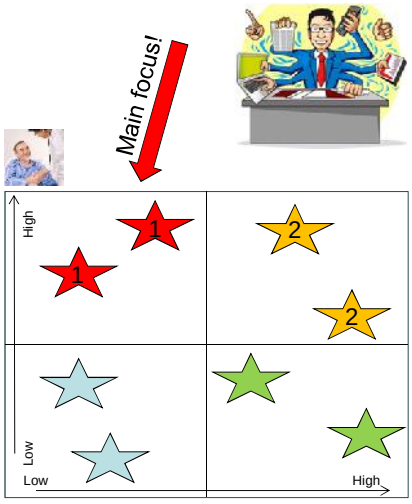
Prioritise activities

- An efficient prioritisation process is important during the short development phase to select the main development activities
  - Science and risk driven
  - Cross functional
  - Management support
- Quality Risk Management
  - Establish an overview of all potential development activities
  - Apply QRM tools to identify the areas with the potential highest risk to the patient as well as current level of process understanding (or later process robustness)



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The Six Sigma Process – DMADV

- Define the areas to be explored and developed
- Identify cross functional team
- Establish a clear scope, timeframe and methodology for the activities, eg. using The Design for Six Sigma tool: DMADV (DMAIC for optimisation)
  - Define
  - Measure
  - Analyse
  - Design/Improve
  - Verify/Control

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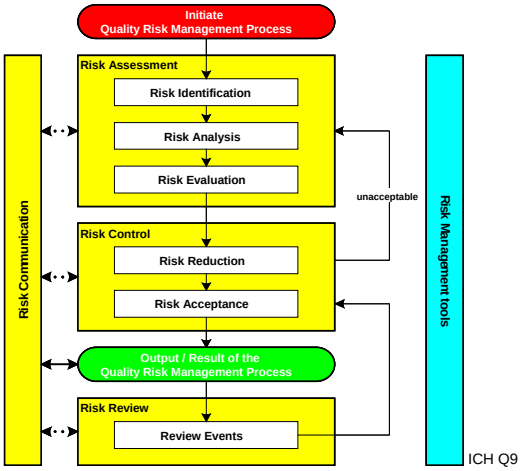
Quality Risk Management Process (ICH Q9)



ICH Q9

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Quality Risk Management is about

Managing the Risk!

- Identifying all the hazards and failure modes, including uncertainties
- Estimating the risk associated with the hazard of the failure mode
- Mitigate any high risks
- Estimate and control the residual risk
- Review and Communicate the risk control and any residual risk (control strategy)

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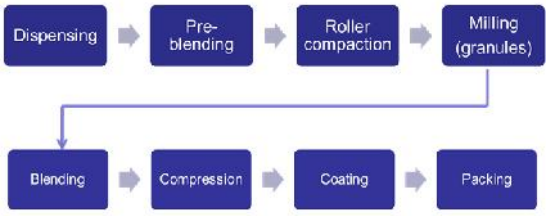
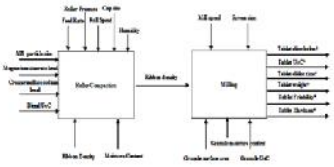
Process mapping

- Provides an overview (facilitates the cross functional work)
- Many different tools (more or less sophisticated)





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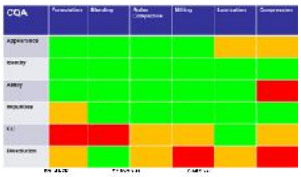
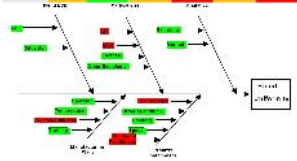
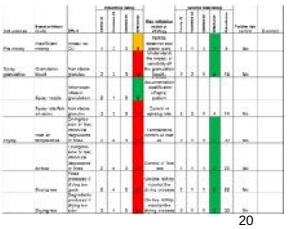
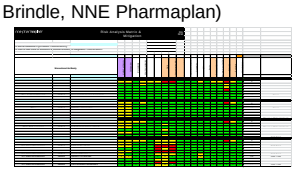
Risk Assessment tools

- Many different –select a few tools with different purposes (Different companies used different tools) – not “one-fit all” solution
- Use the same templates, scales, graphics etc
- Examples:
  - Traffic light (cause/effect) – related to CQAs
  - Fish Bone (Ishikawa) – brainstorm potential CPPs and MAs influencing a CQA
  - FMEA – rank (PRN) the risk of potential CPPs and MAs on CQAs
  - Risk Analysis and Mitigation Matrix (RAMM) – a faster and more pragmatic ranking approach than FMEA (ref C. Watts & A. Brindle, NNE Pharmaplan)









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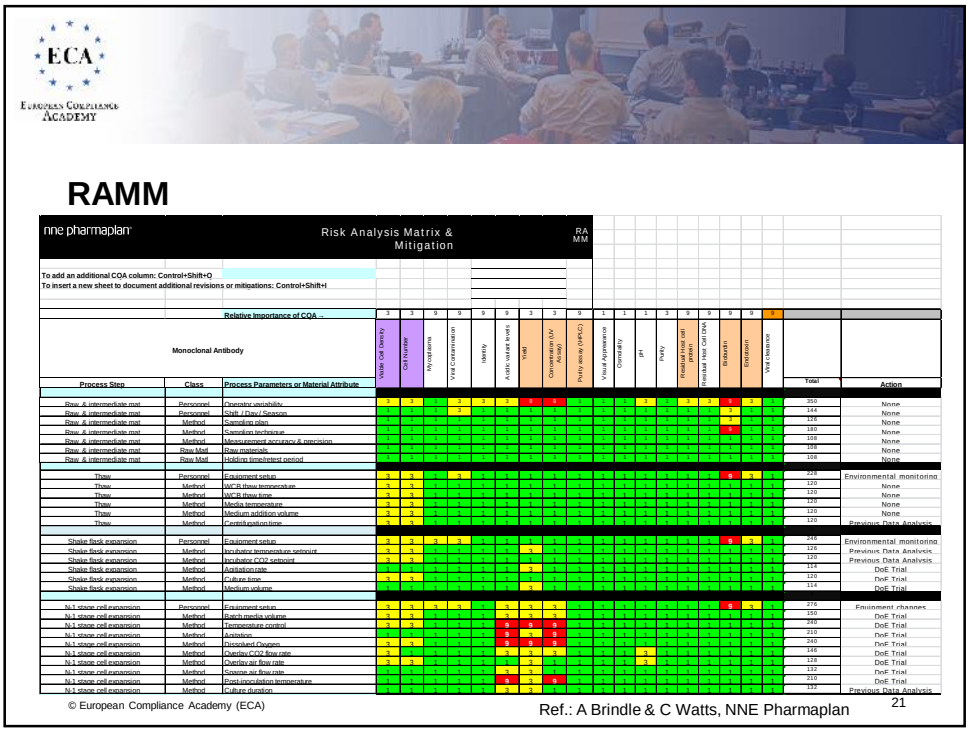

