



### ICH-GCG ASEAN Training Workshop 30th-31stMay 2011, Kuala Lumpur, Malaysia

# Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

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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.



### Session III

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

#### ICH HARMONISED TRIPARTITE GUIDELINE

SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS  ${\bf Q6B}$ 

Current Step 4 version dated 10 March 1999

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.



European Medicines Agency

September 1999 CPMP/ICH/365/96

ICH Topic Q 6 B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

Step 5

NOTE FOR GUIDANCE ON SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS (CPMP/ICH/365/96)

TRANSMISSION TO CPMP	February 1998
RELEASE FOR CONSULTATION	February 1998
DEADLINE FOR COMMENTS	July 1998
FINAL APPROVAL BY CPMP	March 1999
DATE FOR COMING INTO OPERATION	September 1999



#### Issues to be addressed

- General considerations
- Regulatory aspects
- Principles in setting specifications
- Drug substance and drug product
- Justifications of specifications
- Specifications vs. IPCs
- Stability aspects



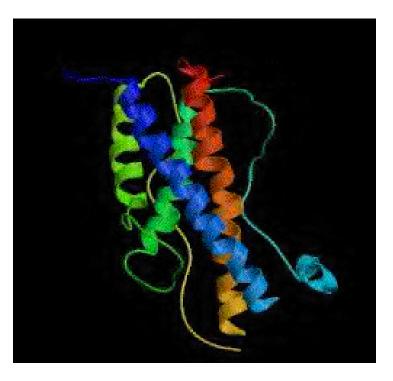
### Scope of ICH Q6B

- Applies to proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates).
- Produced from recombinant or non-recombinant cell-culture expression systems and can be highly purified and characterised using an appropriate set of analytical procedures.
- The principles outlined in this document may also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids
- Does not cover antibiotics, synthetic peptides and polypeptides, heparins, vitamins, cell metabolites, DNA products, allergenic extracts, conventional vaccines, cells, whole blood, and cellular blood components.

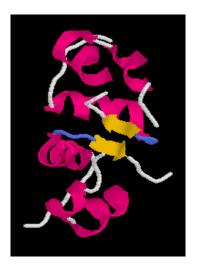


### Insulin vs. Aspirin

#### hGH



#### Insulin



### acetyl salicylic acid





### Special Features of Biologics

- Manufacturing process
- Culture of living organisms, genetic stability, viral safety
- Harvest: complex matrix dependent on raw- a. starting materials and process conditions
- Purification: adapted for the desired protein, removal of impurities, avoidance of contaminants



### Special Features of Biologics

- Structure complex/ variants ++++
- Impurities (DNA, HCP) und contaminants (e.g. viruses) are dependent on the manufacturing process including and raw- and starting materials
- Analytical methods limited, might be insufficient to comprehensively demonstrate quality



### Biotech Products - Current Paradigm

- The process is the product
- The entire manufacturing process determines the quality of a biotech medicinal product
  - Raw-/starting materials (e.g. cell banks, media, reagents)
  - Fermentation
  - Purification
  - Formulation/Filling
- The entire manufacturing process should be described and controlled in detail
- Minor changes may affect quality, safety and efficacy



### Biotech Products (rec. Proteins) on the Market

- Immunmodulators
- Hormones
- Monoclonal Antibodies
- Enzymes
- Growth Factors
- Thrombolytics
- Coagulation Factors
- Vaccines



### **Definition Specification**

Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by the regulatory authorities as conditions of approval. (ICH Q6B)

- specifications are legally binding criteria that a medicinal product must meet
- set of criteria that a drug substance and drug product must meet to fulfil pre-defined standards for commercial use
- assurance that the quality is safe and efficacious over its shelf-life



### **Definition Specification**

- A specification is defined as a:
  - list of tests,
  - with references to analytical procedures,
  - with appropriate acceptance criteria which are numerical limits,
  - or ranges,
  - or other criteria for the tests described.
- It establishes the 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.
- Definition Critical Quality Attribute (CQA) acc. ICH Q8R:

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.



### Definition Specification Conformance to specification

"Conformance to specification" means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria.



### Implementation of ICH Q6B

#### Important, critically discussed aspects

- Better understanding of the relative importance/relevance of specifications as part of a total control strategy
- Concept of heterogeneity for biotech products

