PROCESS VALIDATION

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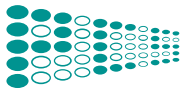
PROCESS VALIDATION: GENERAL PRINCIPLES AND PRACTICES

Process Validation and Drug Quality

Effective process validation contributes significantly to assuring drug quality. The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. This principle incorporates the understanding that the following conditions exist:

- Quality, safety, and efficacy are designed or built into the product.
- Quality cannot be adequately assured merely by in-process and finished-product inspection or testing.
- Each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including specifications.

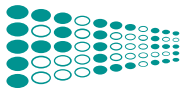


PROCESS VALIDATION: GENERAL PRINCIPLES AND PRACTICES

Approach to Process Validation

Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.

Process validation involves a series of activities taking place during the lifecycle of the product and process.



PROCESS VALIDATION: GENERAL PRINCIPLES AND PRACTICES

Approach to Process Validation, ctd

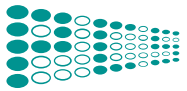
- **Stage 1 – Process Design:** The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
- **Stage 2 – Process Qualification:** During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- **Stage 3 – Continued Process Verification:** Ongoing assurance is gained during routine production that the process remains in a state of control.

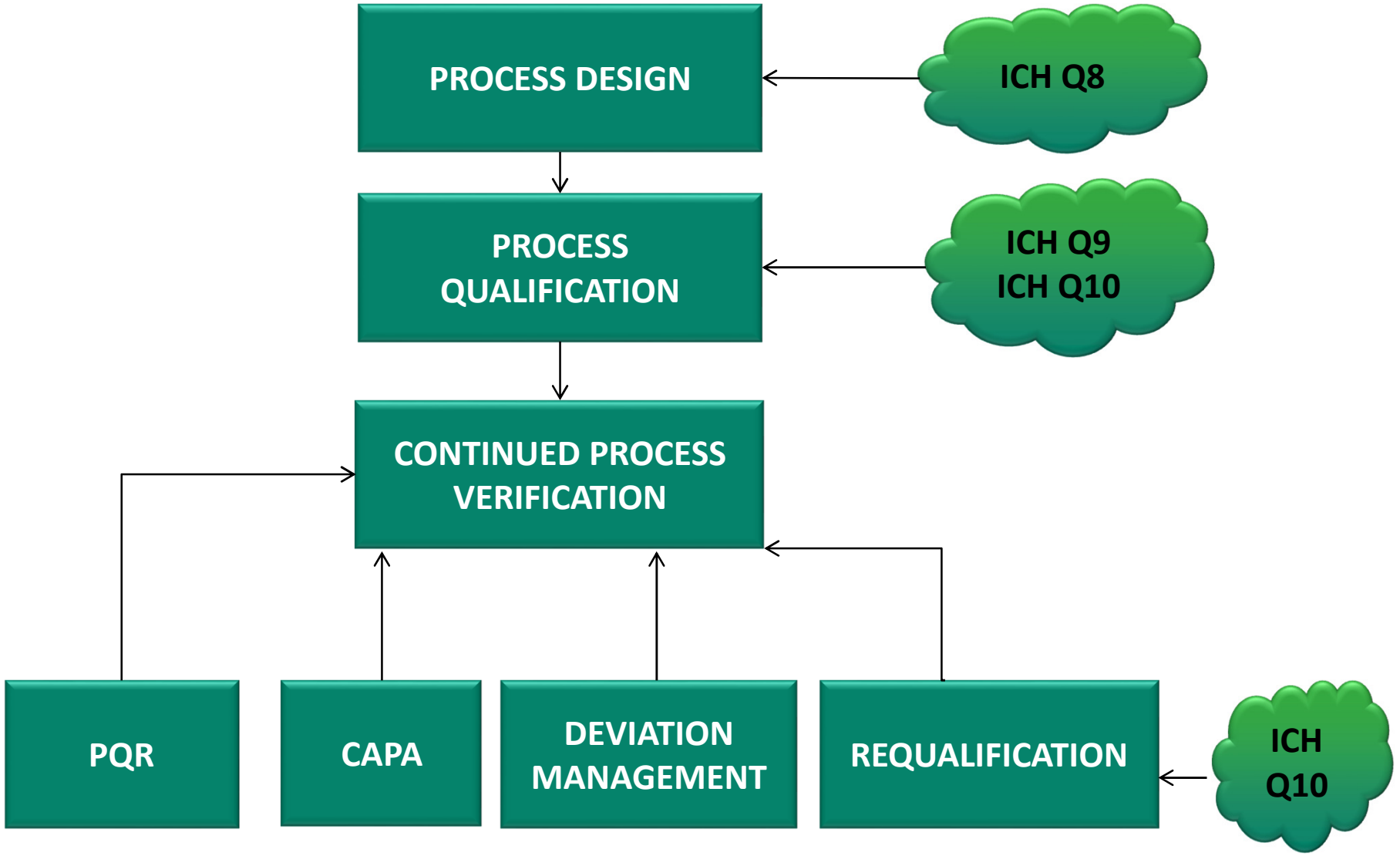
PROCESS VALIDATION: GENERAL PRINCIPLES AND PRACTICES

Approach to Process Validation

A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process that results in products with the desired quality attributes. Manufacturers should:

- Understand the sources of variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process and ultimately on product attributes (and intermediates)
- Control the variation in a manner commensurate with the risk it represents to the process and product





