Regulators perspective on Quality by Design - BWP perspective

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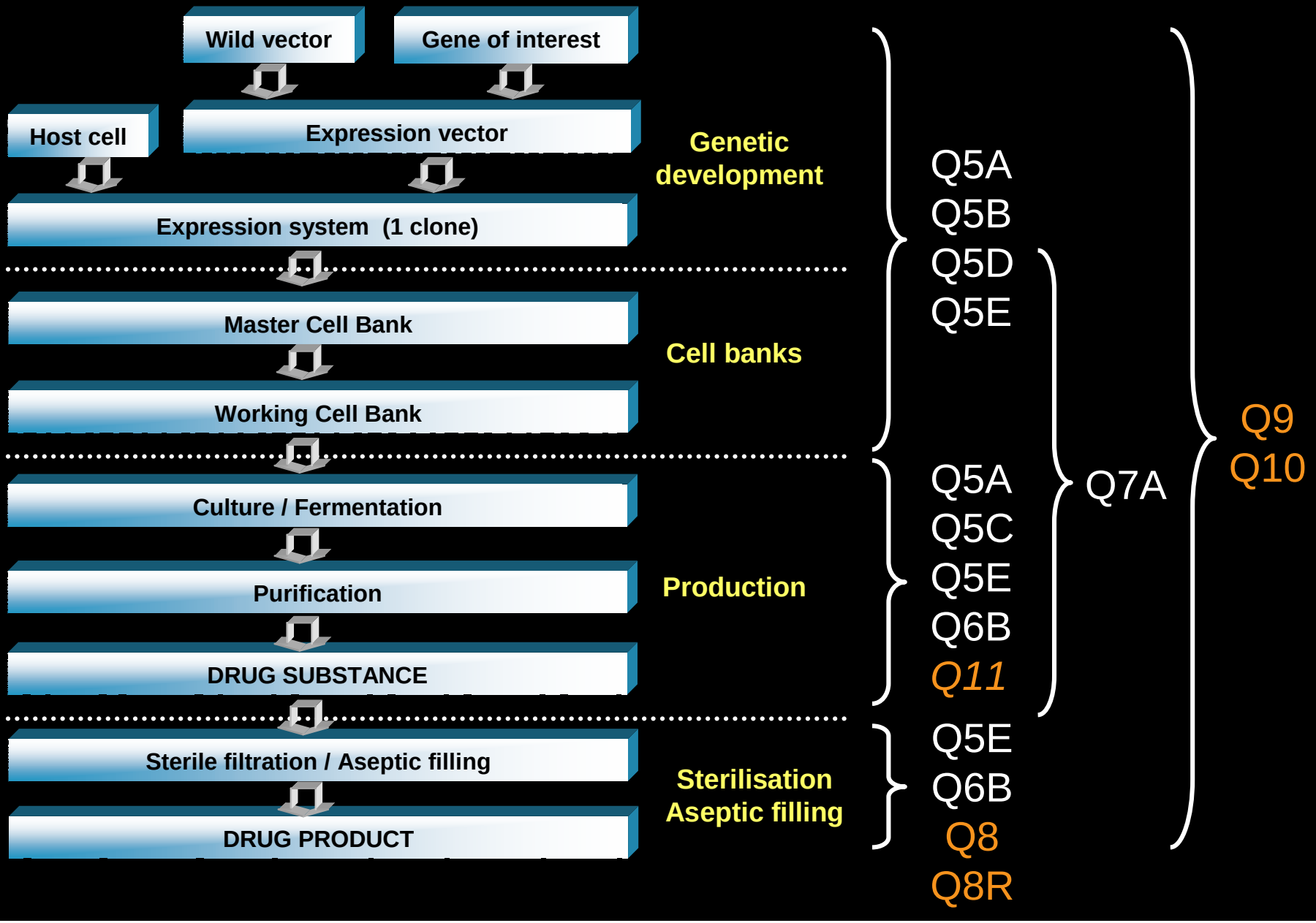
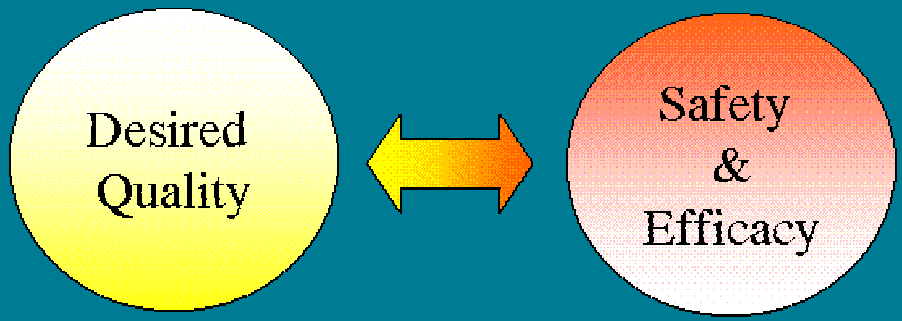
Typical biotech manufacturing process