RAMM

nne pharmaplan — Risk Analysis Matrix & Mitigation — RAMM

To add an additional CQA column: Control+Shift+Q
To insert a new sheet to document additional revisions or mitigations: Control+Shift+I

Relative Importance of CQA →

Monoclonal Antibody			Viable Cell Density	Cell Number	Mycoplasma	Viral Contamination	Identity	Acidic variant levels	Yield	Concentration (UV Assay)	Purity assay (HPLC)	Visual Appearance	Osmolality	pH	Purity	Residual Host cell protein	Residual Host Cell DNA	Bioburden	Endotoxin	Viral clearance		
Process Step	Class	Process Parameters or Material Attribute																			Total	Action
Raw & intermediate mat	Personnel	Operator variability	3	3	1	3	3	3	4	6	1	1	1	3	1	3	3	9	3	1	350	None
Raw & intermediate mat	Personnel	Shift / Day / Season	1	1	1	3	1	1	1	1	1	1	1	1	1	1	1	9	1	1	144	None
Raw & intermediate mat	Method	Sampling plan	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	9	1	1	126	None
Raw & intermediate mat	Method	Sampling technique	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	9	1	1	180	None
Raw & intermediate mat	Method	Measurement accuracy & precision	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	9	1	1	108	None
Raw & intermediate mat	Raw Mat	Raw materials	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	9	1	1	108	None
Raw & intermediate mat	Raw Mat	Holding time/retest period	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	9	1	1	108	None
Thaw	Personnel	Equipment setup	3	3	1	3	1	1	1	1	1	1	1	1	1	1	1	9	3	1	228	Environmental monitoring
Thaw	Method	WCB thaw temperature	3	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	120	None
Thaw	Method	WCB thaw time	3	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	120	None
Thaw	Method	Media temperature	3	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	120	None
Thaw	Method	Medium addition volume	3	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	120	None
Thaw	Method	Centrifugation time	3	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	120	Previous Data Analysis
Shake flask expansion	Personnel	Equipment setup	3	3	3	3	1	1	1	1	1	1	1	1	1	1	1	9	3	1	246	Environmental monitoring
Shake flask expansion	Method	Incubator temperature setpoint	3	3	1	1	1	1	4	1	1	1	1	1	1	1	1	1	1	1	126	Previous Data Analysis
Shake flask expansion	Method	Incubator CO2 setpoint	3	3	1	1	1	1	4	1	1	1	1	1	1	1	1	1	1	1	120	Previous Data Analysis
Shake flask expansion	Method	Agitation rate	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	1	1	114	DoE Trial
Shake flask expansion	Method	Culture time	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	1	1	120	DoE Trial
Shake flask expansion	Method	Medium volume	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	1	1	114	DoE Trial
N-1 stage cell expansion	Personnel	Equipment setup	3	3	3	3	1	3	3	3	1	1	1	1	1	1	1	9	3	1	276	Equipment changes
N-1 stage cell expansion	Method	Batch media volume	3	3	1	1	1	3	3	3	1	1	1	1	1	1	1	1	1	1	150	DoE Trial
N-1 stage cell expansion	Method	Temperature control	3	3	1	1	1	9	4	6	1	1	1	1	1	1	1	1	1	1	240	DoE Trial
N-1 stage cell expansion	Method	Agitation	1	1	1	1	1	9	3	9	1	1	1	1	1	1	1	1	1	1	210	DoE Trial
N-1 stage cell expansion	Method	Dissolved Oxygen	3	3	1	1	1	9	4	8	1	1	1	1	1	1	1	1	1	1	240	DoE Trial
N-1 stage cell expansion	Method	Overlay CO2 flow rate	3	1	1	1	1	3	3	3	1	1	1	3	1	1	1	1	1	1	146	DoE Trial
N-1 stage cell expansion	Method	Overlay air flow rate	3	3	1	1	1	4	3	1	1	1	1	3	1	1	1	1	1	1	128	DoE Trial
N-1 stage cell expansion	Method	Sparge air flow rate	1	1	1	1	1	3	3	1	1	1	1	1	1	1	1	1	1	1	132	DoE Trial
N-1 stage cell expansion	Method	Post-inoculation temperature	1	1	1	1	1	9	3	6	1	1	1	1	1	1	1	1	1	1	210	DoE Trial
N-1 stage cell expansion	Method	Culture duration	1	1	1	1	1	3	3	1	1	1	1	1	1	1	1	1	1	1	132	Previous Data Analysis

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Ref.: A Brindle & C Watts, NNE Pharmaplan