DESIGN PHASE

During the Design Phase

Built to be robust….

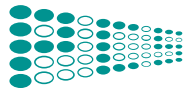
- QbD (Quality by Design)
- DoE (Design of Experiments)

Knowledge-build-up of the process, intermediates, product

Development/Engineering of the Process

- Block Flow Diagram (BFD)
- Process Flow Diagrams (PFD)
- Parameters, determine critical (CCP) and non-critical parameters and Critical Attributes (CQA)

Develop a definition/rational of what is- and what is not critical



DESIGN PHASE

During the Design Phase, *ctd.*

Development/Engineering of Process

Critical (CQA) and non-critical Quality Attributes (specification/characteristics):

- *It is advisable to develop (CQA's) for in-process, intermediates as for product.*
- *Yield expected to be determined per each one-unit-operation*
- *Again: it is sometimes difficult to determine what is critical and non-critical*

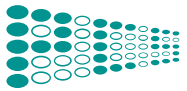
DESIGN PHASE

During the Design Phase, *ctd.*

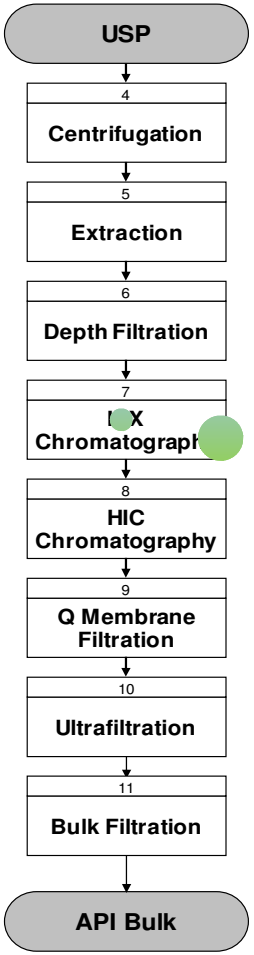
Development/Engineering of Process

- Material Input: Qualified Vendors (!)
- Holding Times (!)
- Sampling plan: develop for use during the commercial phase.

  Advise: develop a process-training manual containing a process-description and an explanation of the rationale for the chosen Parameters and Attributes (specifications in-process/product).



BFD (EXAMPLE)



Concentration of cells
The Cells produced during the former step are centrifuged using a continous- flow centrifuge.The antigen-carbohydrates (CH) are present on the surface of the cells.

Release of HA
The concentrated cells (cell pellet) with intracellular carbohydrates, are solubilized (releasing CH) using a Tween-80-containing extraction buffer.

Cell debris removal
The first purification step is the clarification of the extracted material by the use of depth filters. Cell debris is filtered out of the extracted material, solubilized CH flows through the filter.