Critical Quality Attributes

- Target product profile (Q8R):
  - a prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and hence the safety and efficacy, of a drug product is realised.
  - Includes: Drug product quality criteria (e.g., sterility, purity) appropriate for the intended marketed product.



- Quality (Q6A):
  - The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity.

Critical Quality Attributes

- CQA (Q8R):
  - Associated with drug product, drug substance, intermediates and excipients.
  - include the properties that impart the desired quality, safety, and efficacy.
  - Quality risk management can be used to prioritize the list of potential CQAs for subsequent evaluation.

PHYSICOCHEMICAL CHARACTERISTICS

BIOLOGICAL CHARACTERISTICS

VARIABLE REGION
- Deamidation
- Oxidation
- N-term Pyro-Glu
- Glycosylation
- Glycation

…

CONSTANT REGION
- Deamidation
- Oxidation
- Acetylation
- Glycation
- Glycosylation (fucosylation, sialylation, galactosylation, mannosylation…)
- C-term Lys
- Di-sulfide bond shuffling/ cleavage
- Fragmentation/clipping

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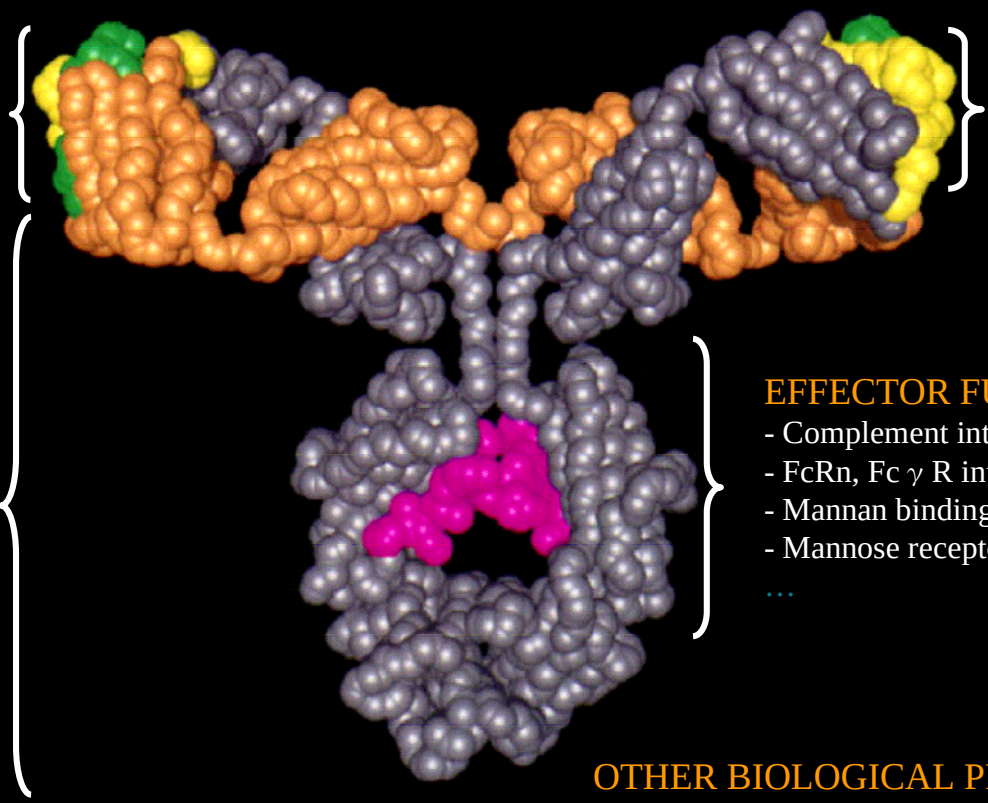