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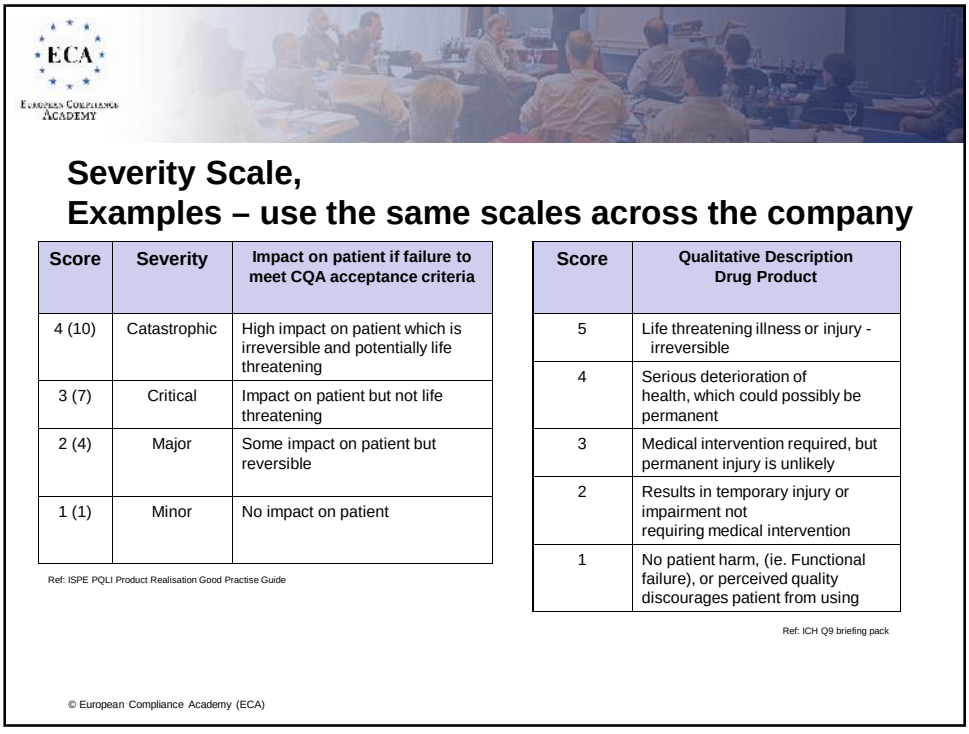

Severity Scale, Examples – use the same scales across the company

Score	Severity	Impact on patient if failure to meet CQA acceptance criteria
4 (10)	Catastrophic	High impact on patient which is irreversible and potentially life threatening
3 (7)	Critical	Impact on patient but not life threatening
2 (4)	Major	Some impact on patient but reversible
1 (1)	Minor	No impact on patient

Ref: ISPE PQLI Product Realisation Good Practise Guide

Score	Qualitative Description Drug Product
5	Life threatening illness or injury - irreversible
4	Serious deterioration of health, which could possibly be permanent
3	Medical intervention required, but permanent injury is unlikely
2	Results in temporary injury or impairment not requiring medical intervention
1	No patient harm, (ie. Functional failure), or perceived quality discourages patient from using

Ref: ICH Q9 briefing pack

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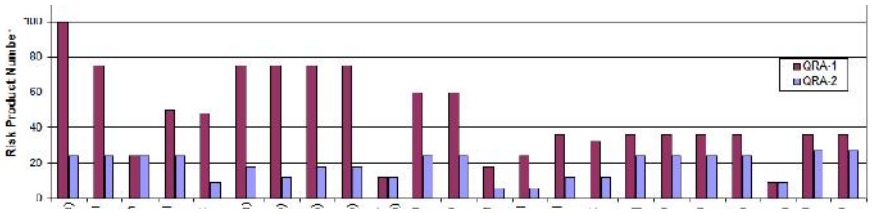
Communicating Risk - using Risk Priority Numbers

Compare RPN before and after risk mitigation and controls are implemented



RPN after initial risk assessment

RPN after risk control in place (mitigation)

Fig: ACE case study

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Cause & Effect Matrix after a control strategy has been implemented

	Variables and Unit Operations					
DP CQAs	Formulation Composition	Blending	Roller Compaction	Milling	Lubrication	Compression
Appearance	Low	Low	Low	Low	No. of revolutions	Control of tablet hardness
Identity	Low	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low	In line control of tablet weight and tablet weight uniformity
Impurities	Excipient Compatability	Low	Low	Low	Low	Low
Content Uniformity	Choice and level of Excipients and excipient particle size	Blend uniformity controlled by NIR	No issue within the ranges studied	Granula SA controlled	Low	In line control of tablet weight and tablet weight uniformity
Dissolution	API particle size, choice and level of excipients	Low	Ribbon Density controlled by NIR	Granula SA controlled	No. of revolutions	Control of tablet hardness

Low risk based on prior knowledge
Control Strategy applied to high risk to mitigate risk
High risk

Reflects:
Process Understanding!
Links back to CQAs!