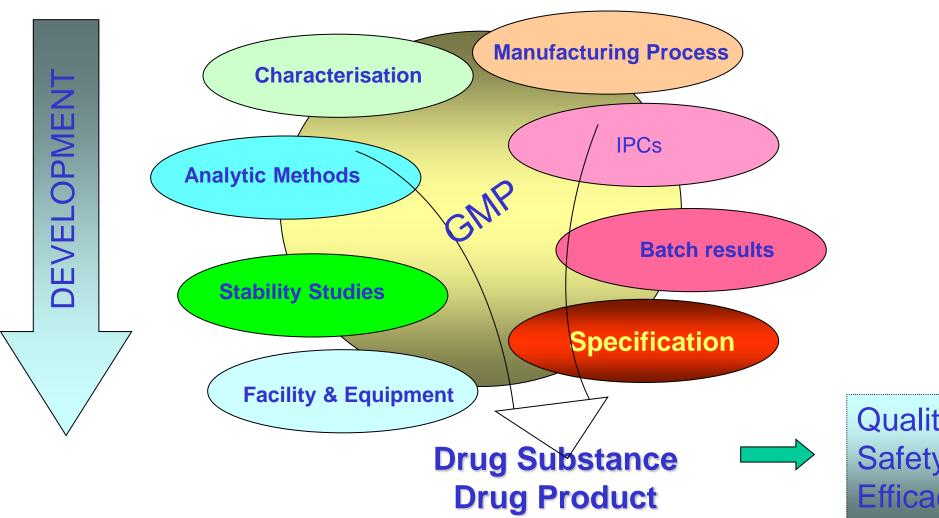


### **General Concepts**

- Specifications are one part of a total control strategy designed to ensure product quality and consistency.
- Other parts of this strategy include
  - thorough product characterisation during development, upon which many of the specifications are based,
  - adherence to Good Manufacturing Practices,
  - a validated manufacturing process,
  - raw materials testing, in-process testing,
  - stability testing, etc.
- Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterisation and should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.



### Specification as part of a total control strategy



Quality Safety



### Control Strategy per ICH Q10 / Q11

 <u>Control Strategy:</u> 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, inprocess controls, finished product specifications, and the associated methods and frequency of monitoring and control.



### CS acc. to ICH Q11 (Step2)

A control strategy can include, but is not limited to, the following:

- Controls on material attributes (including raw materials, starting materials, intermediates, reagents, primary packaging materials for the drug substance, etc.);
- Procedural Controls implicit in the design of the manufacturing process (e.g., choice of reagents or media, sequence of operations);
- In-process controls (including in-process tests and process parameters);
- Controls on drug substance (e.g., release testing).



### Manufacturig Process Development Drug Substance Critical Quality Attributes

- A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.
- Potential drug substance CQAs are used to guide process development. The list of potential CQAs can be modified as drug substance knowledge and process understanding increase.
- Drug substance CQAs typically include those properties or characteristics that affect identity, purity, biological activity and stability



### Manufacturig Process DevelopmentRisk assessment: Linking Material Attributes and Process Parameter to Drug Substance CQAs (ICH Q11, step 2)

- The development program should identify which **material attributes** (e.g., of raw materials, starting materials, reagents, solvents, process aids, intermediates) and process parameters should be controlled.
- Risk assessment can help identify the material attributes and process parameters with the potential for having an effect on drug substance CQAs.
- Those material attributes and process parameters that are found to be important should be addressed by the control strategy
- Using a traditional approach, material specifications and process parameter ranges can be based primarily on batch process history and univariate experiments.
- An enhanced approach can lead to a more thorough understanding of the relationship of material attributes and process parameters to CQAs and the effect of interactions.



## Manufacturig Process Development Risk assessment: Linking Material Attributes and Process Parameter to Drug Substance CQAs (ICH Q11 step2)

Using an enhanced approach, the determination of appropriate material specifications and process parameter ranges could follow a sequence as shown below:

- Identify potential sources of process variability;
- Identify the material attributes and process parameters likely to have the greatest impact on drug substance quality. This can be based on prior knowledge and risk assessment tools
- Design and conduct experiments and/or mechanistic studies (e.g., multivariate Design of Experiments, simulations, modelling) to identify and confirm the links and relationships of material attributes and process parameters to drug substance CQAs;
- Conduct analysis of the data to establish appropriate ranges, including establishment of a design space if desired.



### **Authorities & Requirements**

- ICH Q1A(R2) Stability Testing of New Drugds and Substances
- ICH Q1B Stability testing: Photostability of New drug Substances and Products
- ICH 1C Stability testing of New Dosage Forms
- ICH 1D Bracketing and Matrixing Designs for Dtability testing of New drug Sustances
- ICH Q2 Analytical Validation
- ICH Q4 –Q4B Pharmacopoeias
- ICH Q5A -Q5E
- ICH Q7 GMP
- ICH Q8 Pharmaceutical Development
- ICH Q9 Quality Risk Mangement
- ICH Q10 Pharmaceutical Quality Systems
- ICHQ11 Development and Manufacture of Drug Substance



#### ICH Guidelines Bio

- ICH Q5A: Viral Safety
- ICH Q5B: Genetic Stability
- ICH Q5C: Stability
- ICH Q5D Cell Substrates
- ICH Q6B Specifications
- ICH Q5E Comparability



### http://www.ich.org Guidance Documents Biotechnology

- **Q5A** Quality of biotechnological products: viral safety evaluation of biotechnological products derived from cell lines used for the production of rDNA derived protein products (CPMP/ICH/295/95)
- **Q5B** Quality of biotechnological products: analysis of the expression construct in cell lines used for production of rDNA derived protein products (CPMP/ICH/139/95)
- **Q5C** Quality of biotechnological products: stability testing of biotechnological/biological products (CPMP/ICH/138/95)
- **Q5D** Quality of biotechnological/biological products: derivation and characterisation of cells substrates used for the production of biotechnological/biological products (CPMP/ICH/294/95)
- **Q5E** Note for Guidance Biotechnological/ Biological Products Subject to Changes in their Manufacturing Process (CPMP/ICH/572/03)
- **Q6B** Specifications: tests and procedures for biotechnological/biological products (CPMP/ICH/365/95)
- **S6/S6(R1)** Pre-clinical safety evaluation for biotechnology-derived pharmaceuticals (CPMP/ICH/302/95) and Addendum to S6

