Joint BWP / QWP workshop with stakeholders in relation to **prior knowledge and its use in regulatory applications**

Session 2 - Product design

General considerations

Keith Watson, Abbvie

London, Nov. 23, 2017

efpia
European Federation of Pharmaceutical Industries and Associations

ebe
european biopharmaceutical enterprises

Vaccines Europe
An industry for healthy lives

medicines for europe
better access. better health.

PRIOR KNOWLEDGE and Product Design

"Current use of prior knowledge"

- The Quality Target Product Profile (QTPP), CQA's of drug product and previous experience from related products can support identification of potential CQA's of drug substance

- Drug substance Quality link to Drug product
  - Prior knowledge of drug substance properties e.g. product related impurities, degradation profiles, solubility, stability and permeability can influence development of drug product

- Excipient properties can support formulation development activities
  - Prior knowledge of degradation profiles of excipients, prediction/modelling of their interactions with active/other excipients, influence on stability and solubility of drug product

- Container closure systems and streamlined packaging selection

PRIOR KNOWLEDGE and Product Design
"Platform knowledge"

- Prior knowledge (platform technology) often applied (historically) to monoclonal antibody (MAb) products to improve speed and robustness
- Allows front-loading certain activities
  - Assessment of CQAs, CPPs based on prior knowledge/platform knowledge
  - Focus on analytical characterization early and high priority assays
- Candidate molecule fit with platform may not guarantee success – small differences in molecular structure leading to large difference in behavior for Biotherapeutic products
- Prediction based on prior knowledge and experience from multiple products on the same platform need to be supported with data (ex. small scale)
- Ensuring the accuracy and reliability of analytical methods throughout a product's life cycle.

PRIOR KNOWLEDGE and Product Design
"Setting of CQAs"

- Need to understand all sources of variation that may impact on CQA's
- Leverage prior knowledge and first principles to inform severity
- Learn/copy from previous risk assessments
- Create a library of common risks with classification and scoring
- Then Risk assessment activities can focus efforts on greatest risks

PRIOR KNOWLEDGE and Product Design
"Product-class monographs"

Product-Class monographs offer an opportunity:

- to Inform a list of typical Quality Attributes and information on specific class of product understanding (shared Knowledge) from which a key part of the Testing Strategy can be derived
- to have access to product knowledge, understanding of Quality attributes derived from approved products,
- to differentiate the testing strategy between those for characterization and those for release/comparability
- to provide suitable analytical tools consistent with the defined Quality Attributes related to a defined class of product and their physical standards (Suitability test) to control their performance.
- different analytical methods for quality attributes than those described in the Ph. General Chapters may be used where appropriately justified.
- However may be CHALLENGING for complex biological products like which possess a large number of quality attributes.

PRIOR KNOWLEDGE and Product Design

"Container closure systems"

Prior knowledge of packaging properties:

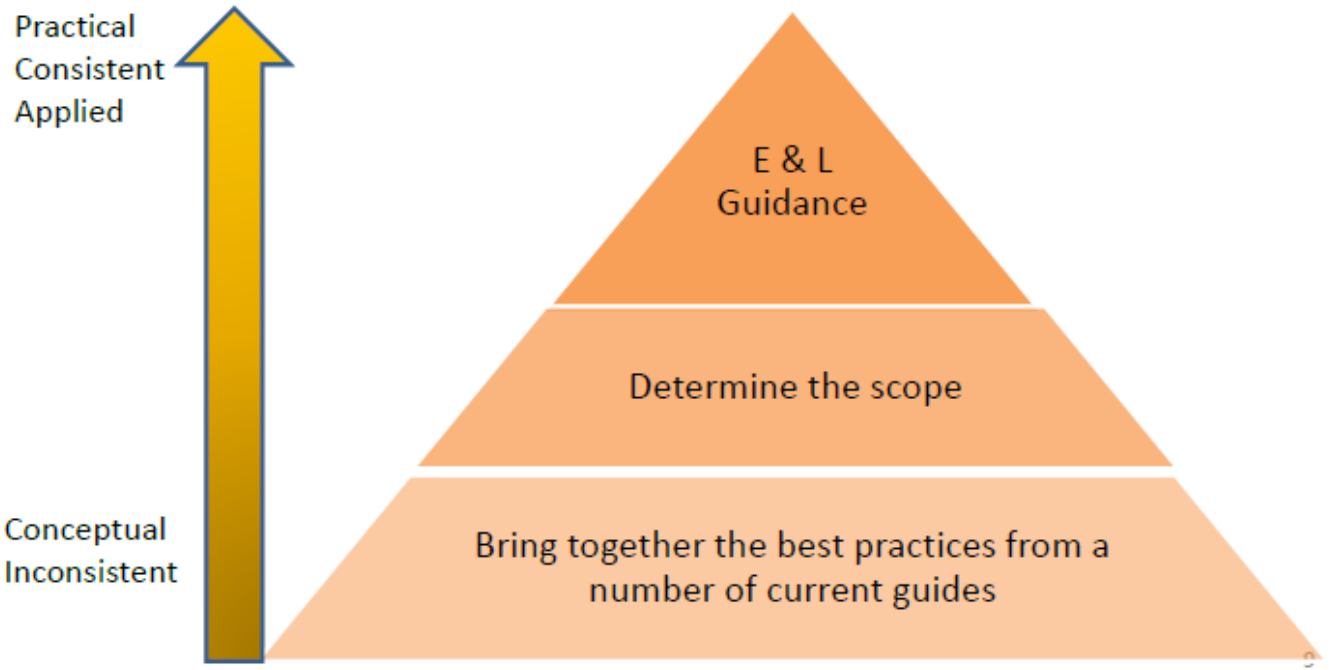
- allows streamlined packaging selection
- use of compendial materials
- pharmacopeial knowledge database
- extensive publicly available data on leachable/extractables
- understanding of adsorption risk

PRIOR KNOWLEDGE and Product Design

"Extractables and leachables"

Proposal (Overview)

- To define a mid- and long-term strategy
- To bring efficiency through consistency for both regulators and industry
- To acknowledge the global nature of manufacturing operations



PRIOR KNOWLEDGE and Product Design

"Extractables and leachables"

Proposal (Details)

Scope and Principles

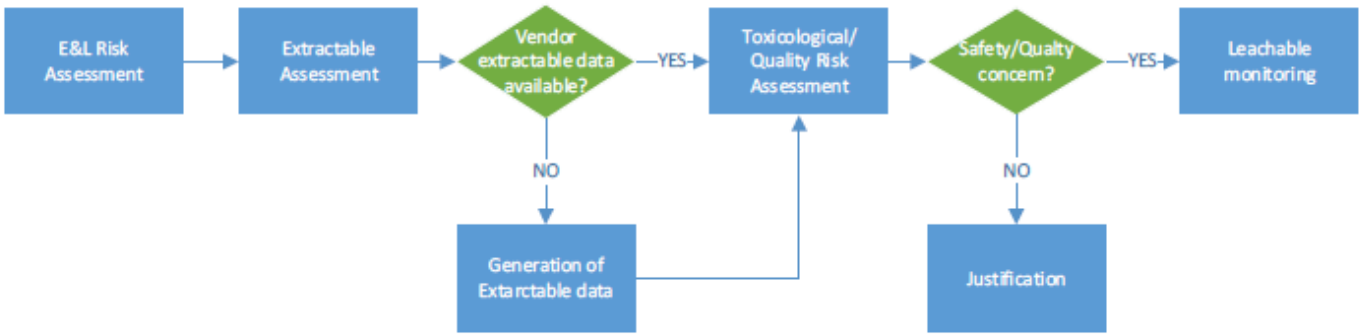
- Scope:
  - Biotherapeutic products (+ chemical products)
  - Manufacturing (e.g. SUS) and packaging components
- Principles:
  - Formal guidance
  - Clear and Practical expectations
    - Consistency in Terminology
    - Risk Based approach