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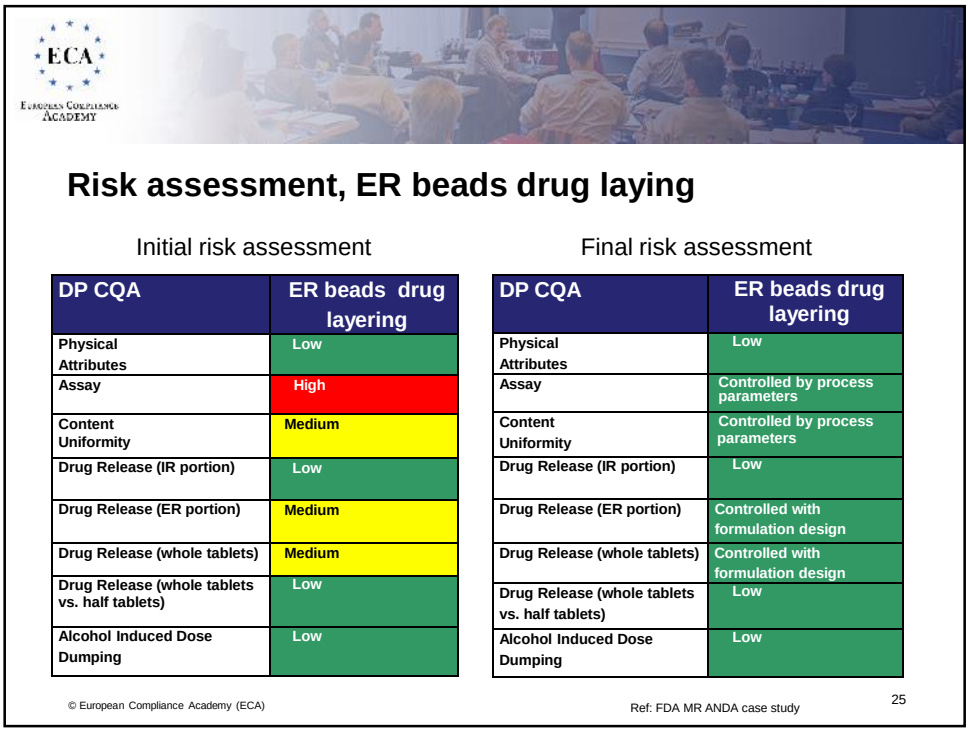
Ref: Ace Case Study



Risk assessment, ER beads drug laying

Initial risk assessment

DP CQA	ER beads drug layering
Physical Attributes	Low
Assay	High
Content Uniformity	Medium
Drug Release (IR portion)	Low
Drug Release (ER portion)	Medium
Drug Release (whole tablets)	Medium
Drug Release (whole tablets vs. half tablets)	Low
Alcohol Induced Dose Dumping	Low

Final risk assessment

DP CQA	ER beads drug layering
Physical Attributes	Low
Assay	Controlled by process parameters
Content Uniformity	Controlled by process parameters
Drug Release (IR portion)	Low
Drug Release (ER portion)	Controlled with formulation design
Drug Release (whole tablets)	Controlled with formulation design
Drug Release (whole tablets vs. half tablets)	Low
Alcohol Induced Dose Dumping	Low

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Ref: FDA MR ANDA case study

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Design of Experiments

- DoE is a very strong tool that helps to:
  - Gain process understanding
  - Identify CPPs and MAs
- Can be applied for
  - Product design, eg formulation or chemical composition
  - Process design
  - Process robustness
  - Process optimisation
  - Analytical methods
  - Process validation

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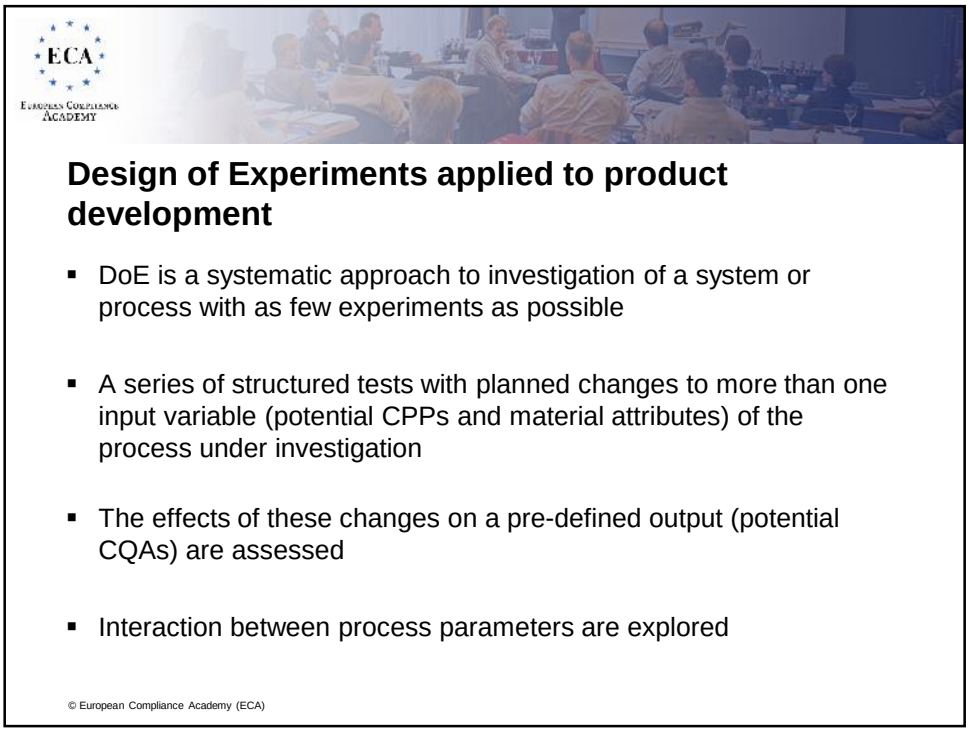

Design of Experiments applied to product development

- DoE is a systematic approach to investigation of a system or process with as few experiments as possible
- A series of structured tests with planned changes to more than one input variable (potential CPPs and material attributes) of the process under investigation
- The effects of these changes on a pre-defined output (potential CQAs) are assessed
- Interaction between process parameters are explored