**Cell Banks** 

Manufacturing Process

**Drug Substance** 

**Drug Product** 

Impact of ICH

guidelines on

different production

steps

nstitute for Drugs Medical Devices

ICH Q5B:

**Genetic Stability** 

ICH Q5D Cell Substrates

ICH Q5A: Viral Safety Evaluation

**ICH Q6B Specifications for biotech products** 

modif. from Current Opinion in Biotechnology, 9, 1998

ICH Q5C: Stability for biotechnological products

ICH Q5E Comparability – Changes of Manufacturing Process

ICH Q11 Development and Manufacture of Drug Substance ICH Q8 (R)
Pharmaceutical
Development

ICH Q9 Quality Risk Management / ICH Q10 Pharmaceutical Quality Systems

The BfArM is a Federal Institute within the portfolio of the Federal Ministry of Health



### Concept of Heterogeneity in ICH Q6B

- The desired product can be a mixture of anticipated posttranslationally modified forms (e.g., glycoforms)
- An inherent degree of structural heterogeneity occurs in proteins due to the biosynthetic processes used by living organisms to produce them
- Heterogeneity of a recombinant protein may originate from
  - fermentation (including post-translational modifications)
  - downstream processing
  - storage



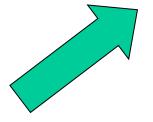
### Concept of Heterogeneity in ICH Q6B

- The manufacturer should define the pattern of heterogeneity of the desired product and demonstrate consistency with that of the lots used in preclinical and clinical studies.
- Since the heterogeneity of these products defines their quality, the degree and profile of this heterogeneity should be characterised, to assure lot-to-lot consistency. When these variants of the desired product have properties comparable to those of the desired product with respect to activity, efficacy and safety, they are considered product-related substances.
- When process changes and degradation products result in heterogeneity patterns which differ from those observed in the material used during preclinical and clinical development, the significance of these alterations should be evaluated (Q5E).



### Special Features of Biologics -Why are They Different?

### **Variability**





#### living systems

intrinsic, natural variability

(e.g. glyco structures)

### process induced variability

- conditions for fermentation
- purification strategy

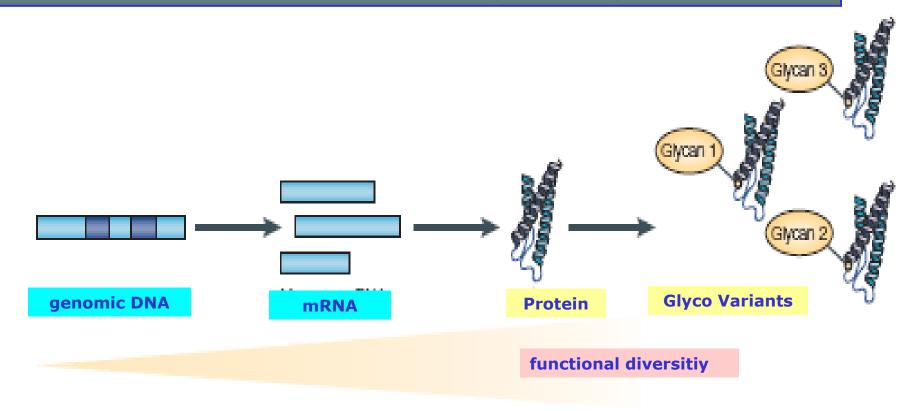




**Microheterogenity** 



### Glycosylation as Part of Structural and Functional Complexity

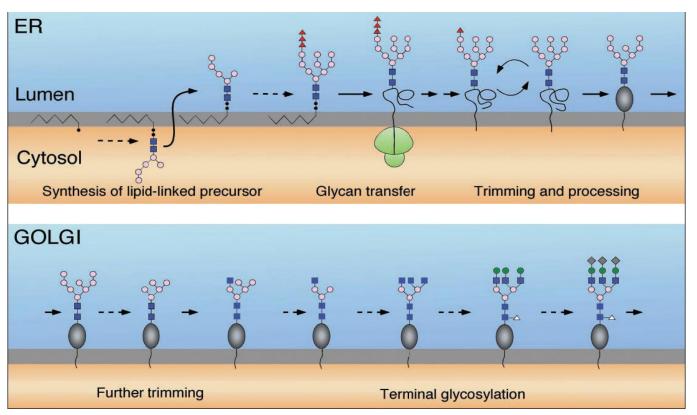


one gene ≠ one protein

Nature Review Drug Discovery, 2004(10) 863-73



### Heterogeneity and Glycosylation



- ■=N-Acetylglucosamin
- O=Mannose
- **▲=Glucose**
- =Galactose
- ◆=Sialic acid

Ari Helenius and Markus Aebi (2001); Science 291, 2364-2369



#### **Example: Impact of glycosylation of Mab**

GlcNAc/ Mannose		Ligand for Mannose Binding Protein <del>&gt;</del> complement activation (Malhotra <i>et al.</i> , Nat. Med. 1995)
Sialic acid	◆ ■ ■ • • • • • • • • • • • • • • • • •	Suppression of ADCC (anti-inflammatory activity) (Kaneko <i>et al.</i> , Science 2006)
Galactose		Placental transport (Kibe <i>et al</i> ., J. Clin. Biochem. Nutr. 1996)
bisecting GlcNAc		Prevents core fucosylation → enhanced ADCC (Umaña <i>et al</i> ., Nat. Biotech. 1999)
absence of core Fucose		Enhanced ADCC (Okazaki <i>et al</i> ., J. Mol. Biol. 2004)
α(1-3)-Gal	<b>1</b> -3 ■ <b>1</b>	Non-human/antigenic (Cooper, Xenotransplantation 1998)

Source: GB Kress, EMEA workshop on biosimilar MAB, 2009



### Heterogeneity

- Oligosaccharide structures
  - Microheterogeneity
    - Pool of variable structures
- What is the range of variability concerning the oligosaccharide structures?

