ICH
harmonisation for better health

Control of biologics

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Disclaimer:

- **The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.**

Specification for biologics (Q6B)

- **A specification:**
  - A list of tests, references to analytical procedures, AND appropriate acceptance criteria
  - Set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use.
  - "*Conformance to specification*" means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria.

- **Acceptance criteria:**
  - Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures which the drug substance or drug product or materials at other stages of their manufacture should meet.

Specification for biologics (Q6B)

- **Tests should take into account:**
  - Characterization studies
    - performed in development phase
    - following significant process changes
    - Relevant and up-to-date methods
  - Analytical considerations
    - reference standards and materials
    - validated
  - Manufacturing process and Process controls
  - Pharmacopoeial specifications
  - Shelf-life
  - Statistical concept

Specification for biologics (Q6B)

- ***Characterization of a biotechnological or biological product includes the determination of:***
  - *physicochemical properties,*
  - *biological activity,*
  - *immunochemical properties,*
  - *purity and*
  - *impurities.*

- **New analytical technology and modifications to existing technology are continually being developed and should be utilized when appropriate…**

Specification for biologics (Q6B)

- **Physicochemical properties**
  - Include a determination of the composition, physical properties, and primary structure of the desired product.
  - Information regarding higher-order structure: fidelity generally inferred by its biological activity
  - Inherent degree of structural heterogeneity:
    - desired product: can be a mixture of anticipated variants (e.g. post-translationally modified forms)
    - pattern of heterogeneity should be defined
    - consistency of that heterogeneity with that of the lots used in preclinical and clinical studies should be demonstrated
    - may be produced during manufacture and/or storage of the drug substance or drug product.
    - Product-related substances: variants of the desired product with comparable properties to those of the desired product with respect to activity, efficacy and safety.

Specification for biologics (Q6B)

- **Physicochemical properties**
  - Analytical methods to elucidate physicochemical properties are listed in Appendix 6.1. … should be considered…

- **1 - Structural characterization and confirmation**
  - Amino acid sequence
  - Amino acid composition
  - Terminal amino acid sequence
  - Peptide map
  - Sulfhydryl group(s) and disulfide bridges
  - Carbohydrate structure

- **2 - Physicochemical properties**
  - Molecular weight or size
  - Isoform pattern
  - Extinction coefficient (or molar absorptivity)
  - Electrophoretic patterns
  - Liquid chromatographic patterns
  - Spectroscopic profiles

Specification for biologics (Q6B)

- **Biological activity:**
  - Describes the specific ability or capacity of a product to achieve a defined biological effect.
  - A valid biological assay to measure the biological activity should be provided by the manufacturer. Examples of procedures used to measure biological activity include:
    - Animal-based biological assays,
    - Cell culture-based biological assays,
    - Biochemical assays,
    - Other procedures such as ligand and receptor binding assays, may be acceptable.

Specification for biologics (Q6B)

- Potency (expressed in units):
  - quantitative measure of biological activity based on the attribute of the product which is linked to the relevant biological properties, whereas, quantity (expressed in mass) is a physicochemical measure of protein content.
  - The results of biological assays should be expressed in units of activity calibrated against an international or national reference standard, when available and appropriate for the assay utilized.
  - Where no such reference standard exists, a characterized in-house reference material should be established and assay results of production lots reported as in-house units.

Specification for biologics (Q6B)

- Mimicking the biological activity in the clinical situation:
  - not always necessary.
  - correlation between the expected clinical response and the activity in the biological assay should be established in pharmacodynamic or clinical studies.
- A biological assay may be replaced by physicochemical tests only in those instances where:
  - sufficient physicochemical information about the drug, including higher-order structure, can be thoroughly established by such physicochemical methods, and relevant correlation to biologic activity demonstrated; and
  - there exists a well-established manufacturing history.
  - Where physicochemical tests alone are used to quantitate the biological activity (based on appropriate correlation), results should be expressed in mass.

Specification for biologics (Q6B)

- **Immunochemical properties**
  - When an antibody is the desired product, its immunological properties should be fully characterized.
    - Binding assays of the antibody to purified antigens and defined regions of antigens
    - Determine affinity, avidity and immunoreactivity (including cross-reactivity).
    - Target molecule bearing the relevant epitope should be biochemically defined and the epitope itself defined, when feasible.
  - Immunochemical properties may serve to establish:
    - identify protein or epitope of protein, homogeneity or purity, or quantification.
  - If part of lot release criteria:
    - all relevant information pertaining to the antibody should be made available.