Capture of CH
CH-cont ing Depth Filtrate is ar
on th and the flow throu
elute ected.

Further purification
CH containing Eluat
column and the flow
collected.

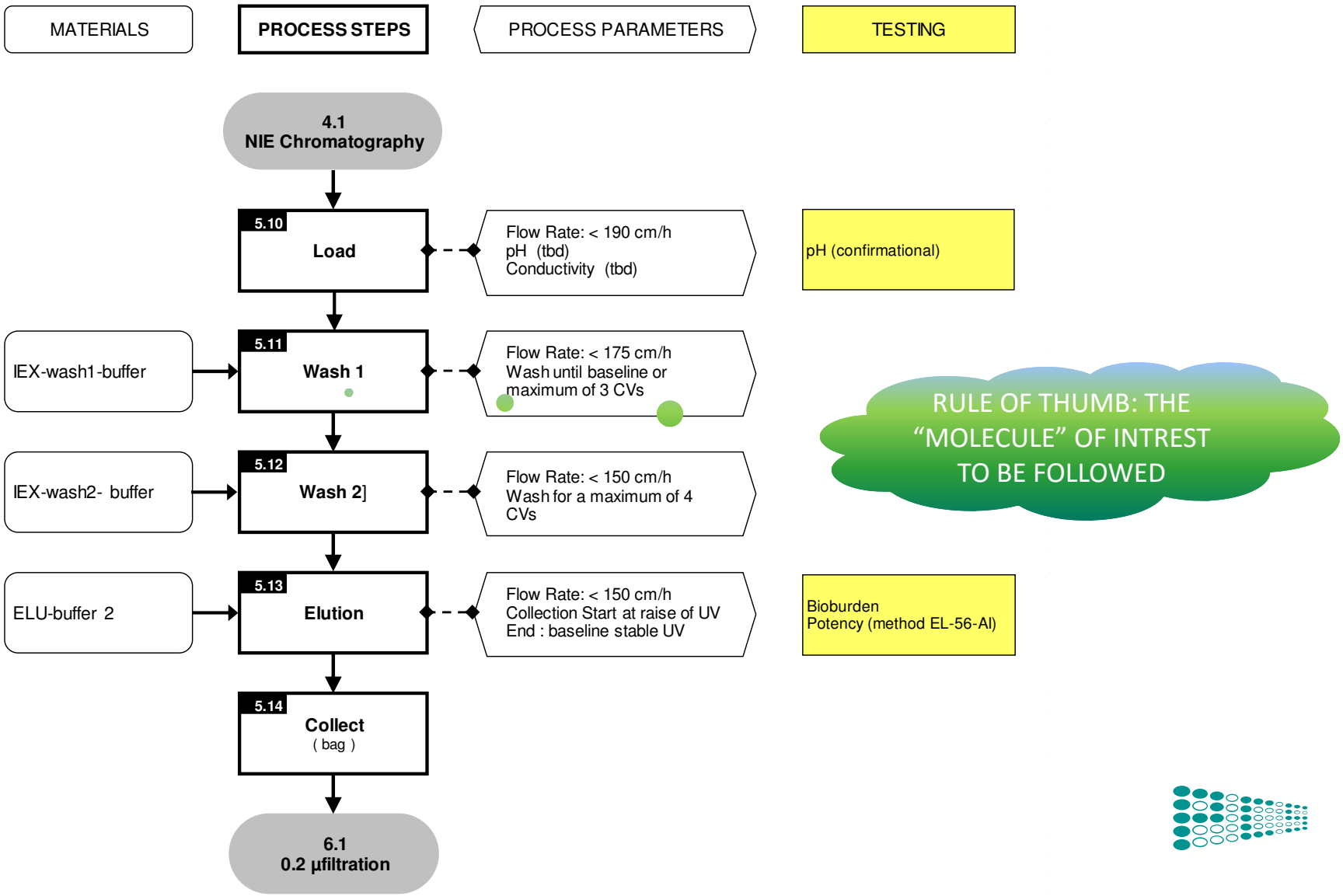
DNA Removal
The CH product flows t
filter.