Impact on safety and efficacy ?



### ICH Q6B Glyco-variants

- For glycoproteins, the carbohydrate content (neutral sugars, amino sugars and sialic acid) is determined. In addition, the structure of the carbohydrate chains, the oligosaccharide pattern (antennary profile) and the glycosylation sites of the polypeptide is analyzed, to the extent possible
- The manufacturer should define the pattern of heterogeneity of the desired product and demonstrate consistency with that of the lots used in preclinical and clinical studies. If a consistent pattern of product heterogeneity is demonstrated, an evaluation of activity, efficacy, safety (including immunogenicity) of individual forms may not be necessary



### Target criteria for the characterisation of the structural features of the carbohydrate moiety (proposal for MAA)

- Antennary profile (in particular ratio of tetra- to diantennary structures)
- N-acetyl-lactosamine extension
- Sialylation state (degree of sialylation; linkage type between NeuAc and Galβ1-4GlcNAc-
- Site-specific glycosylation
- Glycosylation site occupancy
- Presence of high mannose/HMP residues
- Absence/limitation of N-glycolylNeuAc and/or diacetylated NeuAc, Galα1-3Gal as immunogenic elements



#### Characterisation

- Characterisation of a biotechnological or biological product by appropriate techniques is necessary to allow relevant specifications to be established.
- determination of
  - physicochemical properties,
  - biological activity,
  - immunochemical properties,
  - purity
  - impurities
- New analytical technology and modifications to existing technology are continually being developed and should be utilized when appropriate...



### Characterisation and Comparability

- Extensive characterisation is performed in the development phase and, where necessary, following significant process changes (⇒ICH Q5E).
- At the time of submission, the product should have been compared with an appropriate reference standard, if available.
- (When feasible and relevant, it should be compared with its natural counterpart)
- At the time of submission, the manufacturer should have established appropriately characterised in-house reference materials, which will serve for biological and physicochemical testing of production lots.



## Need for Combination of Numerous Orthogonale Analytical Methods

Method	Molecular- weight	Charge	Puritiy	Aktivity	Prim structur	Sek./Tert. structur	Quart,- structur
Mass-Spec	+++++	+	+++	-	+++++	-	-
CD	-	-	+	-	-	+++	+++
NMR	+	-	+	-	+	+++++	-
SEC-HPLC	+++	-	++	-	-	+	++
RP-HPLC	+	+	+++	-	+++	+	-
IEX-HPLC	-	+++++	++	-	++	-	-
SDS-PAGE	+++	-	++	-	++	+(+)	+(+)
IEF	-	+++	++	-	++	+	-
Bioassay	-	-	-	++++	++	++++	++++
Receptor- binding	-	-	-	++(+)	+	+++	+++



#### Characterization of Proteins

- Size, MW
  - SEC-HPLC, MS-ESI, MALDI
- Amino acid analysis/Sequence
- N-terminal / C-terminal Sequencing
- Disulfide bridges
- Peptide map
  - Tryptic Digest + RP-HPLC + MS + Sequence
- Chromatographic profile
- Electrophoresis pattern (SDS-PAGE, IEF, CZE)
- Spectroscopic profile
- Disulfid Bridges
- Extinction coefficient

?? routine
testing ??



#### Characterization of Proteins

- Glycosylation
  - Carbohydrate structure
  - Glycan profile
  - Exoglycosidase sequencing
  - Sialic acid
  - Antennarity profile
- Microheterogeneity
- Biological activity



#### PHYSICOCHEMICAL CHARACTERISTICS

#### **BIOLOGICAL CHARACTERISTICS**

#### **VARIABLE REGION**

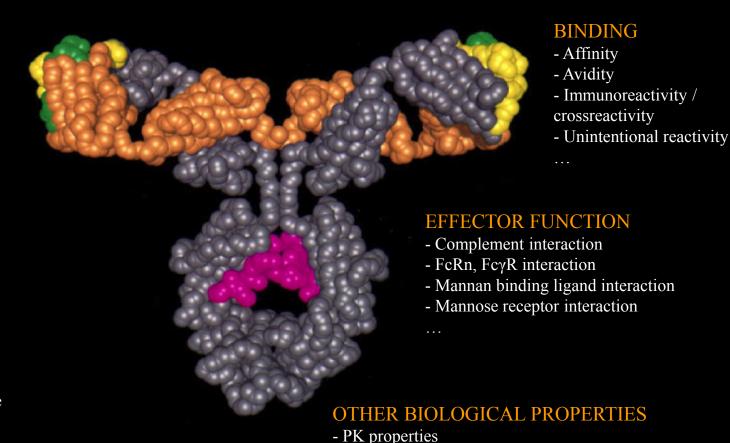
- Deamidation
- Oxidation
- N-term Pyro-Glu
- Glycosylation
- Glycation
- Conformation

...