BINDING
- Affinity
- Avidity
- Immunoreactivity / crossreactivity
- Unintentional reactivity

…

EFFECTOR FUNCTION
- Complement interaction
- FcRn, Fc γ R interaction
- Mannan binding ligand interaction
- Mannose receptor interaction

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OTHER BIOLOGICAL PROPERTIES
- PK properties
- Epitope / Immunogenicity
- Modulatory region (Tregitope …)

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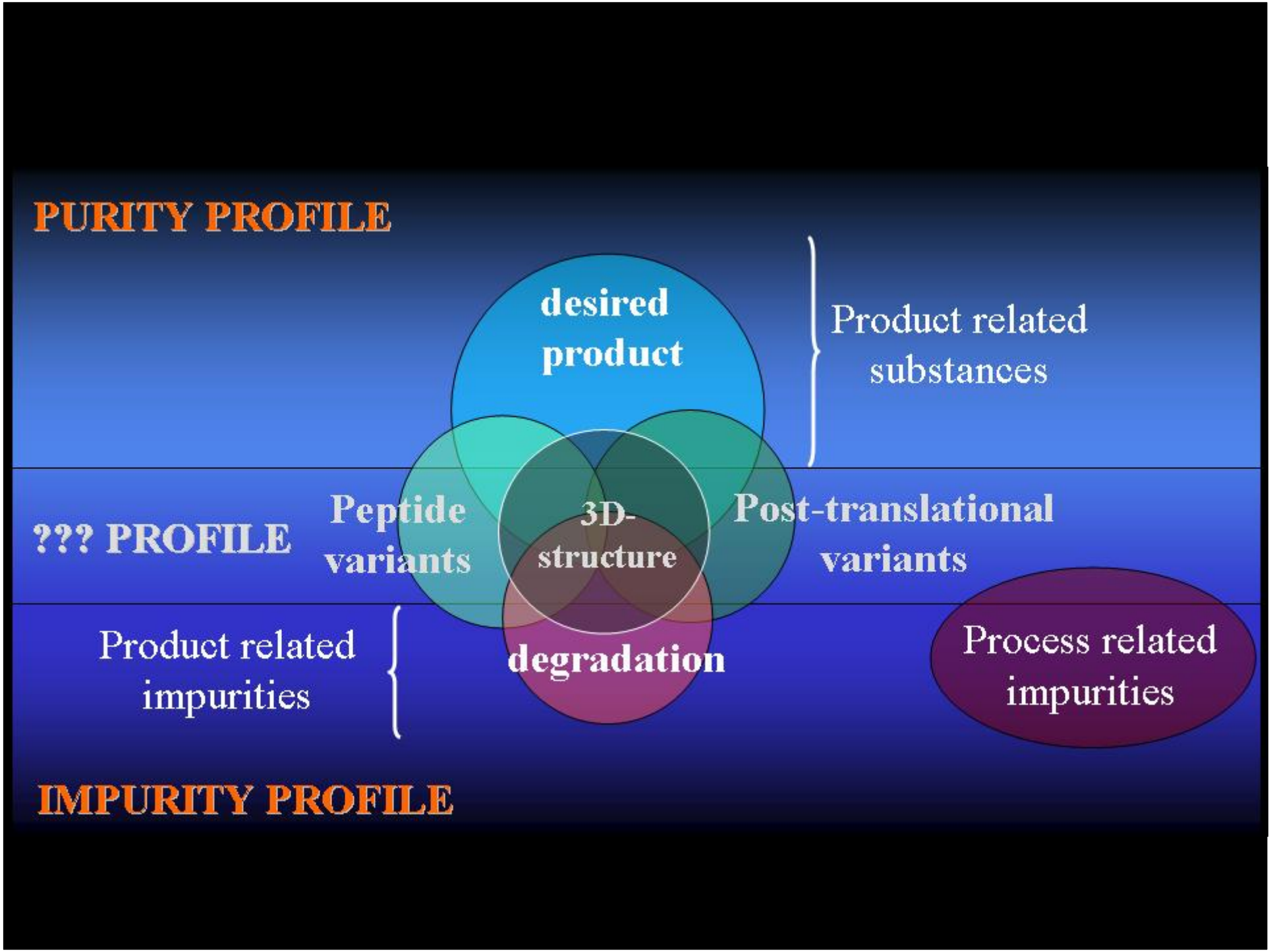
Desired quality ??? CQA ???