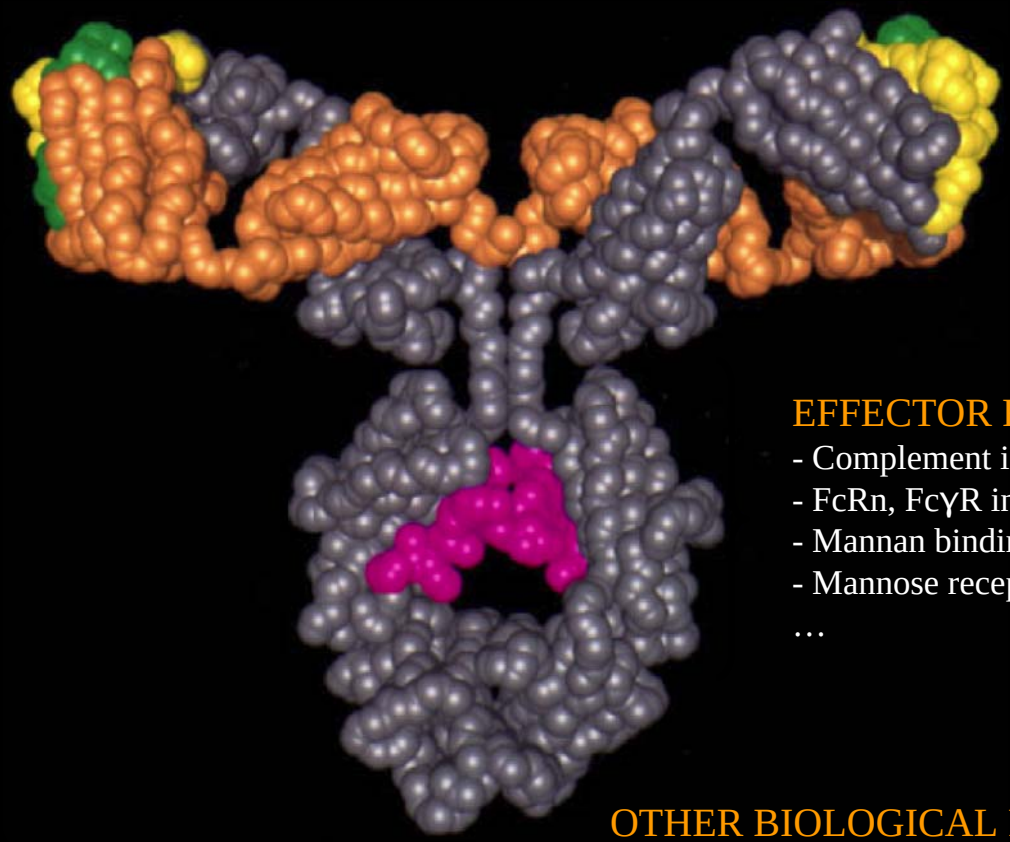
PHYSICOCHEMICAL CHARACTERISTICS

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

…

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

…



BIOLOGICAL CHARACTERISTICS

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

…

EFFECTOR FUNCTION
- Complement interaction
- FcRn, FcγR interaction
- Mannan binding ligand interaction
- Mannose receptor interaction