#### **CONSTANT REGION**

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

• •



- Epitope / Immunogenicity

- Modulatory region (Tregitope ...)



## Physicochemical properties

- Determination of the composition, physical properties, and primary structure of the desired product.
- In some cases information regarding higher-order structure of the desired product may be obtained by appropriate physicochemical methodologies



## Biological activity

- Biological activity describes the specific ability or capacity of a product to achieve a defined biological effect
- Valid Bioassay, e.g.:
- Cell culture-based bioassays, which measure biochemical or physiological response at the cellular level;
- Bioassays, which measure biological activities such as enzymatic reaction rates or biological responses induced by immunological interactions.
- Ligand and receptor binding assays
- Animal-based biological assays, which measure an organism's biological response to the product;
- Mimicking the biological activity in the clinical situation is not always necessary/posssible.



## Biological activity

- The results of biological assays should be expressed in units of activity calibrated against an international or national reference standard,
- Where no such reference standard exists, a characterised in-house reference material should be established and assay results of production lots reported as in-house units.



## Biological activity

 For complex molecules, the physicochemical information may be extensive but unable to confirm the higher-order structure which, however, can be inferred from the biological activity. In such cases, a biological assay, with wider confidence limits, may be acceptable when combined with a specific quantitative measure

## **Bioassay**

- In vitro
  - Cell based Assay
  - Binding Assay
  - Enzymatic Assay

- rel. SD 5 25 % \*
- rel. SD 5 20 % \*
- rel. SD 2,5 -10 % \*

- In vivo
  - Animal model⇒ ⇒ ⇒ Animal Welfare

<sup>\*</sup>approx, acceptance case-by-case Careful choice and assay design, RSD<10%



## Biological activity - Replacement

A bioassay to measure the biological activity of the product 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.
- For the purpose of lot release, the choice of relevant quantitative assay (biological and/or physicochemical) should be justified by the manufacturer.



## 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.

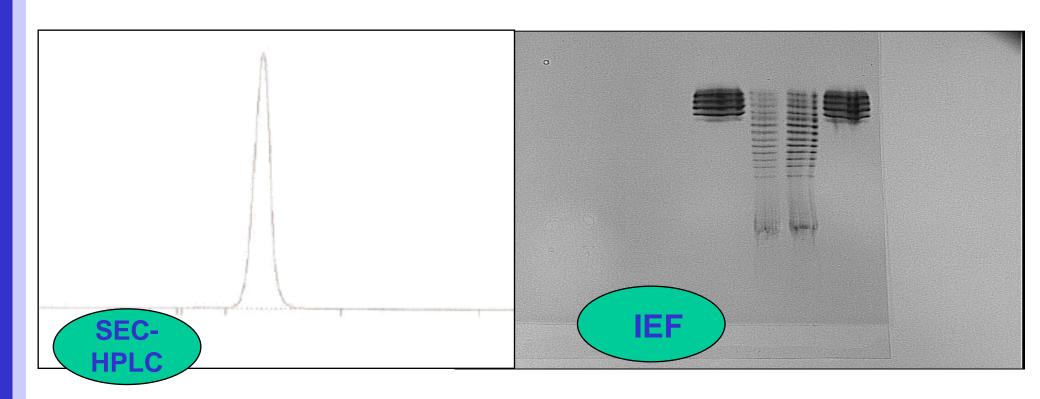


## **Purity**

- The determination of absolute, as well as relative purity are highly method-dependent.
- Consequently, the purity of the drug substance and drug product is assessed by a combination of analytical procedures.
- Heterogeneity needs to be considered
- For the purpose of lot release, an appropriate subset of methods should be selected and justified for determination of purity.



## **Purity and Microheterogeneity**





## **Specification - Purity**

- Determination of absolute, as well as relative purity
- Results are highly method-dependent analytical challenges
- Relative purity of a biological product expressed in terms of specific activity (units of biological activity per mg of product)
- Purity of the drug substance and drug product is assessed by a combination of analytical procedures.
- The drug substance can include several molecular entities or variants.
- Individual and/or collective acceptance criteria for product-related substances should be set, as appropriate.
- For the purpose of lot release, an appropriate subset of methods should be selected and justified for determination of purity.

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## **Impurities**

 Impurities may be either process or productrelated.

 When adequate quantities of impurities can be generated, these materials should be characterised to the extent possible and, where possible, their biological activities should be evaluated.



#### Categories of Impurities

- Process-Related Impurities
  - derived from cell substrates (e.g., host cell proteins, host cell DNA),
  - cell culture (e.g., inducers, antibiotics, or media components),
  - downstream processing (e.g., processing reagents or column leachables).
- Product-Related Impurities
- Contaminants (viruses, bacteria, fungi..)