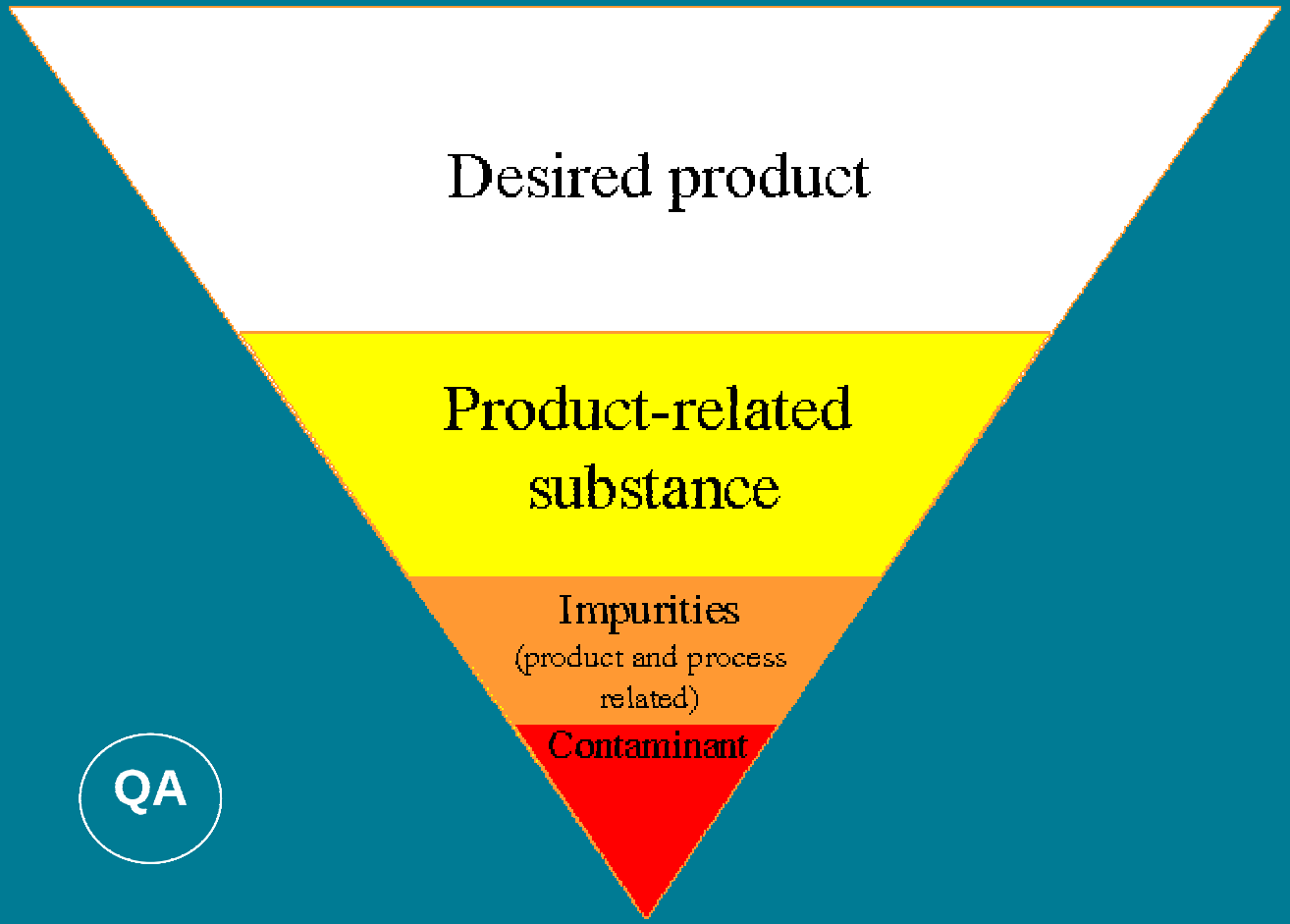

PURITY PROFILE
desired product
Product related substances
??? PROFILE
Peptide variants
3D-structure
Post-translational variants
Product related impurities
degradation
Process related impurities
IMPURITY PROFILE