PRIOR KNOWLEDGE and Product Design

"Extractables and leachables"

Proposal (Details)

E&L Risk Management Flow



FUTURE USE OF PRIOR KNOWLEDGE

"Physiology based modelling"

Journal of Pharmaceutical Sciences 106 (2017) 734-737

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Clinical Trials and Translational Medicine Commentaries

Maximizing the Impact of Physiologically Based Oral Absorption Modeling and Simulation

John I. Chung [1, *], Ron C. Kelly [1], Jan Wahlstrom [2], Benjamin Wu [3], Tian Wu [1], Fernando Alvarez-Nunez [1]

[1] Amgen Inc., Drug Product Technologies, Thousand Oaks, California 91320
[2] Amgen Inc., Pharmacokinetics and Drug Metabolism, Thousand Oaks, California 91320
[3] Amgen Inc., Medical Sciences, Thousand Oaks, California 91320

Utilizing Physiologically Based Pharmacokinetic Modeling to Inform Formulation and Clinical Development for a Compound with pH-Dependent Solubility

JOHN CHUNG,[1] FERNANDO ALVAREZ-NUNEZ,[1] VINCENT CHOW,[2] DOMINICK DAURIO,[1] JOHN DAVIS,[2] MICHAEL DODDS,[2] MAURICE EMERY,[3] KEVIN LITWILER,[4] ANNE PACCALY,[2] JOANNA PENG,[2] BROOKE ROCK,[2] LARRY WIENKERS,[2] CHARLES YANC ZHIGANG YU,[3] JAN WAHLSTROM[2]

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Journal of Pharmaceutical Sciences xxx (2017) 1-6

Contents lists available at ScienceDirect

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Clinical Trials and Translational Medicine Commentary

Physiologically Based Oral Absorption Modelling to Study Gut-Level Drug Interactions

John Chung [1, *], Filippos Kesisoglou [2]

[1] Drug Product Technologies, Amgen, Inc., Thousand Oaks, California 91320
[2] Biopharmaceutics and Specialty Dosage Forms, Pharmaceutical Sciences and Clinical Supply, Merck & Company, Inc., West Point, Pennsylvania 19486

Journal of Pharmaceutical Sciences xxx (2016) 1–12

Contents lists available at ScienceDirect

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journal homepage: www.jpharmsci.org

Research Article

Physiologically Based Absorption Modeling to Impact Biopharmaceutics and Formulation Strategies in Drug Development—Industry Case Studies

Filippos Kesisoglou [1, *], John Chung [2], Judith van Asperen [3], Tycho Heimbach [4]

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[4] Drug Metabolism and Pharmacokinetics, Novartis Institutes for Biomedical Research, East Hanover, New Jersey 07936

FUTURE USE OF PRIOR KNOWLEDGE
"GASTROPLUS"

- Use of a combination of advanced bio-relevant *in vitro* and *in silico* physiologically based PK models (PBPK)
- Use of pH 6.8 buffer more clinically relevant media for input into PBPK model for modified release dosage form plasma concentration prediction
- Advanced *in vitro* dissolution models (TNO-TIM1) for *in-vivo* prediction
- Advanced *in silico* PBPK models for formulation selection
- Routinely part of FIH strategy for small molecule
- Build absorption model in GastroPlus
- Validate absorption with preclinical species
- Evaluate food effect, particle size, co-administration with pH modifiers
- Project PK profile and determine whether a platform formulation or solubility enhancing formulation can achieve effective plasma concentrations
- Use of *in silico* tools
- GastroPlus for oral absorption modeling, and SimCyp for DDI
- External Benchmarking
- IQ Consortium: Formulation Bioperformance Working Group
- GastroPlus User Group
- FDA collaboration with Simulations Plus for Long Acting Injectables

PRIOR KNOWLEDGE and Product Design
"Questions and points for consideration"

- How to justify applicability of knowledge from products within same class e.g. mAbs versus mAbs manufactured using platform technologies?