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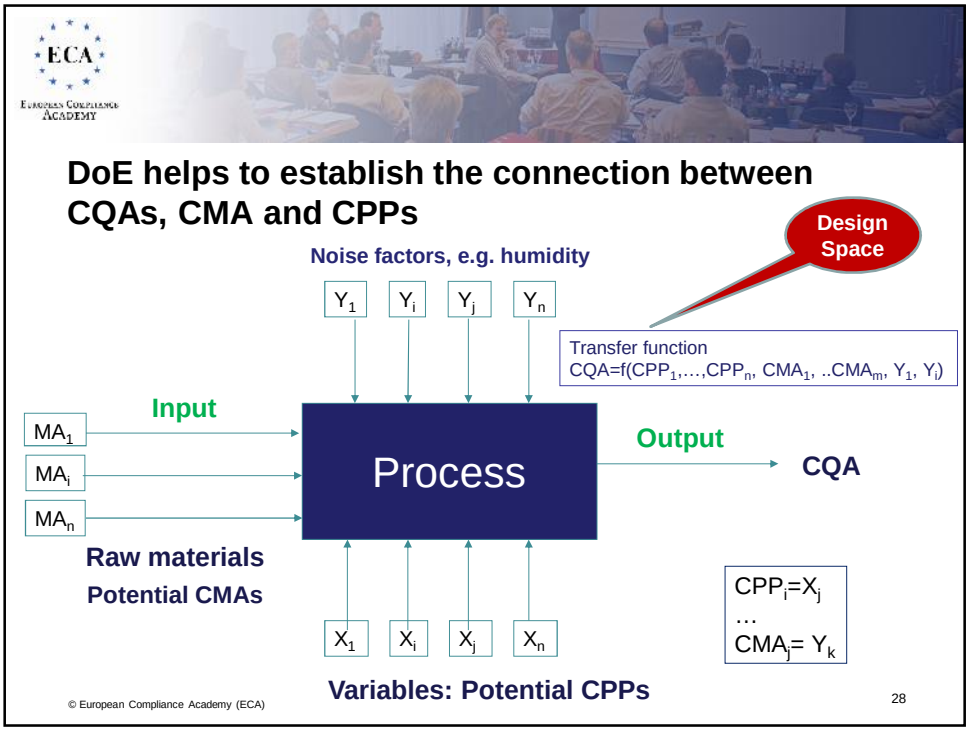

DoE helps to establish the connection between CQAs, CMA and CPPs

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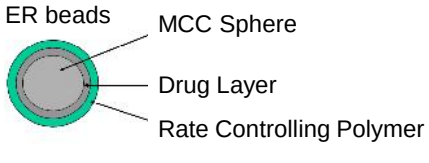
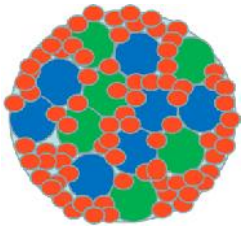
Example based on the FDA MR ANDA case study

- Modified Release (MR) Tablet
- **Extended release (ER) beads**, **immediate release (IR) granules** and **other excipients** are compressed into tablets, with similar physical attributes to the RLD





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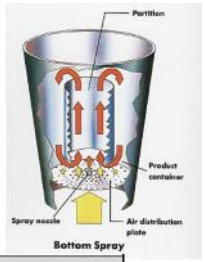
ER Bead process development

- Bottom-spray fluid bed drug layering process
- Risk assessment
  - Equipment
  - Preparation solution for drug layering
  - Pre-heating
  - Spraying
  - Drying
- How does the spraying influence CQAs and in-process material attributes?



Spraying	Risk	Justification
Inlet air dew point	Medium	The dew point of inlet air indicates inlet air humidity. This parameter needs to be controlled to assure consistency. Dew point of 5-15° C is selected based on previous experience.
Shaking interval/duration	Low	Shaking to prevent beads trapped in filter bag set at 60 sec/5sec based on prior knowledge.
Inlet air temperature	Medium	Inlet temperature will be adjusted to reach the desired product temperature. The range of 50-70°C is selected based on trial batches in GPCG-1.
Product temperature	High	Investigate with DOE
Air flow rate	High	Investigate with DOE
Spray rate/nozzle	High	Investigate with DOE
Atomization air pressure	High	Investigate with DOE

DoE

Ref: FDA MR ANDA case study (with modifications)

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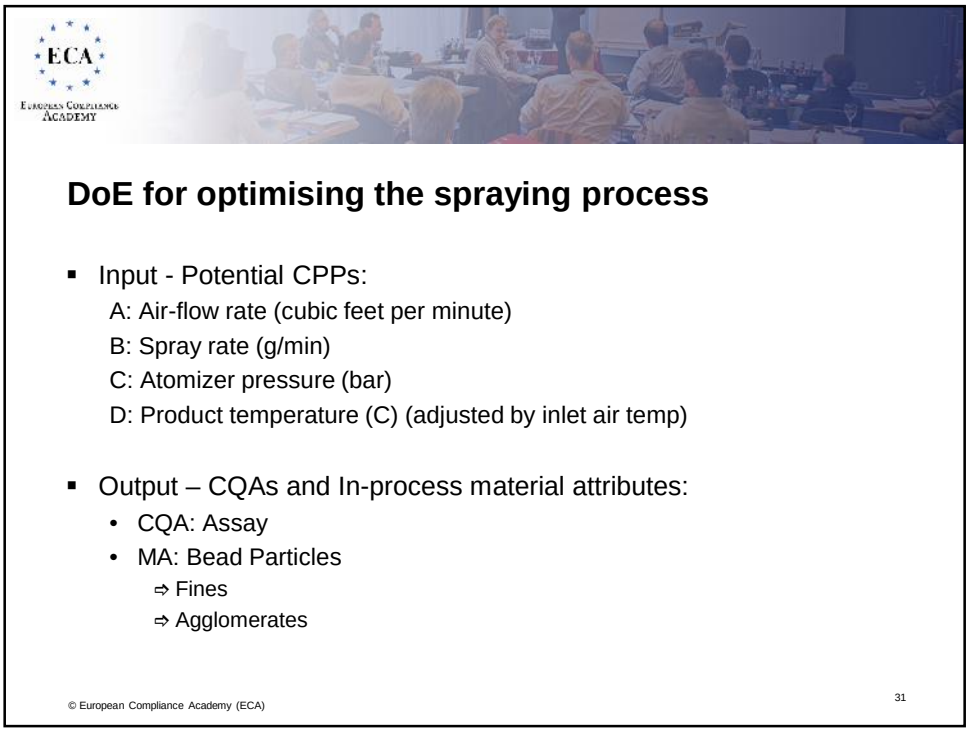