…

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

…

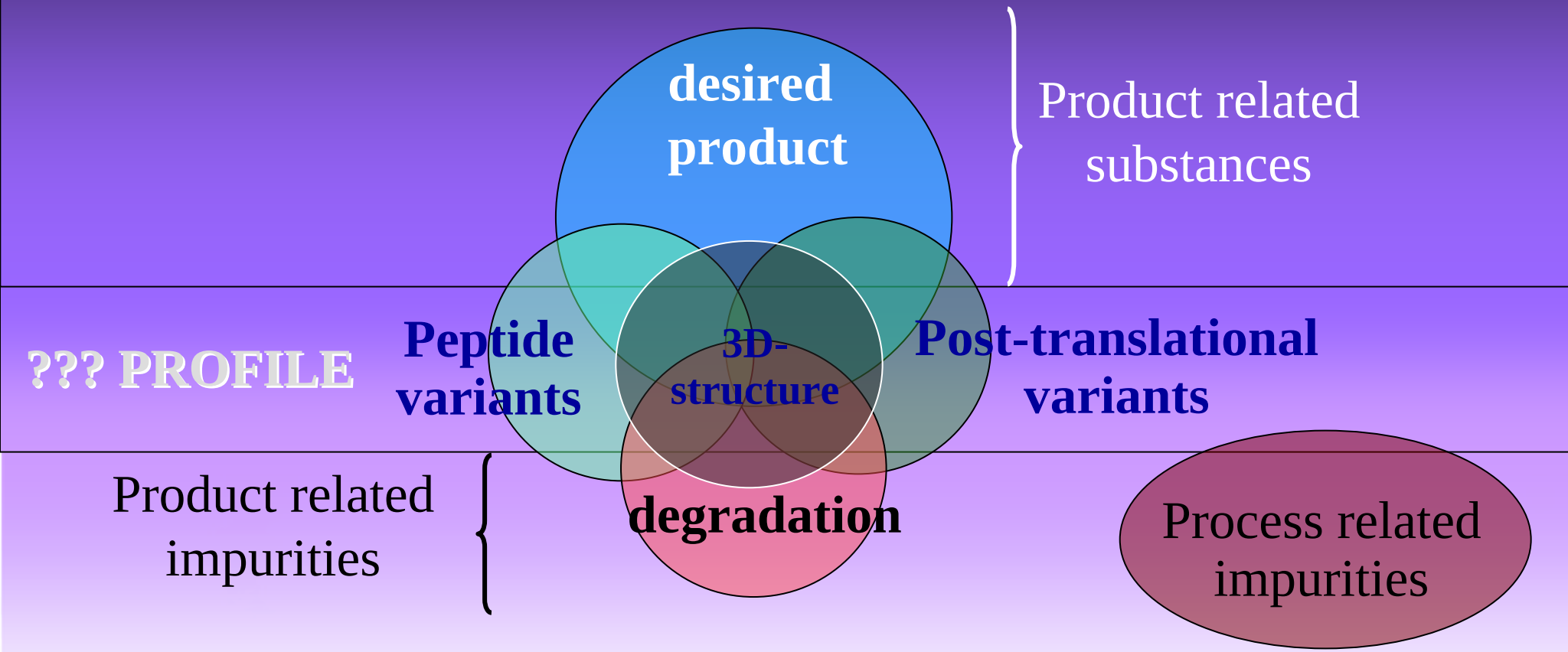
Specification of biotech product

- **Purity profile**
  - Desired Product
    - The protein which has the expected structure, OR
    - The protein which is expected from the DNA sequence and anticipated post-translational modification, and from the intended downstream modification to produce an active biological molecule.
  - Product-Related Substances
    - 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.

Specification for biologics (Q6B)

- **Impurity profile:**
  - Process-Related Impurities
    - Derived from the manufacturing process.
    - They may be derived from cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g., inducers, antibiotics, or media components), or downstream processing (e.g., processing reagents or column leachables).
  - Product-Related Impurities
    - 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.

PURITY PROFILE



IMPURITY PROFILE

Specification for biologics (Q6B)

- **Considerations in setting specifications:**
  - Process controls
    - Process related considerations:
      - Adequate design of a process and knowledge of its capability
      - 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 concept may be implemented after marketing authorization.
    - In-process acceptance criteria and action limits
      - Recorded as action limits or reported as acceptance criteria.
      - Performing such testing may eliminate the need for testing of the drug substance or drug product
      - Internal action limits:
        - to assess the consistency of the process at less critical steps
        - responsibility of the manufacturer, may be used to initiate investigation or further action.

Specification for biologics (Q6B)

- **Justification of specifications:**
  - Manufacturing process
    - Data obtained from lots used to demonstrate manufacturing consistency
    - Process changes and degradation products produced during storage may differ from those observed in the material used during preclinical and clinical development: significance to be evaluated.
  - Stability of drug substance and drug product
    - Inherent complexity: no single stability-indicating assay or parameter that profiles the stability characteristics.
    - Manufacturer: should propose a stability-indicating profile
    - Product-specific
  - Preclinical and clinical studies
    - Quality of the material made at commercial scale should be representative of the lots used in preclinical and clinical studies.
  - Analytical procedures
    - Critical quality attributes may include items such as potency, the nature and quantity of product-related substances, product-related impurities, and process-related impurities.
    - Can be assessed by multiple analytical procedures, each yielding different results

Specification for biologics (Q6B)

- **Acceptance criteria should be established and justified based on:**
  - data from lots used for demonstration of manufacturing consistency,
  - relevant development data,
  - data from stability studies, and
  - data obtained from lots used in preclinical and/or clinical studies.