Buffer Exchange
Using a diafiltration technique, the product is buff eller
containing excipients for final formulation

Final Filtration
The product is conditioned for storage and secured by final filtration using a sterilizing filter.

RULE OF THUMB: THE "MOLECULE" OF INTREST TO BE FOLLOWED

PFD (EXAMPLE)


MATERIALS
PROCESS STEPS
PROCESS PARAMETERS
TESTING
4.1
NIE Chromatography
5.10
Load
Flow Rate: < 190 cm/h
pH (tbd)
Conductivity (tbd)
pH (confirmational)
lEX-wash1-buffer
5.11
Wash 1
Flow Rate: < 175 cm/h
Wash until baseline or
maximum of 3 CVs
lEX-wash2- buffer
5.12
Wash 2]
Flow Rate: < 150 cm/h
Wash for a maximum of 4
CVs
ELU-buffer 2
5.13
Elution
Flow Rate: < 150 cm/h
Collection Start at raise of UV
End : baseline stable UV
Bioburden
Potency (method EL-56-Al)
5.14
Collect
(bag)
6.1
0.2 µfiltration
RULE OF THUMB: THE
“MOLECULE” OF INTREST
TO BE FOLLOWED

STAGE 1 DESIGN PHASE

During the Design Phase, *ctd.*

- The final goal BEFORE commercial phase is: process-robustness.

  In other words: as few improvizations as possible when the product/process goes commercial.

- Whereby the process is fully defined, after which training (knowledge-transfer) to operations can proceed at an optimal level.
- QA is indispensable for correctly and critically defining and recording required implementation of needed applicable QMS-elements (e.g. training etc.)

STAGE 2 PPQ PHASE

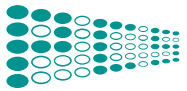
PPQ (FDA-term)

- Process Performance Qualification (PPQ) preceded by Qualification of equipment, facilities, utilities, personnell etc.
- Defined test-functions to show process-robustness
- Number of batches (when does the PPQ-fase stop): rationale is present.
- Not in the guidelines but widely used: CpK

  However; in an older draft –late 90's- Annex 15 (EU) mentioned CpK.

STAGE 2: PPQ PHASE

- Demonstrate that commercial manufacture performs as expected
- “Not all process ranges need be explored” during process validation *(Stage 1 information to be used)*
- Process validation has “higher level of sampling, testing and scrutiny”
- Performed according to classical protocol/report system
- Standard 3 batches paradigm is out, appropriate determined number of batches to be justified: science/data driven
- In case ancient process: reconsider PV.

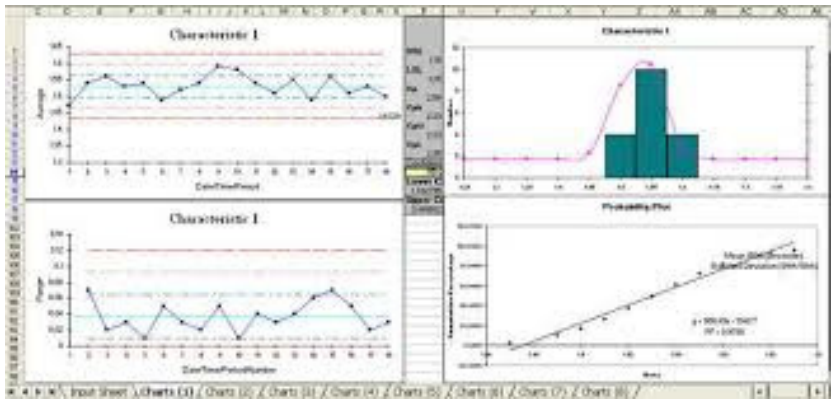


STAGE 3 CPV PHASE

Continued Process Verification (CPV)

After initial process-validation activities, process should be monitored (Process-vigilance) for trends and process-improvements.