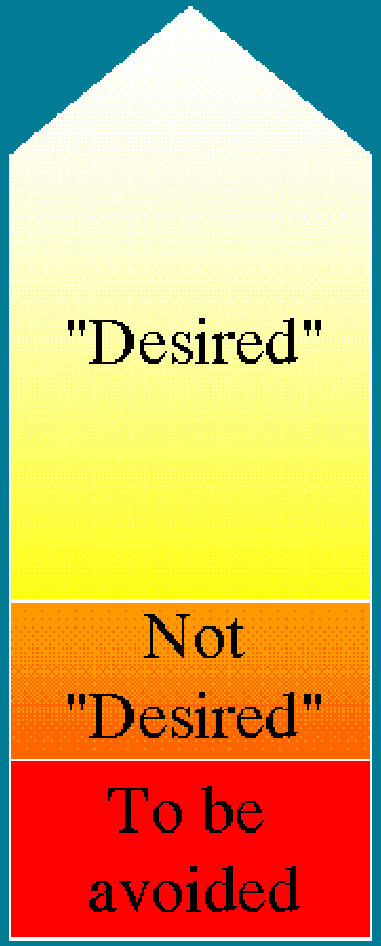
Critical Quality Attributes

- **Desired Product (Q6B):**
  - (1) The protein which has the expected structure, or
  - (2) the protein which is expected from the DNA sequence and anticipated post-translational modification (including glycoforms), and from the intended downstream modification to produce an active biological molecule.
- **Product-Related Substances (Q6B):**
  - Molecular variants of the desired product formed during manufacture and/or storage which are active and have no deleterious effect on the safety and efficacy of the drug product. These variants possess properties comparable to the desired product and are not considered impurities.
- **Product-Related Impurities (Q6B):**
  - Molecular variants of the desired product (e.g., precursors, certain degradation products arising during manufacture and/or storage) which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety.

Desired Quality not limited to product-related impurities !!!