DoE for optimising the spraying process

- Input - Potential CPPs:
  - A: Air-flow rate (cubic feet per minute)
  - B: Spray rate (g/min)
  - C: Atomizer pressure (bar)
  - D: Product temperature (C) (adjusted by inlet air temp)
- Output – CQAs and In-process material attributes:
  - CQA: Assay
  - MA: Bead Particles
    - ⇨ Fines
    - ⇨ Agglomerates

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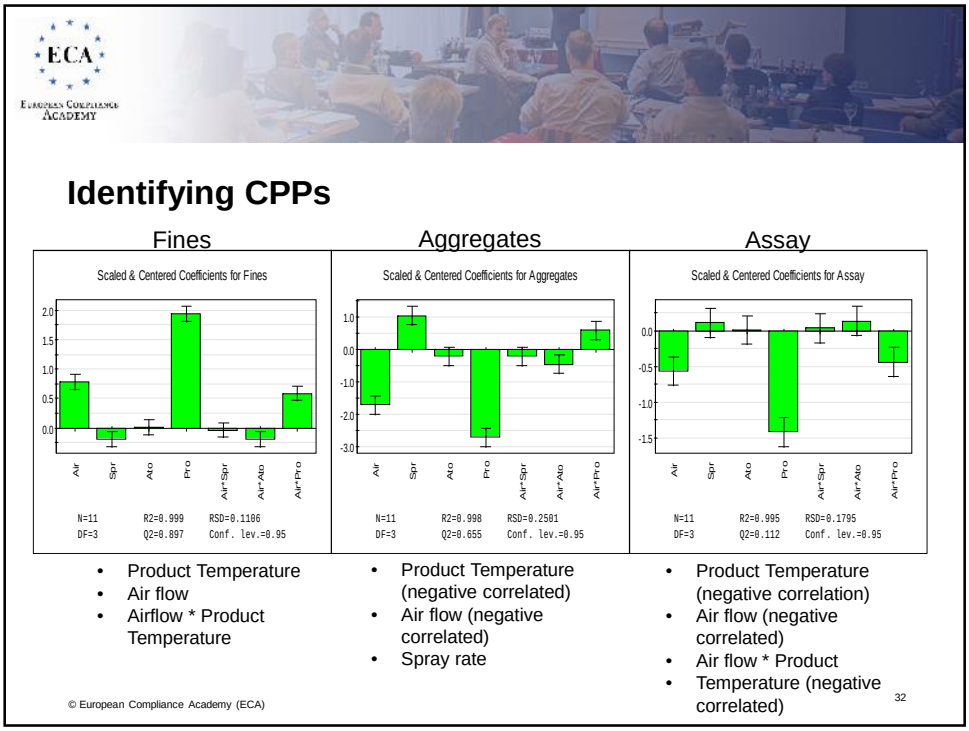

Identifying CPPs

Fines

- Product Temperature
- Air flow
- Airflow * Product Temperature

Aggregates

- Product Temperature (negative correlated)
- Air flow (negative correlated)
- Spray rate

Assay

- Product Temperature (negative correlation)
- Air flow (negative correlated)
- Air flow * Product
- Temperature (negative correlated)

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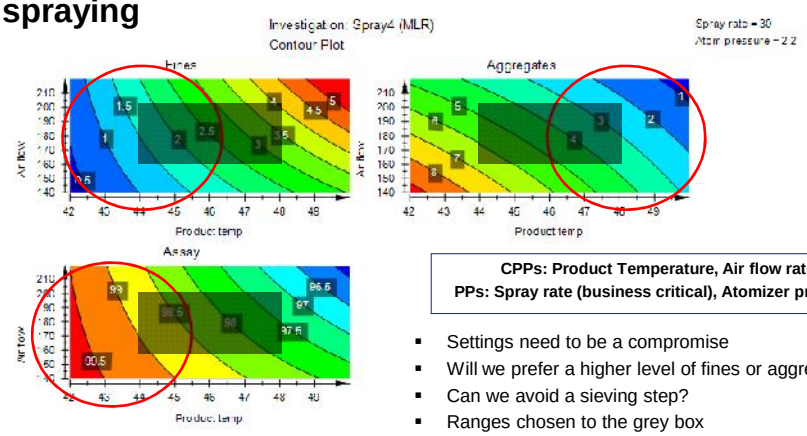
Choosing the right ranges/design space for spraying



CPPs: Product Temperature, Air flow rate
PPs: Spray rate (business critical), Atomizer pressure

- Settings need to be a compromise
- Will we prefer a higher level of fines or aggregates
- Can we avoid a sieving step?
- Ranges chosen to the grey box
- The grey box could also be used as a design space

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PAT

- PAT is still in its premature stage in many Generic companies
- Cost, skill sets and traditions are the main obstacles
- But the sector can gain significantly if PAT tools are applied during development, eg. in process chemistry
- Outcome: Process understanding gained faster and easier to identify CPPs, MAs and establishing a proper Control Strategy

- But PAT interest is increasing every day, particularly DoE, MVDA, NIR, FBRM and Raman technologies

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Templates

- Helps to make the activity:
  - A consistent way of working
  - More systematic
  - Science & Risk based approach are build into the templates
  - A constructive tool for cross-functional team work
  - Easier to share
  - Already filled-out template can be re-used
  - Faster to execute
  - Relevant aspects covered
- Everyone using the same tool, avoid inventing the wheel twice!
- Can be used for, e.g.:
  - QTPP, CQAs, Risk Assessment tools (cause/effect matrix, fishbone, FMEA, RAMM, etc) incl reference to prior knowledge, DoE incl justification for proposed experiments, CPPs, CMAs, Design Space, Ranges, Control Strategy, Process Validation etc