- Data-points, depending on the process and circumstances
- Such as (examples, not limited to):
  - *CpK's*
  - *Data-mining*
  - *Statistics*
  - *OOT's (Out of Trends)*
  - *Reporting*
  - *Metrics / Quality Reporting*
  - *Management Review*



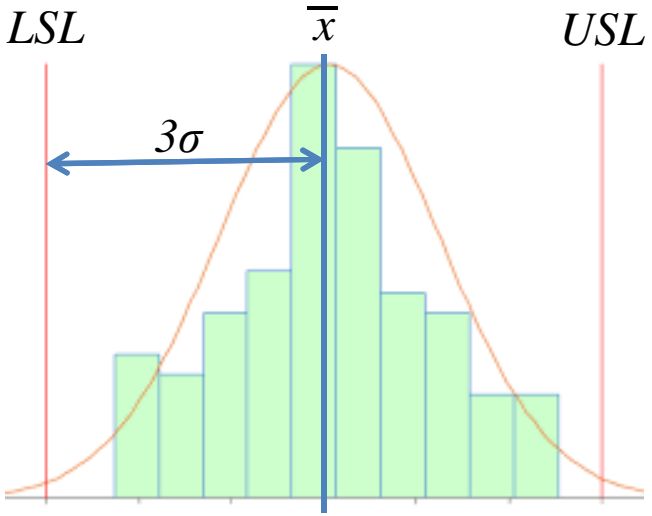
STAGE 3 CPV PHASE

Continued Process Verification (CPV)

- Not in the guidelines but widely used: CpK

  CpK ≤ 1 ; 1 < CpK < 1,33 ; CpK ≥ 1,33

$$Cpk = \min\left\{ \frac{USL - \bar{x}}{3\sigma} , \frac{\bar{x} - LSL}{3\sigma} \right\}$$

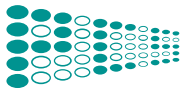


STAGE 3: CPV PHASE

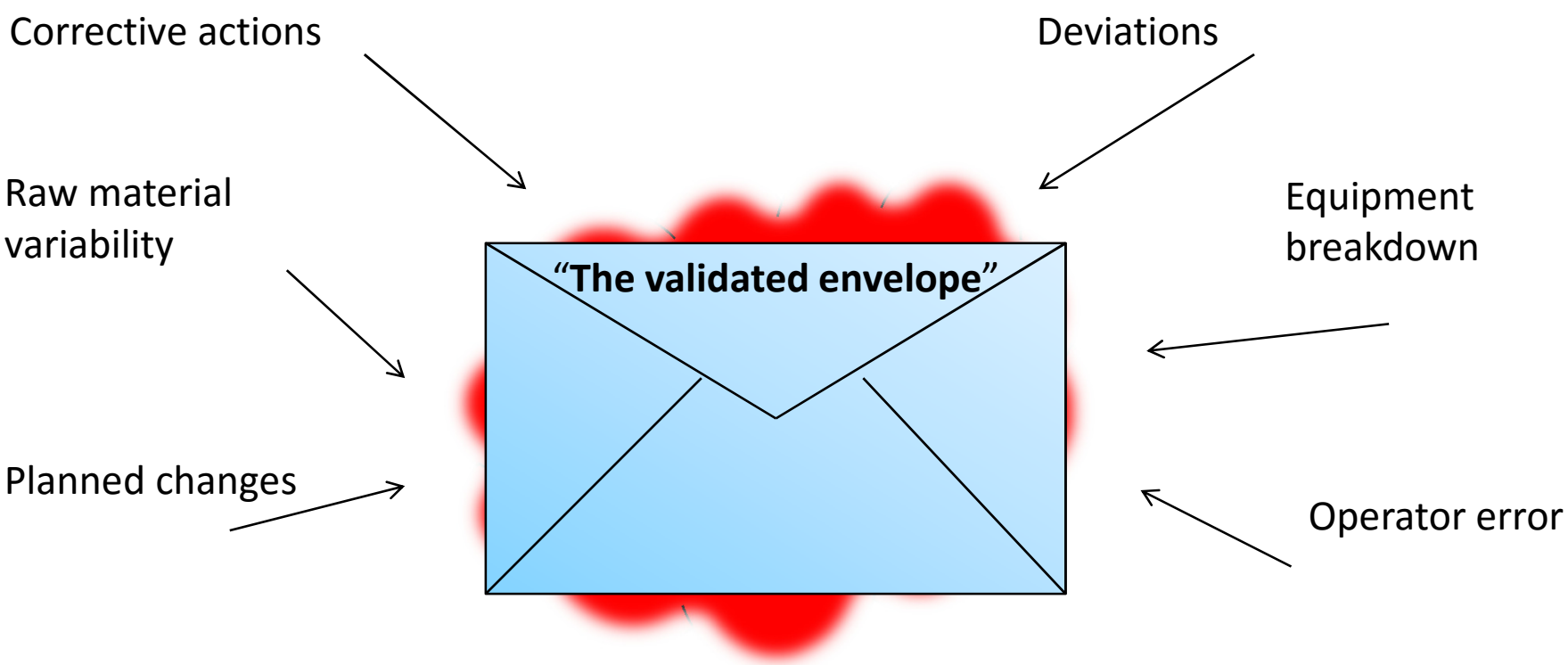
- “Continual assurance” that process is in a state of control
- Process operates within the “validated state”
- Adherence to cGMP requirements to detect “undesired process variability”
- “Ongoing programme to collect and analyse product and process data must be established” (e.g. APQR)
- Use of statistical trend analysis “recommended”
- “Quality Unit should review this information”
- Higher level of sampling and testing should continue during initial phase of commercial manufacture (concurrent validation)