- Can prior knowledge be transferred across different classes of products e.g. mAbs versus fusion proteins?

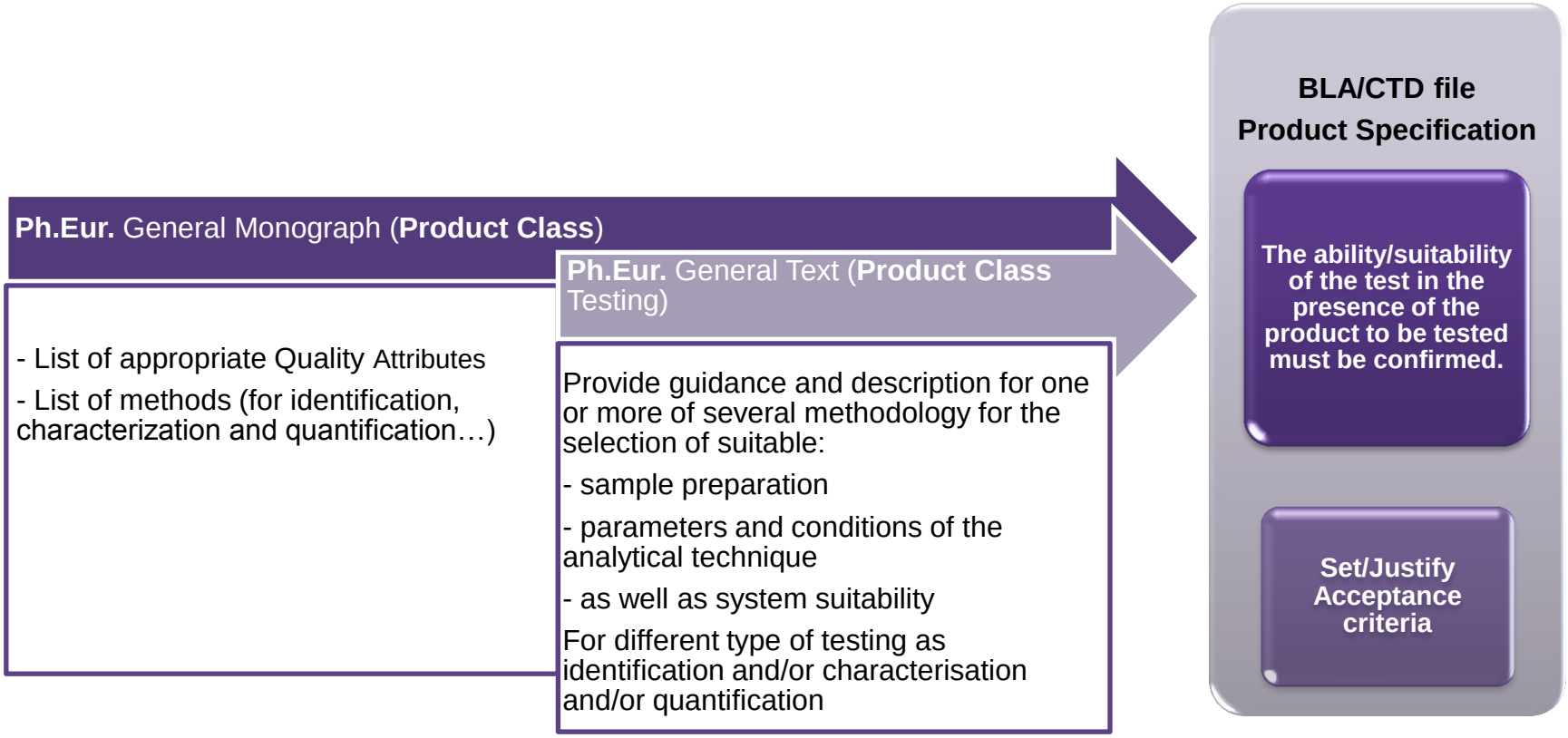
- Is it possible to apply "core" CQAs/CPPs to a class of product e.g. mAbs and generate "class monographs"?