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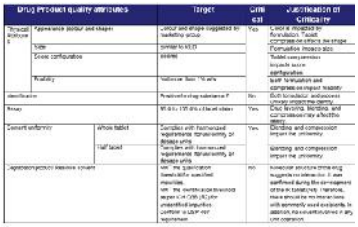
Example, CQAs

- Have a procedure in place on how to identify and determine CQAs, how to document, review frequency, who should be involved, milestones, approval etc
- Generic list of CQAs for each typical formulation class, e.g. based on release mechanism as well as formulation class (oral solid; oral liquid; injection; suspension)
- Criticality assessment procedure, i.e. how to determine if a QA is Critical
- The link from the CQAs/QAs to the QTPP
- Target range for the CQAs/QAs, including justification
- References



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Outline

- Is there a business case for the Generic Industry to apply QbD principles?
- How to implement QbD from a practical point of view
  - How can QbD help prioritise development activities
  - QbD Roadmap
  - QRM tools
  - DoE
  - PAT
  - Templates
- Result of a successful implementation
  - Process Validation
  - Development activities, QbR, ANDAs
  - Industry Progress

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Process Validation, definition (FDA)

"Process validation is the **collection and evaluation of data**, from the **process design stage** throughout production, which **establishes scientific evidence** that a process is capable of **consistently** delivering **quality products**."

FDA PV guide

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Process validation – goal and success criteria

- Homogeneity within a batch and consistency between batches are goals of process validation activities
- A successful process validation depends on the level of:
  - General process understanding
  - Understanding sources of variation
  - Understanding the impact of process and material variability on the product quality
  - Established controls to control variation in a manner commensurate with the risk it represents to the process and product

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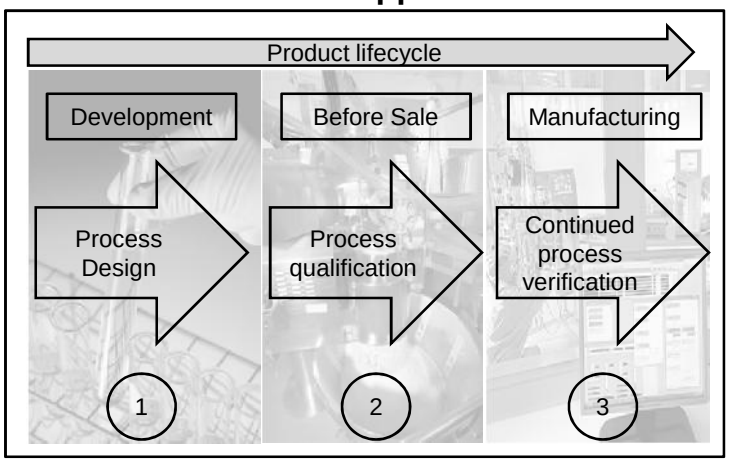
FDAs Process Validation approach



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Validation lifecycle stages

Stage 1: Process Design

- Defines the commercial process including a control strategy based on knowledge gained through development and scale-up

Stage 2: Process Qualification

- Confirms the process design as being capable of reproducible commercial manufacturing

Stage 3: Continued Process Verification

- On-going assurance that during routine production the process remains in a state of control

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PV stage 1 - examples of deliverables

Elements	Description
Quality Attributes (CQAs)	Important Product Characteristics
Process Flow Diagram	Description of unit operations, including draft batch record
Quality Risk Assessment	Risk/Criticality/impact assessment of incoming raw and in-process materials and unit operations on drug product quality of unit operations and material attributes on drug product quality
Process Parameters (CPPs)	Identification of any critical process parameters that should be monitored and/or controlled to ensure product quality
Material Attribute (CMAs)	Any excipient quality attributes that has been identified to have an impact on the CQAs. Specifications for these
Scale issues	Expected or Predicted impact of scale at this stage (may not yet be known, but should be predicted at a minimum)
Operating ranges (eg Design Space)	For all relevant process parameters and quality attributes, any ranges, design spaces, models
Control strategy	Mechanisms to sample, measure and control the drug product quality incl. any material attributes or process parameters

Link between QbD and PV

- QbD and Process Validation are interlinked
- PV stage 1 is sometimes called “QbD”…
- Many Process Validation elements are nearly “given for free” if working in a QbD framework, e.g. Stage 1, and Stage 3
- Stage 2.2 – Process Performance Qualification is “verifying the control strategy”
- Application of prior knowledge including experience from similar products can be used to justify appropriate validation/verification activities
- Maintaining a state of control is exactly what should be the output of an enhanced QbD approach!

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Process Validation – Legacy Products
The 7 Step Model

- The 7 step model was developed by NNE Pharmaplan to help organizations implement the FDA Process Validation Guidance
- It was designed to cope with legacy products in potentially high pressure situations, including Generics
- It is a Science & Risk based QbD approach
- Each step has associated tools, methodologies and skills sets which are required for speedy and successful execution

- The model has successfully been used in the Generic Industry for:
  - Closing compliance issues in relation to Process Validation
  - Establishing a Stage 3 CPV plan