STAGE 3: CPV PHASE

- Timely assessment of defects, complaints, OOL/OOT, yields, batch records etc.
- “Production line operators and quality unit staff to provide feedback on process performance”
- “Recommend quality unit met periodically with production staff to evaluate data”
- Data used to feed a CAPA system after full evaluation
- Changes driven by CAPA to be implemented via change control system
- Significant changes may result in new process design, process qualification (and licensing)
- Remark check product performance, recalls, complaints and the more, to assure that you didn’t “missed” something in your IPC/QC -testing



THE VALIDATED ENVELOPE



How far can the process move out of the validated envelope before it is no longer valid?

CPV PHASE / OPERATIONS

- All non-validated conditions represent a potential risk to product (and regulatory compliance) and should be avoided
- Wherever possible, the validated envelope should be wide enough to include anticipated conditions (e.g. largest and smallest batch sizes, processing times, conditions, etc.)
- Certain failure modes (e.g. power loss) can be identified using risk assessment tools (e.g. FMEA) and can be prospectively validated.
- Validation cannot foresee all situations that may arise

CPV PHASE / OPERATIONS

- Decision on non-validated situations will be made based upon risk assessment principles (ICH Q9)
- Decisions to be made include:
  - Impact of event on product quality
  - Impact of event on other products/batches/regulatory impact assessment
  - Need for additional supporting data (e.g. stability)
  - Corrective actions
  - Preventative actions

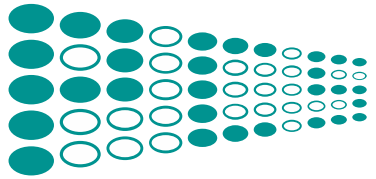
CPV PHASE / OPERATIONS

- Access to all relevant data (current event, historical situation trends)
- Appropriate subject matter experts (Production, QC, Engineering)
- Use of standardised risk assessment methodology to ensure impact is correctly defined
- Use of standardised investigational tools to ensure plausible root cause analysis and definition of most appropriate CAPAs
- Thorough documentation of decision-making process, including justification for actions taken
- Avoidance of “box ticking” attitude and “quick fixes”

IN CONCLUSION

1. Process controls to be established during Design Phase (**Phase 1**)
2. To be defined (rational based) number of batches to be included during PPQ (**Phase 2**), protocol driven.
   - Commercialization started
   - Report to be issued to conclude the PPQ Phase
3. Monitoring/vigilance of process during further manufacturing continues: (Continuous) Verification Phase (**Phase 3**)

THANK YOU FOR YOU ATTENTION



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