- Can prior knowledge be applied to extractables/leachables or similar container closure systems?

PRIOR KNOWLEDGE and Product Design

“Back up slides”

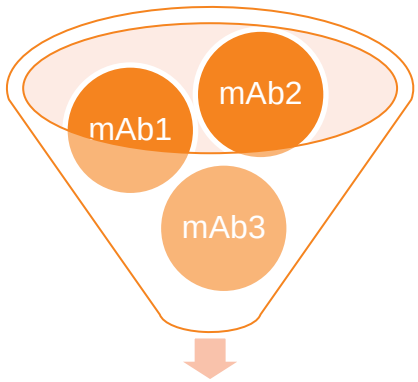
Industry Expectations/Perspectives



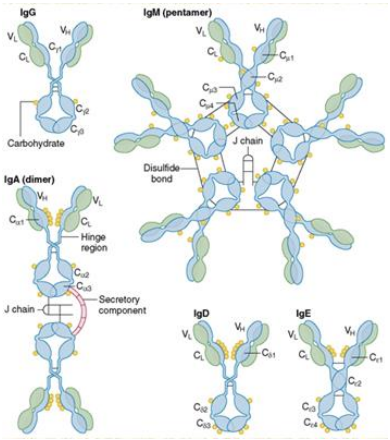
The combination of the Product Class Monograph(s) and Product Class General Text should replace Product-specific monograph(s)

Illustrative Example
«Product Class Monograph for Monoclonal Antibody»

Joint collaboration
EDQM/Industry/HAs



Product Class Monograph
for MONOCLONAL ANTIBODY



Quality Attribute Characteristics	Quality Attribute Product Variant / Degradants	Quality Attribute Process related Imp. / contaminants
- Molecular Mass and size - Primary structure (e.g Amino Acid sequence, Amino acid composition - Higher order structure (Secondary and tertiary structure)	- Size Heterogeneity - Charge Heterogenity	- Host Cell protein - Residual DNA - Residual Protein A
- Disulfide bonds, Free thiols, Cysteinylated & glutathionylated variants - Thioether bonds - Gycosylation (N and O-linked), glycation - Level and type sialylation - Amino acid modifications, substitutions - Amino acid Mis-incorporation	- Aggregation/Fragmentation/Clips - Proteinaceous subvisible particles: ≥2µm, ≥ 10µm and ≥25µm - Half-antibody - Disulfide isoforms - Deamidation / Oxidation - Carboxy and amino terminal modifications - Pyroglutamic acid - Leader sequence	- Microbial (bacteria, yeast, fungi) - Mycoplasma - Viruses (endogenous and adventitious) - Endotoxin
- Biological activity / Potency - Content		- Culture media residues - Downstream-derived impurities

Illustrative Example «Characteristics»