## **Process-related Impurities**

#### Cell substrate-derived

- Host Cell DNA
- Host Cell Proteins

#### Cell culture-derived

- Antibiotics
- Inducer
- Serum
- Media components

#### Purifcation process-derived

- Enzymes
- Process Reagents
- Solvents
- Carrier
- Ligands
- Inorganic salts
- Column leachables



# Product-related Impurities and Modifications (Examples)

## Product-related Impurities and Modifications

- Truncated, clipped/cleaved forms
- S-S bonds mismatched
- N- / C-terminal heterogeneity
- Glycosylationheterogeneity
- Amino acid substitution
- Aggregates/Dimers/Multimer
- Dissociation
- Isomerisation

#### **Possible Modifications**

- Acetylation
- Acylation
- Addition of lipid
- Deamidation/Amidation
- Oxidation
- Glycation
- Carbamylation
- Formylation
- Methylation
- Norleucin
- N-/O-Glycosylation
- Phosphorylation
- Sulphation



#### Product-Related Substances and Impurities

- Desired Product (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 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 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.



## Product-related Impurities/Substances

#### **Degradation Products**

- Molecular variants resulting from changes in the desired product or product-related substances brought about over time
- by the action of e.g., light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system.
- changes may occur as a result of manufacture and/or storage
   (e.g., deamidation, isomerisation, oxidation, aggregation, proteolysis

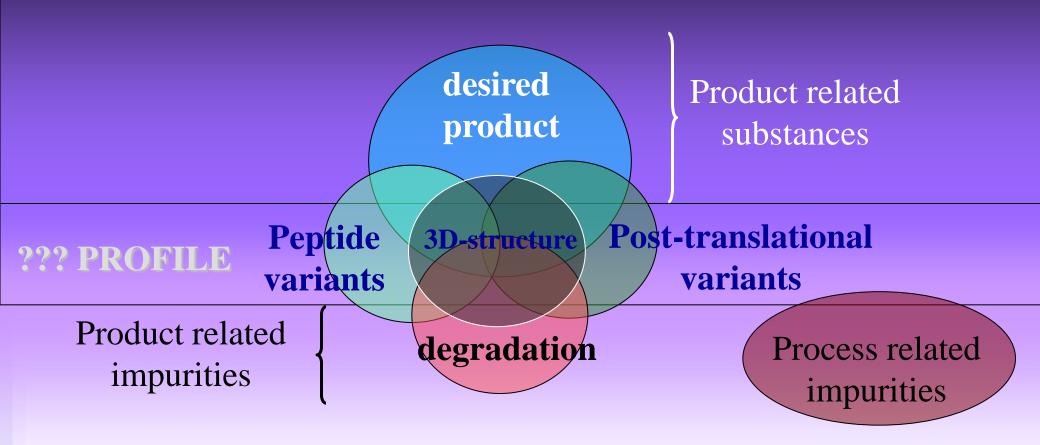
⇒⇒ Stability studies (Release vs. Shelf-life limits)



#### **Contaminants**

- Contaminants in a product include all adventitiously introduced materials not intended to be part of the manufacturing process, such as chemical and biochemical materials (e.g., microbial proteases), and/or microbial species.
- Contaminants should be strictly avoided and/or suitably controlled with appropriate in-process acceptance criteria or action limits for drug substance or drug product specifications
- For adventitious viral or mycoplasma contamination, the concept of action limits is not applicable

#### PURITY PROFILE



#### **IMPURITY PROFILE**



## **Specifications**

- Specification should be base on thorough knowledge of the product and the process
- Science based
- Developing and setting specifications difficult task
- Consequences of "wrong" specification



## Acceptance criteria

Acceptance criteria should be established and justified based on:

- data obtained from lots used in preclinical and/or clinical studies,
- data from lots used for demonstration of manufacturing consistency
- data from stability studies,
- relevant development data.



## Specifications/ Acceptance criteria

#### are required for

- raw-/starting materials (e.g. cell lines)
- in process controls (manufacturing process)
- release drug substance
- release drug product
- container/closure system
- excipients
- shelf life

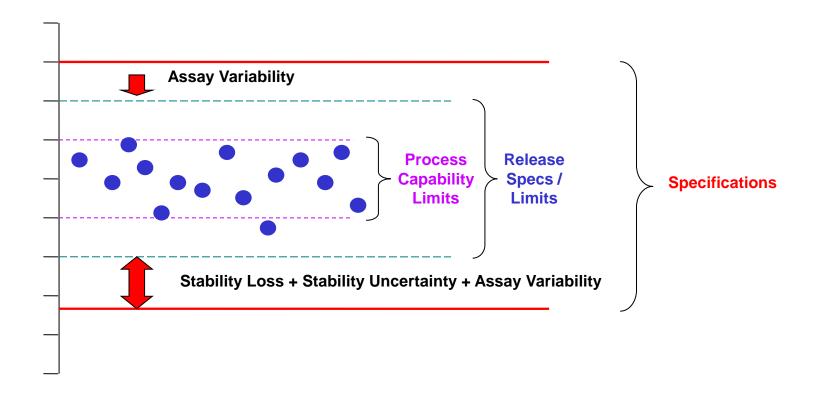


## Specifications Elements - Considerations - Justification

- manufacturing process /consistency runs
- linkage to preclinical and clinical batches and studies
- linked to analytical methods
- IPC acceptance criteria/action limits
- account for stability (release vs shelf life), orthogonal methods
- "selected" impurities
- degradations products
- characterization
- biological activity
- reference standards/materials
- consideration EP monographs