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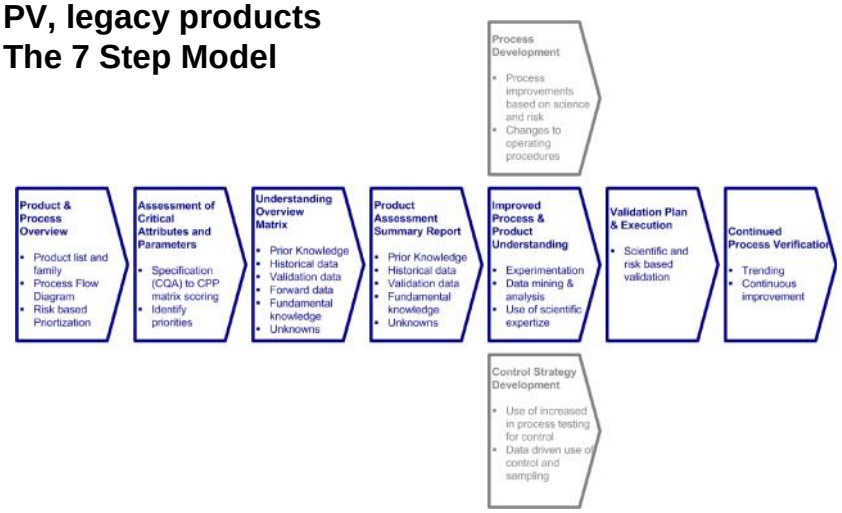
PV, legacy products
The 7 Step Model



Ref: A Brindle & L Lundsberg, NNE Pharmaplan

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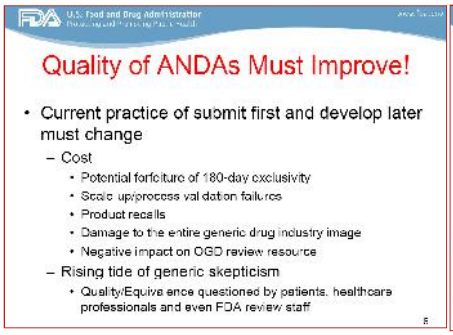
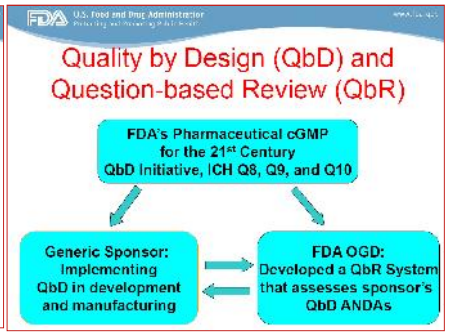
FDA, OGDs – QbD and ANDAs





Ref: Lawrence X. Yu, Ph. D., *Deputy Director for Science and Chemistry Office of Generic Drugs, Food and Drug Administration*
GPhA Fall Technical Workshop, October 20-21, 2010

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Question-Based Review (QbR)

- The QbR is a framework for CMC assessment of ANDAs
- QbR is a set of questions to be answered in the Overall Quality Summary
- A guide to the reviewer in the evaluation of whether a product is of high quality and in the determination of the level of risk associated with the manufacture and design of the product
- Transparency to sponsors about the logic that reviewers invoke in their CMC reviews
- QbD helps answering the current questions
- QbR to be updated to reflect QbD

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FDA Expectations from January 2013

- ANDA to contain at least the minimum information on pharmaceutical development described by ICH Q8(R2):
  - Quality target product profile (QTPP)
  - Critical quality attributes (CQAs) of the drug product
  - CQAs of the drug substance and excipients.
  - Selection of an appropriate manufacturing process.
  - Control strategy
- Additional
  - Information that conveys an understanding of the development of the drug product and its manufacturing process
  - Identification of those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality that support the safety and efficacy of the drug product
  - Justifications for the control strategy

Ref.: FDA, CDER, OPS, MAPP 5016.1
08.02.2011 &
K Webber, Deputy Director FDA, CDER, OPS; EGA/ISPE Brussels June 2012

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Proposed new QbR Questions, 2.3.P Drug Product, examples

2.3.P.2 Pharmaceutical Development

- What are the characteristics of the RLD Product?
- What are the elements, targets and justifications of the Quality Target Product Profile (QTPP)?
- For each quality attribute of the drug product, what is the target and how is it justified? How were the critical quality attributes (CQAs) selected?
- If applicable, what in-vitro bio-performance evaluations (i.e., dissolution method, flux assay, etc.) were used during pharmaceutical development and how were they developed?

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2.3.P.2.2 Drug Product

- How was the drug product designed to meet the drug product QTPP and CQAs?
- How were the excipient types and grades selected?
- What formulation development studies, including screening, characterization, optimization, and verification (robustness), if any, were conducted?
- What attributes of the drug substance, excipients, and in-process materials were identified as critical via risk assessment and Design of Experiments when appropriate and how are they related to the drug product CQAs?

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2.3.P.2.3 Manufacturing Process Development

- What is the rationale for selecting this manufacturing process for the drug product?
- What process development studies, including screening, characterization, optimization, and verification (robustness), if any, were conducted and at what scale?
- What is the process map listing input material attributes, process parameters, and output material quality attributes for all of the unit operations in the manufacturing process?

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2.3.P.2.3 Manufacturing Process Development

- For each unit operation, what process parameters and material attributes (drug substance, excipients and in-process materials) were identified as critical via risk assessment and Design of Experiments when appropriate and how are they related to the drug product CQAs?
- What is the Control Strategy for CMAs of input materials, CPPs of manufacturing process, and CQAs of output materials for each unit operation?
- How was scale dependence for each process step evaluated during pharmaceutical development? How did the critical process parameters change across scale?

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How are the industry progressing

- Many generic companies are now implementing QbD principles
  - FDA/GPhA case studies being used for inspiration
  - QRM being implemented
  - DoE is becoming more popular
  - Process Analysers and Real Time Release Testing less widespread
  - Several papers been presented by the Industry
- First full QbD ANDA has been submitted (to my knowledge)
- QbD principles being applied in API, drug product and for biologics

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Conclusion

- QbD is also for the Generic Industry and they are catching up with passion and significant dedication!
- Should have a positive influence on First-to-File as more understanding gained during development and “file first, develop later” can be avoided
- QbR will be QbD oriented
- FDA expects “minimal approach”, Q8
- EMA expects similar (company experiences)
- Future challenges will be to invest in PAT
- … but no reason for not getting on board and make it a business driver!

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Thank you for your attention!

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