Stability for biologics (Q5C)

- **Regulatory guidelines**
  - ICH
    - Q5C: main guideline for biologics
    - Q1: some principles applicable
  - EMEA
    - CPMP/QWP/609/96: Declaration of storage conditions
    - CPMP/QWP/2934/99: In-use stability testing
    - CPMP/QWP/159/96: Maximum shelf-life for sterile products after first opening or following reconstitution

Stability for biologics (Q5C)

- **Stability protocol**
  - Accelerated and stress conditions :
    - strongly suggested for DS and DP
    - useful for accidental exposures (e.g. transportation)
    - help to reveal patterns of degradation and suitability of methods

Long term	Accelerated	Stress
≤-20°±5°C	+5°±3°C and/or +25±2°C/60%RH	temperature, pH, light, oxidation, shaking, freeze/thaw …
+5°±3°C	+25±2°C/60%RH	
+25±2°C/60%RH or +30±2°C/65%RH	+40±2°C/75%RH	

Stability for biologics (Q5C)

- **Stability protocol**
  - Testing frequency:
    - Shelf-life ≤1 year: Month 0, 1, 2, 3, 6, 9 and 12
    - Shelf-life >1 year: Month 0, 3, 6, 9, 12, 18, 24, 36, 48…
  - Specification:
    - Includes stability indicating parameter
    - Limits of acceptable degradation: justified taking into account levels observed in materials used in non-clinical / clinical studies
    - Shelf-life specification acceptable, where appropriately justified
    - All test parameters may not be performed at all timepoints

Stability for biologics (Q5C)

- **Stability data for Drug substance**
  - At least 3 batches representative of the manufacturing scale of production
  - "Representative" data :
    - Representative of the quality of batches used in pre-clinical and clinical studies
    - Representative manufacturing process and storage conditions
    - Representative containers
  - Minimum 6 months data at the time of submission

Stability for biologics (Q5C)

- **Stability data for Intermediates**
  - May be critical to the production
  - Hold time / storage step should be identified
  - Storage conditions should be defined
  - Appropriate validation and/or stability study should be performed
    - Usually documented in section on process validation (3.2.S.2.5 or 3.2.P.3.5) when hold time / short storage
    - Usually documented in section on stability (3.2.S.7 or 3.2.P.8) when significant storage period

Stability for biologics (Q5C)

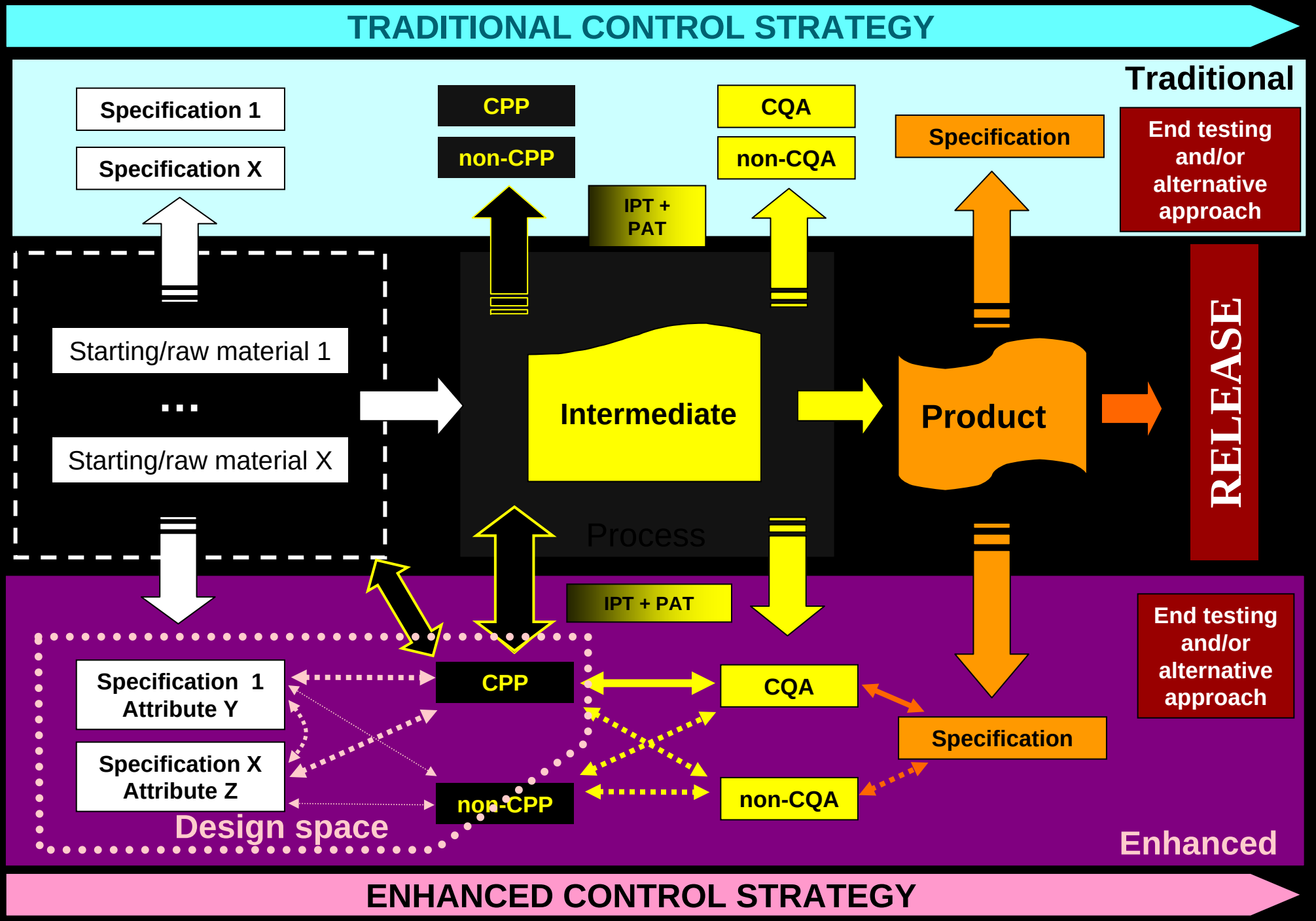
- **Stability data for Drug Product**
  - Should be provided on at least 3 batches of final container product, representative of manufacturing scale
  - Container should be representative of the one used in preclinical and clinical studies
  - Minimum of 6 months data
  - Expiry dating based on representative stability data
  - *In some situation, representative pilot scale data may be submitted, with a commitment to place the first 3 manufacturing scale batches, to establish the dating for a product*