## Setting of Specifications based on "Process Capability"





## Setting Impurity Specifications

- Known safety/toxicity/bioactivity
- Safety profile of the product
- Impact on product quality/ stability
- Manufacturing capability/consistency
- Minimization of potential immunogenicity
- Dose and route of administration



## Specifications - Impurities

- process and product related to be characterised as far as possible
- determination of biological activity- if appl.
- acceptance criteria acc. to clinical batches and consistency runs
- For certain impurities, testing of either the drug substance or the drug product may not be necessary if efficient control or removal to acceptable levels is demonstrated by suitable studies. (Validation ⇒ IPC)
- verification at commercial scale
- only limited data are available at the time of submission.
- concept may be implemented after marketing authorization



#### Different Status of IPCs

- all critical steps
- action-limits or acceptance criteria

**⇒**⇒legally binding

- IPCs may replace defined release tests
- internal IPCs less critical steps

⇒⇒ Critical Process Parameter vs non Critical Process Parameter

Exp.: Number of IPCs classic vs. biotech

- L-Thyroxin 67

- Interferon alpha 244 (Source Schering-Plough)



#### Process-related considerations

- Adequate design of a process
- Knowledge of its capability
- Manufacturing process is controlled and reproducible, yielding a drug substance or drug product that meets specifications.
- 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 (Process Validation/Evaluation, e.g. small scale studies.)



# In-process acceptance criteria and action limits

- In-process tests are performed at critical decision making steps and at other steps where data serve to confirm consistency of the process during the production of either the drug substance or the drug product.
- The results of in-process testing may be 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
- Data obtained during development and validation runs should provide the basis for provisional action limits to be set for the manufacturing process.
- These limits, which are the responsibility of the manufacturer, may be used to initiate
- investigation or further action. They should be further refined as additional manufacturing experience and data are obtained after product approval.



#### In Process Controls

#### IPCs are of significant importance to demonstrate

- consistency of the manufacturing process in a defined production site under defined condition
- equivalence after a change of the manufacturing process
   ⇒ Comparability (ICH Q5E)
- equivalence after "Up-Scaling"⇒ Comparability
- equivalence in a new manufacturing site
  - □ Comparability



#### In Process Controls

#### Examples:\*

#### **Fermentation**

- cell number/ cell mass
- vitality of cells
- growth rate
- pH medium
- pO2
- temperature
- protein /IB
- product titer
- adventitious agents/virus

#### **Purification**

- yield
- specific activity
- purity
- removal of impurities
- endotoxin
- bioburden

In-process testing for adventitious agents at the end of cell culture is an example of testing for which acceptance criteria should be established.

\*not exhaustive



# Raw materials and excipient specifications

- The quality of the raw materials used in the production of the drug substance (or drug product) should meet standards, appropriate for their intended use.
- Biological raw materials or reagents may require evaluation to establish the presence or absence of endogenous or adventitious agents (TSE, Virus)
- Certain affinity chromatography (for example, employing monoclonal antibodies, Protein A, Affi Blue) should be accompanied by appropriate measures to ensure that such process-related impurities or potential contaminants arising from their production and use do not compromise the quality and safety of the drug substance or drug product.
- The quality of the excipients used as well as the container/closure systems, should meet pharmacopoeial standards, where available and appropriate. Otherwise, suitable acceptance criteria should be established for the non-pharmacopoeial excipients.



## Setting Specifications - Considerations-

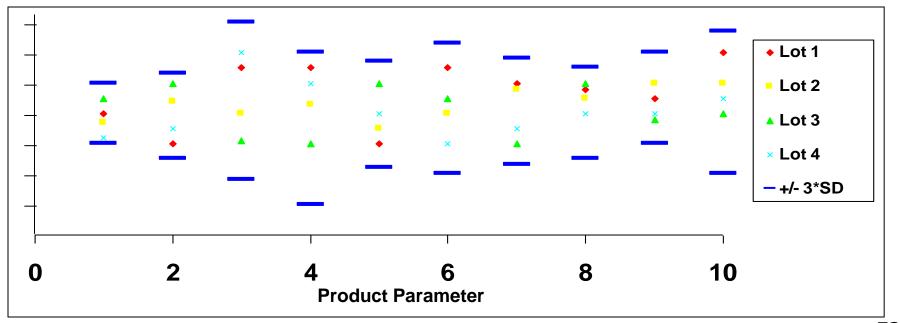
- Which (key / critical??) product quality attributes should be specified and merit control throughout the clinical development?
- How often should preliminary specification be revised? What data are needed (e.g. number of runs, status of method validation)?
- How to define the clinical range/exposure (% of variants/impurities or total patient exposure?
- Is it possible to justify specifications outside the clinical range?