Critical Quality Attributes



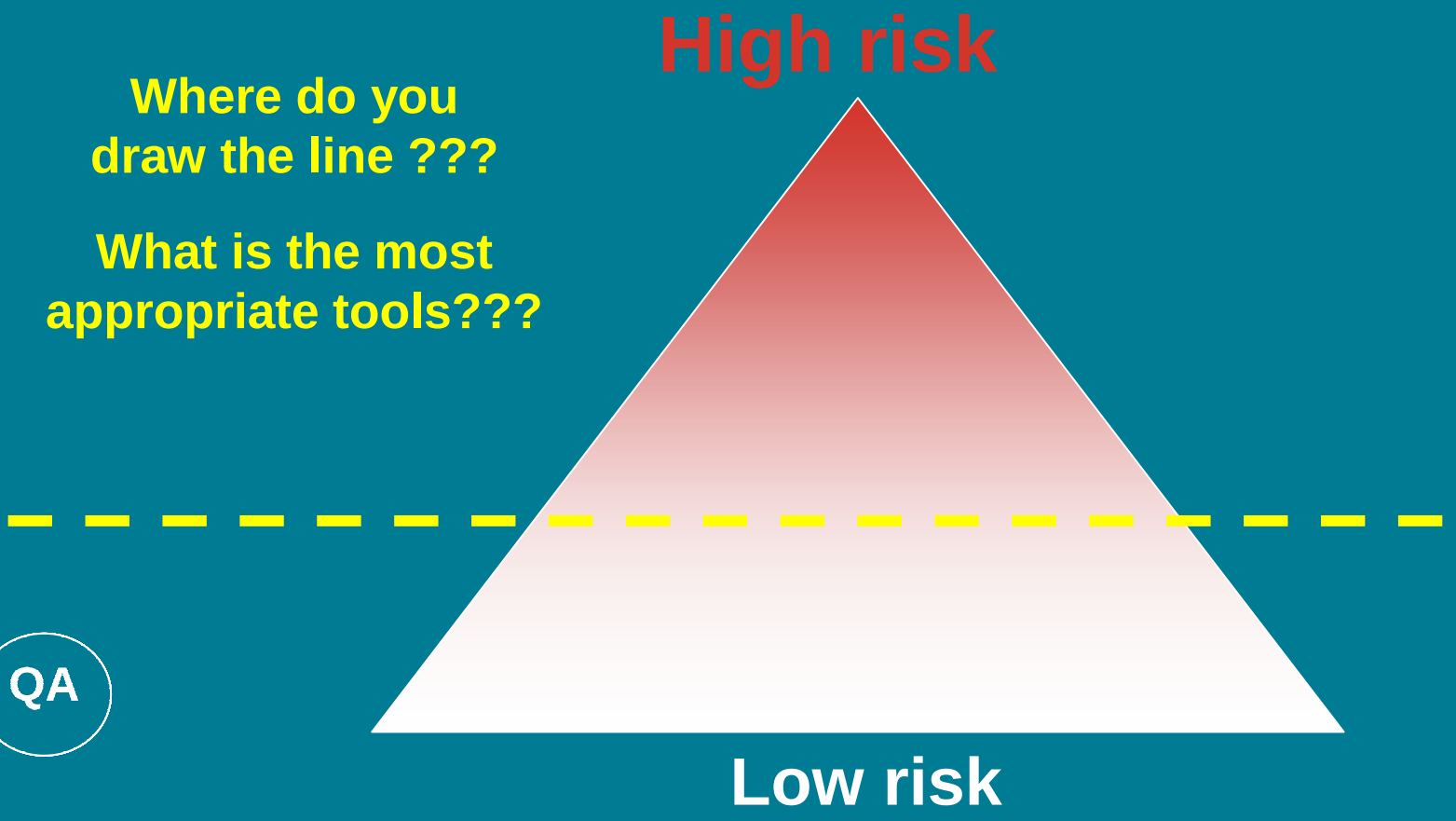


QA

Critical Quality Attributes

Where do you draw the line ???

What is the most appropriate tools???



QA

Critical Process Parameters

- Critical Process Parameter
  - ICHQ8R:
    - 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.
    - Risk assessment: can aid in identifying which material attributes and process parameters have an effect on product CQAs.
  - Must take into account relevant guidances (e.g. ICH Q5 series)

- **Production and quality control of Medicinal products derived by Recombinant DNA technology (3AB1a)**
  - Special attention to factors that may compromise the consistency, safety and efficacy of rDNA-derived products, e.g.:
    - Genetic stability
    - Protein from foreign hosts may deviate structurally, biologically or immunologically from their natural counterparts…
    - Manufacturing procedure will influence the nature, range and amount of potential impurities in the final product…
    - Unintended variability in the culture during production may lead to changes which favour the expression of other genes in the host/vector system or which cause alteration in the product.
    - Extensive “scale-up” at the level of fermentation and/or purification occurs as laboratory developments progress to full scale commercial production, and this may have considerable consequences for the quality of the product including effects on its conformational structure, yield and/or in quantitative and qualitative differences in impurities…

Submitted?

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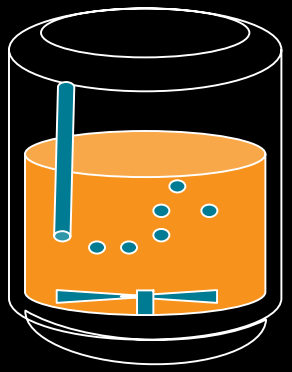

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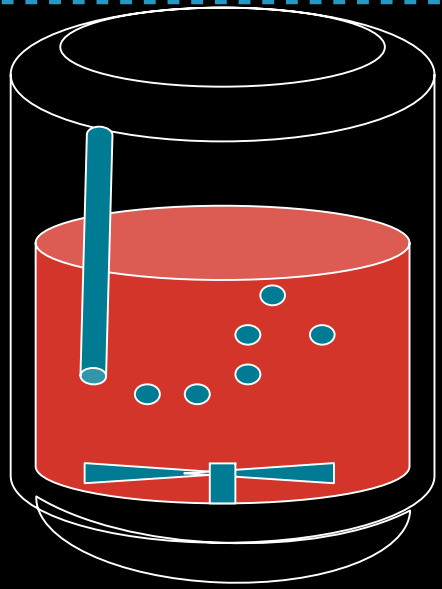