Stability for biologics (Q5C)

- **Stability data for Drug Product**
  - Sample selection:
    - Homothetic (only differing by fill volume): bracketing or matrixing approach acceptable
    - Non-homothetic: each presentation should be included
  - Container/closure interaction:
    - Especially for liquid formulations
    - Inverted/horizontal position + upright position
    - To determine the effect on product quality (i.e. not just stability…)

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 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
Intermediate
Process
Product
RELEASE
IPT + PAT
Specification 1 Attribute Y
Specification X Attribute Z
CPP
non-CPP
CQA
non-CQA
Specification
End testing and/or alternative approach
Design space
Enhanced
ENHANCED CONTROL STRATEGY

Quality profile

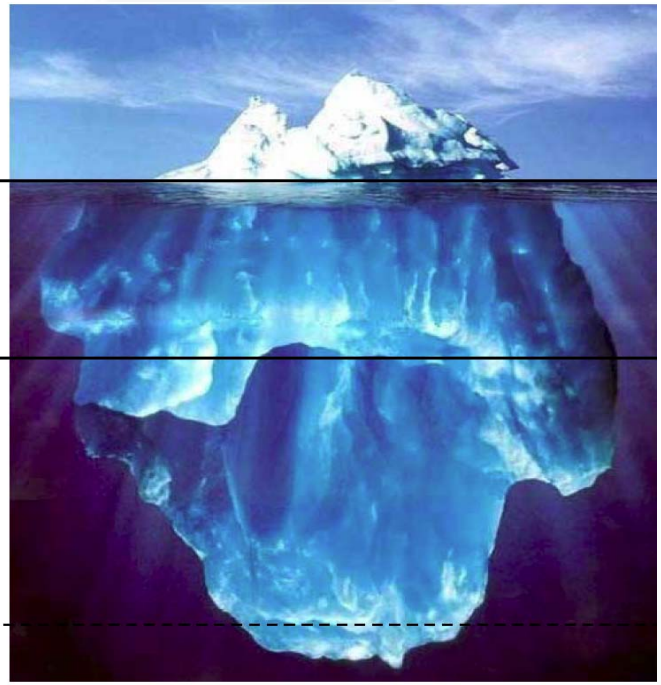
Release Tests (Specifications)

Extended Characterization
(Process & Product)

Process Control

- Procedures
- Materials
- In-process testing
- Monitoring
- Validation

Unknown
Learned over time – update control strategy



from: Koszlowski, S. & Swann, P. (2006) Adv. Drug Delivery Revs.

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Thank You!