#### **Experience Clinical Trials**

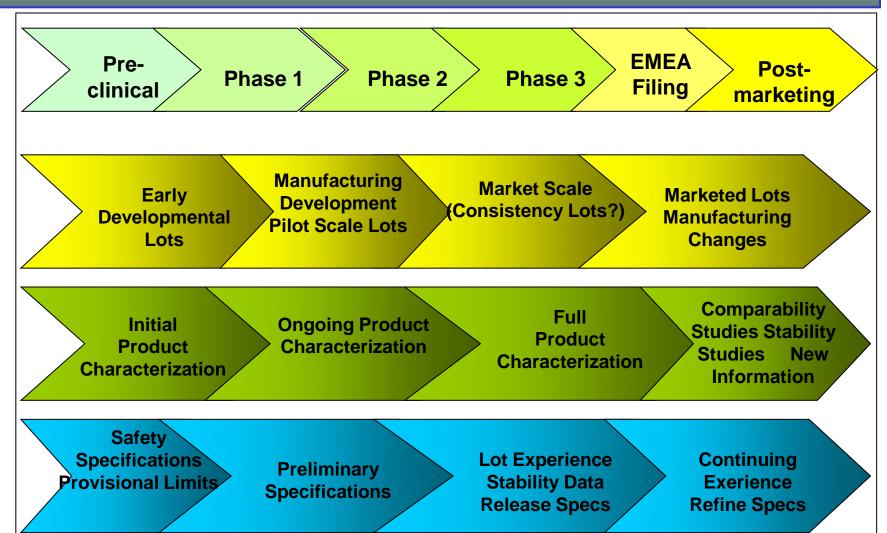
- Ideal: Phase III Batch cover the entire range of specs
- Testing of a limited number of batches in Phase III

**○** Can Specs based on the manufacturing history have wider limits than covered by phase III studies





### Quality/Specification Life Cycle





#### Pharmacopoeial Specifications

- Pharmacopoeias contain important requirements pertaining to certain analytical procedures and acceptance criteria
- part of the evaluation of either the drug substance or drug product, where relevant
- generally include, but are not limited to tests for sterility, endotoxins, microbial limits, volume in container, uniformity of dosage units and particulate matter.



# SPECIFICATIONS Selection of tests

- Selection of tests to be included in the specifications is product specific.
- The rationale used to establish the acceptable range of acceptance criteria should be described.
  - data obtained from lots used in preclinical and/or clinical studies,
  - data from lots used for demonstration of manufacturing consistency, and
  - data from stability studies, relevant development data.



# SPECIFICATIONS Selection of tests

- There can be circumstances in which routine testing of an attribute of the drug substance and drug product can be substituted by a suitable control earlier (i.e., upstream) in the manufacturing process (e.g., surrogate control, DNA).
- In such circumstances, test results should be considered as in-process acceptance criteria
- Requires a sufficient understanding of sources of variability and their impact on downstream processes, in-process materials (including intermediates), and drug substance/ drug product quality.
- Before shifting controls upstream, applicants should determine that factors later in the process (i.e., downstream) from the point of control will not compromise effective control.
- RTRT (real time release testing)



## Considerations in Developing a Control Strategy (acc.to ICHQ11 step2)

#### Traditional and enhanced approach,

- For drug substances that are particularly sensitive to factors such as temperature changes, oxidation, light, ionic content, and shear (e.g., most biotechnological products), these factors should be considered before implementing upstream approaches to attribute control.
- When in-process controls are used in lieu of testing of specific drug substance attributes, these controls should be described and justified. A drug substance should have a specification even when utilising real time release testing.



## **Drug Substance Specification**

The following tests and acceptance criteria are considered applicable to all drug substances:

- Appearance and description
- Identity (more than 1 test)
- Quantity
- Purity (Combination of methods)
- Impurities (process/product related)
- Potency
- Variants
- pH-, bioburden, endotoxin etc.

Other tests are product dependent.



#### Drug Product Specification

The following tests and acceptance criteria are considered applicable to all drug products:

**Pharmacopoeial requirements** apply to the relevant dosage forms. include, but are not limited to

- sterility,
- endotoxin,
- microbial limits,
- volume in container,
- particulate matter,
- uniformity of dosage units,
- moisture content for lyophilised drug products

#### **General tests**

pH and osmolarity



## Drug Product Specification

The following tests and acceptance criteria are considered applicable to all drug products:

- Appearance and description
- Identity (more than 1 test may be necessary)
- Quantity ( Protein content or Units)
- Purity (Combination of methods)
- Degradation Products
- Impurities
- Potency (When an appropriate potency assay is used for the drug substance, an alternative method (physicochemical and/or biological) may suffice for quantitative assessment of the drug product. Rationale to be provided.



#### Drug Product Specification and Stability

#### **Purity and impurities**

- Impurities may be generated or increased during manufacture and/or storage of the drug product.
- These may be either the same as those occurring in the drug substance itself, process related, or degradation products which form specifically in the drug product during formulation or during storage.
- If impurities are qualitatively and quantitatively (i.e., relative amounts and/or concentrations) the same as in the drug substance, testing is not necessary.
- If impurities are known to be introduced or formed during the production and/or storage of the drug product, the levels of these impurities should be determined and acceptance criteria established.
- Acceptance criteria and analytical procedures should be developed, to measure changes in the drug substance during the manufacture and/or storage of the drug product.
- The choice and optimisation of analytical procedures should focus on the separation of the desired product and product-related substances from impurities including degradation products, and from excipients.



#### Release Limits vs. Shelf-life Limits

- The concept of release limits vs. shelf-life limits may be applied where justified.
- This concept pertains to the establishment of limits, which are tighter for the release than for the shelf-life of the drug substance or drug product.
- Examples where this may be applicable include potency and degradation products.

#### ⇒⇒ Stability Studies

In some regions, the concept of release limits may only beapplicable to in-house limits and not to the regulatory shelf-life limits.