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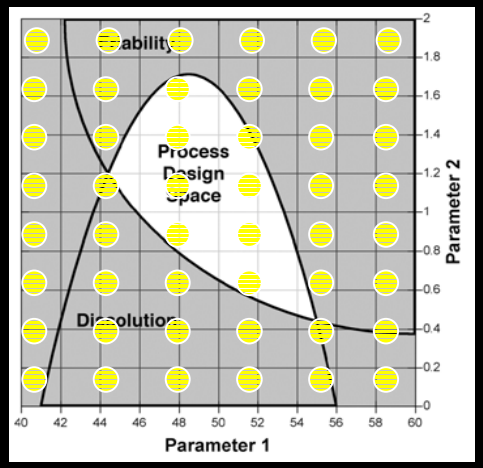
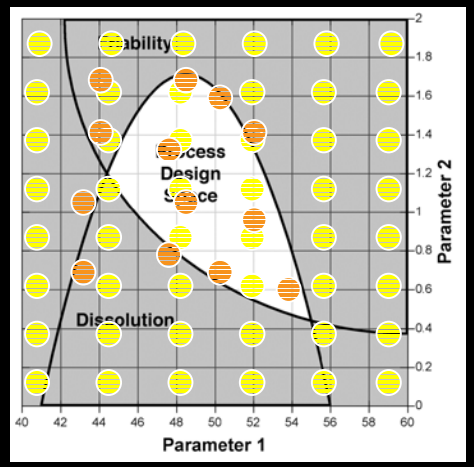
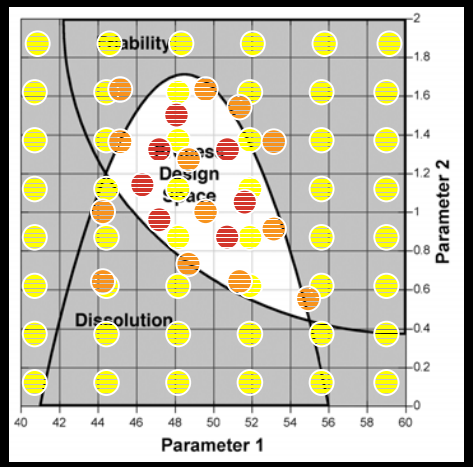


« Process characterisation »



Clinical trials



Commercial

Comparability? Validation?