Quality Attribute	General Chapters	Example of Method /Intended purpose
MOLECULAR WEIGHT		2.2.43. Mass spectrometry 2.2.46. Chromatographic separation techniques (SEC)
IgG-type monoclonal antibodies have a molecular weight of approximately 150 kD. Each molecule consists of two heavy and two light polypeptide chains that have a molecular weight of approximately 50 and 25 kD, respectively		
PRIMARY SEQUENCE AND AMINO ACID SUBSTITUTION		2.2.55. Peptide mapping (QC, Characterization, Stability) 2.2.56. Amino acid analysis 2.2.43. Mass spectrometry
Unintended amino acid substitutions, also known as sequence variants, are a concern during the production of recombinant human monoclonal antibodies that are being developed as therapeutics. As such, detection of potential sequence variants during clone selection and bioprocess development are important to the biotechnology industry. Alterations in the primary structure of a protein can occur as the result of changes at the nucleic acid or protein level and fall into three broad categories: mutations at the DNA level, misin¬corporation at the protein level due to mistranslation or improper tRNA acylation, and miscleavage during the post-translational processing.		
N-LINKED AND O-LINKED GLYCANS (pattern of glycosylation of the glycoprotein)	2.2.59. Glycan analysis of glycoproteins .	CE (2.2.47) and MS (2.2.43) SEC (2.2.30) SDS-PAGE (2.2.31
All glycan structures should be characterised and their locations identified. Particular attention should be paid to the degree of mannosylation, galactosylation, fucosylation and Sialylation		
SIALYLATION	2.2.59. Glycan analysis of glycoproteins .	IEC (2.2.46), IEF (2.2.54) or CE (2.2.47)
Unlike serum glycoproteins that contain surface-exposed glycans that are 60–95% sialylated, only about 10% of Fc glycans of human serum IgG are sialylated and <5% of Fc glycans of recombinant IgGs produced in CHO cells are sialylated		
SITE-SPECIFIC GLYCOSYLATION PROPERTIES, ON THE DEGREE OF OCCUPANCY, AND ON THE OLIGOSACCHARIDE STRUCTURES		LC (2.2.29) and CE (2.2.47)
Only low levels of non-glycosylated molecules are usually observed in recombinant monoclonal antibodies. It is established that glycosylation of IgG-Fc is essential for optimal expression of biological activities mediated through **FcgRI, FcgRII, FcgRIII** and the **C1q** component of complement. This is mainly due to the impact of glycosylation heterogeneity of the Fc region of IgGs on the conformational structure of the lower hinge region which makes no direct contact with the carbohydrate moieties and forms the major FcgR-binding site		

Illustrative Example
«Product Variants/Degradants»

Quality Attribute	General Chapters	Example of Method /Intended purpose
AGGREGATION		AUC (characterization), SEC (IPC, QC, stability, characterization)
Factors affecting aggregation include primary structure (surface content of hydrophobic groups), secondary structure, temperature, pH, protein concentration, freeze-thawing, freeze-drying, spray-drying, shearing/shaking, refolding and reconstitution.		
FRAGMENTATION		Bioanalyzer (IPC), SDS-PAGE+ CE (QC, characterization, stability)
Fragmentation pertains to disruption of a covalent bond as a result of either spontaneous or enzymatic reaction. Fragmentation can be generated during cell culture (Various proteases can be found in cell culture supernatants), may be modulated by the purification process and may accrue during storage		
C TERMINAL MODIFICATION (lysine truncation and amidation)		SEC, SDS-Page+CE, RP-HPLC, LC/MS peptide mapping AUC (QC, characterization, stability)
Truncation of the C-terminal lysine of antibodies due to carboxypeptidase activity in cell culture; Amidation refers to the replacement of a protein's C-terminal carboxyl group with an amide functional group ($CONH_2$). C-terminal amidation can be considered to be a general C-terminal modification among therapeutic mAbs		
OXIDATION		SEC, SDS-Page+CE, RP-HPLC, LC/MS peptide mapping AUC (QC, characterization, stability)
Protein oxidation is a covalent modification of an amino-acid that is induced by reactive oxygen and is often a result of stress or contamination. Protein oxidation occurs predominantly on methionine residues. The human IgG1 has 2 or 3 methionine residues in the Fc domain depending on the allotype: Met255 in the CH2 domain, Met361 and Met431 in the CH3 domain. Met255 and Met431, in particular, are located at the CH2-CH3 interface which is the consensus binding site that interacts with several natural proteins including Protein A, Protein G and FcRn.		
DEAMIDATION/ISOMERISATION		SEC, SDS-Page+CE, RP-HPLC, LC/MS peptide mapping AUC (QC, characterization, stability)
Deamidation of asparagine residues is one of the most common post-translational modifications occurring in therapeutic proteins produced using recombinant DNA technology. In this reaction, the asparagine residue is, converted into aspartate and iso-aspartate residues.		