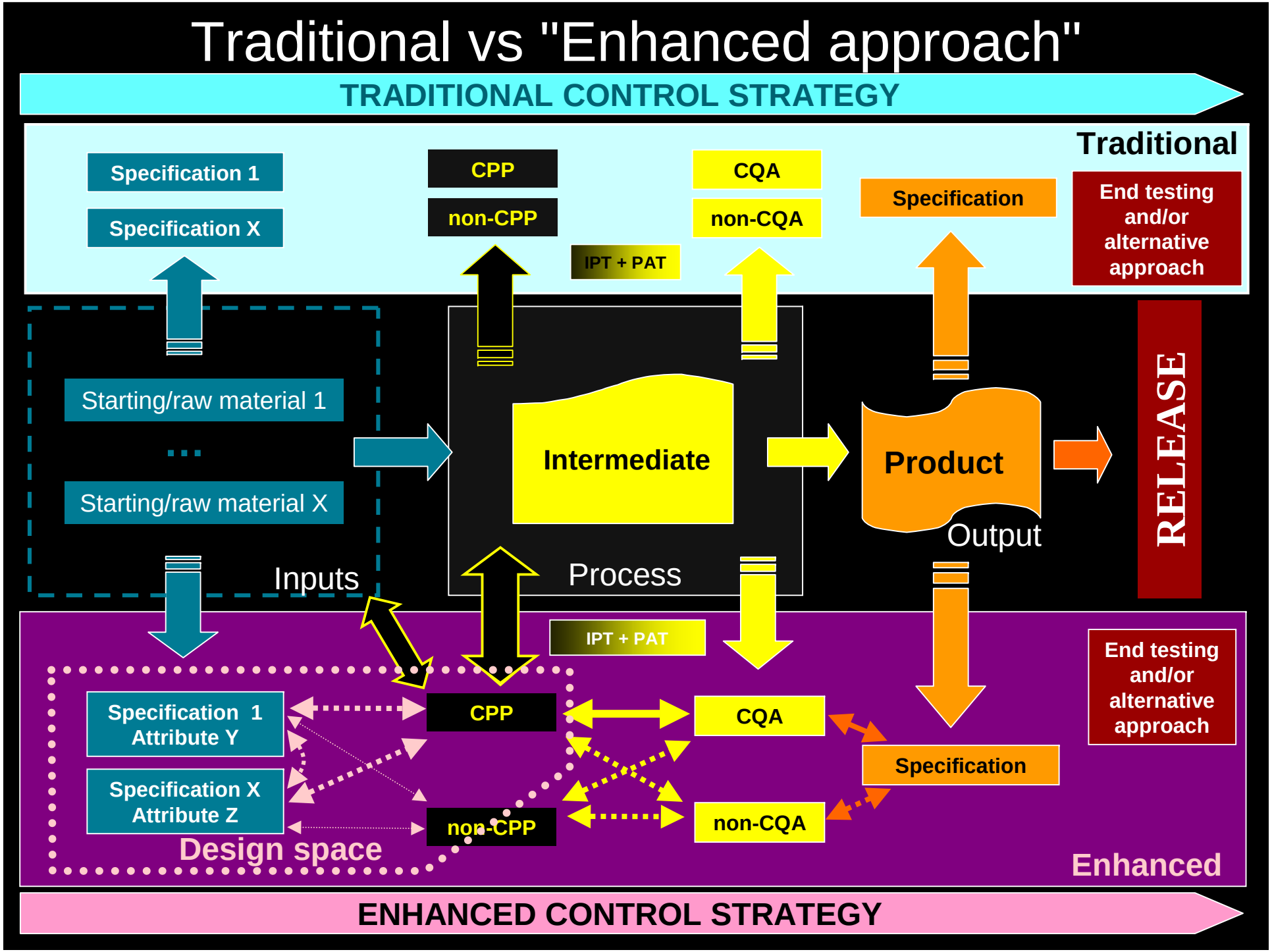
Design space

- ***Selection of Variables***
  - explanation on variables considered, how they affect the process and product quality, and which parameters were included or excluded

- Scale:
  - May have considerable consequences for the quality of the product including effects on its conformational structure, yield and/or in quantitative and qualitative differences in impurities…
  - Importance of commercial scale verification

Control strategy

- Control Strategy (ICH Q10) :
  - 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.


Traditional vs "Enhanced approach"
TRADITIONAL CONTROL STRATEGY
Traditional
Specification 1
Specification X
CPP
non-CPP
IPT + PAT
CQA
non-CQA
Specification
End testing and/or alternative approach
Starting/raw material 1
...
Starting/raw material X
Inputs
Intermediate
Process
Product
Output
RELEASE
IPT + PAT
End testing and/or alternative approach
Specification 1 Attribute Y
Specification X Attribute Z
CPP
non-CPP
CQA
non-CQA
Specification
Design space
Enhanced
ENHANCED CONTROL STRATEGY

- Process control (Q6B)
  - Adequate design of a process and knowledge of its capability are part of the strategy used to develop a manufacturing process
  - Limits are justified based on critical information gained from the entire process spanning the period from early development through commercial scale production.
  - For certain impurities, testing of either the drug substance or the drug product may not be necessary and may not need to be included in the specifications if efficient control or removal to acceptable levels is demonstrated by suitable studies
  - This testing can include verification at commercial scale in accordance with regional regulations.
  - Use of internal action limits:
    - important to assess the consistency of the process at less critical steps
    - responsibility of the manufacturer, may be used to initiate investigation or further action
    - further refined as additional manufacturing experience and data are obtained after product approval.

- Specification (Q6B):
  - "Conformance to specification" means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria.
  - one part of a total control strategy designed to ensure product quality and consistency
  - to confirm the quality rather than to characterize the product

Alternatives to end product testing possible…

Conclusion

- Q8, Q8R, Q9… Applicable to biologics
- How to find right balance between:
  - Industry vs Authority expectations?
  - Submitted data vs data available upon request?
  - Assessment vs Inspection?
  - Regulatory flexibity vs freedom?
  - Accomodate history, present… future…

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A lot of topics to discuss…