Illustrative Example
«Product Variants/Degradants»

Quality Attribute	General Chapters	Method /Intended purpose
HALFMER AND FAB' ARM EXCHANGE		Bioanalyser and CE-SDS under non reducing conditions
Example IgG4. Several publications suggests that IgG4 is prone to Fab arm exchange. Fab Arm exchange requires the dissociation of two heavy chain. The formation of half antibodies is controlled by a destabilised core hinge region and non-covalent interactions of CH3 domain region. Fab arm exchange does occur between IgG4 antibodies resulting in bispecific antibodies. The bispecific antibody is a concern due to: binding avidity, PK, PD and a potential impact on safety		
N-TERMINAL PYROGLUTAMIC ACID		Bioanalyzer , SDS-PAGE+ CE (QC, characterization, stability)
Pyroglutamic acid at the N terminus of the heavy chain is formed by post-translational cyclisation of the N-terminal glutamine residue.		
CYSTEINE VARIANTS		Bioanalyzer , SDS-PAGE+ CE ; Mass Spectrometry; CEX/ICE (QC, characterization, stability)
Reactions with non-disulphide bonded cysteines can lead to a variety of PTMs including thioethers, glutathione or other process adducts and free cysteinylated chains.		
PRESENCE OF PREPRO AND PRO PEPTIDE		Mass Spectrometry, N-terminal sequencing (characterization)
The N-terminus of the heavy or light chains may be extended from the desired mature sequence due to incomplete proteolytic processing of the leader sequence		
PROTEINACEOUS SUBVISIBLE PARTICLES: ≥2MM, ≥ 10MM AND ≥25MM		HIAC, MFI , Light Obscuration, microscope, visual inspection
Large protein assemblies with repetitive arrays in which the protein molecules have native conformation are potentially very potent antigens capable of inducing immune responses.		

Illustrative Example
«Process Related Impurities»

Quality Attribute	General Chapters	Example of Method /Intended purpose
HOST CELL DNA		qPCR (IPC, QC, characterization)
The nucleic acid includes host cell genomic, inserted vector, total DNA, and total RNA. DNA deriving from continuous cell lines that have an infinite life span due to the deregulation of genes that control growth is considered to have potential to confer the capacity for unregulated cell growth or tumorigenic activity upon other cells.		
HOST CELL PROTEINS	2.6.34 Host Cell protein (under study)	Elisa (IPC, QC, characterization)
Host cell/source–derived impurities include proteins derived from host cell, source tissues, or body fluids. Host cell proteins (HCP) are the indigenous proteins co-expressed by the host cell and which can co-purify with the active substance. Since HCPs are foreign to humans, they can be directly immunogenic. Therefore, HCPs may cause adverse events in patients even at low levels and especially in patients with natural anti-animal antibodies.		
RESIDUAL PROTEIN A		ELISA (ICP, QC, characterization)
The capability of this resin for the purification of monoclonal antibodies and Fc-fusion proteins relates to the affinity of Protein A for a specific site found on human IgG1, IgG2 and IgG4 . One disadvantage of this selective affinity-purification method is that some active Protein A may leach out of the resin and might be carried through into the drug substance.		
RESIDUAL HORMONE (Culture media residues)		ELISA (characterization, IPC)
Insulin, a hormone that is central to regulating glucose metabolism in the body, is commonly used as a serum-free medium additive to promote cell growth, lengthen cell survival and protein production. Insulin is a common component of the cell culture medium used for the manufacture of monoclonal antibody.		