Informational Chapter A:

Since the content of this chapter is part of CDER/OPQ's early thinking which may ultimately be incorporated for use in development of Draft Pharmaceutical Quality/Chemistry Manufacturing and Controls (PQ/CMC) Data Elements and Terminology, we are presenting this as a "Informational Chapter" to distinguish it from the main PQ/CMC Chapters. The main Chapters of the Data Elements and Terminology living document represent information for comment on the developing comprehensive content for PQ/CMC. Informational Chapters will be used to represent presentations of thinking that are in earlier development for which an office or center would like input from the public.

Background

The Center for Drug Evaluation and Research (CDER) Office of Pharmaceutical Quality (OPQ) at the FDA (Agency) is requesting comment on the draft controlled terminology/vocabulary defined by the CDER/OPQ SMEs for a set of coded quality attributes data elements and their categorization for therapeutic protein products. Building on the Agency's previous Federal Register notices published on July 11, 2017, March 18, 2022, and May 1, 2023, requesting comments on PQ/CMC data elements and controlled terminology, the Agency is continuing to seek comment on the accuracy, suitability, and appropriateness of terminologies for a set of coded quality attribute data elements and their categorization for therapeutic proteins. In addition, the progress toward the establishment of standardized terminologies will require further interactions between the Agency, interested parties, and various stakeholders including industry. Accordingly, FDA is planning to request comment on additional coded quality attribute data elements and terminologies over time.

Quality attributes for biological products do not have a set of controlled terminology and systematic naming taxonomy to group the terms, and consequently this limit poses a critical challenge in the development of systems for structured regulatory submissions. Consequently, the use of agreed upon terminology for protein quality attributes in a standardized format should increase the efficiency of FDA's review of information in Module 3 of eCTD submissions for an Investigational New Drug Application (IND) and a Biologics License Application (BLA). The terminology and taxonomy described herein would apply to protein therapeutics only.

Review of these elements and definitions should be conducted by personnel in pharmaceutical companies who will be able to determine if the element definitions and controlled terminologies are understandable and meaningful.

eCTD mapping: Used with General Information (3.2.S.1), Characterization (3.2.S.3.1, 3.2.S.3.2), Specifications (3.2.S.4.1, 3.2.S.4.5, 3.2.P.5.1, 3.2.P.5.6), Batch Information (3.2.S.4.4 and 3.2.P.5.4), Stability (3.2.S.7.1 - 3.2.S.7.3; 3.2.P.8.1 - 3.2.P.8.3), Analytical Procedures (3.2.S.4.2, 3.2.S.4.3, 3.2.P.5.2, 3.2.P.5.3), and other relevant sections and the corresponding sections in Module 2.

CQA Controlled Terminology

The following table contains the controlled terminology/vocabulary defined by the CDER/OPQ SMEs for a set of coded CQA data elements for therapeutic proteins products. The controlled terminology table contains only those CQA data elements for which a value set has been defined.

For additional reference, see Figure 1 at the end of this document for a visual representation of this information.

Data Element Name: Denotes the name of the PQ/CMC element.

Valid Values: The allowable values for a given PQ/CMC data element.

Value Identifier: Identifier for the level of the given valid value.

Valid Value Meaning: The description of the allowable value for the given PQ/CMC data element (defined by the Agency SMEs).

Data Element Name	Valid Values	Value Identifier	Valid Value Meaning
Main Taxonomical Category	Active Ingredient	1	The therapeutic protein that provides meaningful activity with respect to the intended use of the product
	Structure	2	Construction and modifications to the active ingredient
	Function	3	The biological activity of the active ingredient
	Process-Related Impurities	4	Impurities that are derived from the manufacturing process
	Material Properties	5	Attributes related to either the drug substance or drug product that are reflective of the entire material
	Formulation	6	Ingredients in the finished dosage form other than the therapeutic protein
1 - Active Ingredient	Charge	1.1	Reflective to evaluation of the overall isoelectric point (pI) profile of the molecule
	Mass	1.2	Evaluation of the molecular weight of the active ingredient, may or may not include pre-measurement treatment of the sample
	Absorbance	1.3	Assessment of the interaction of the drug

			substance or drug product with light of a specified wavelength
2 – Structure	Primary Structure	2.1	The characteristic sequence of alpha amino acids forming a protein
	Higher Order Structure	2.2	Collective term for secondary, tertiary, and quaternary structure that reflects correct folding and three-dimensional shape of a protein
	Size Variants	2.3	Modifications to the structure of the protein that result in changes to the weight or length of the protein, including fragmentation and higher weight species
	Linked Non-Protein Polymer	2.4	Covalent modifications to the protein that include addition of components that are not alpha amino acid chains, includes glycosylation and conjugation
3 – Function	Cellular Evaluation	3.1	Evaluation of biological activity that utilizes a cell-based output
	Binding	3.2	Evaluation of biological activity that utilizes the measurement of protein interaction with a specific target
	Enzymatic Evaluation	3.3	Evaluation of biological activity that measures catalysis performed by the protein
	Animal/Tissue	3.4	Evaluation of biological activity that measures animal outcome or organ functionality measured using *in vivo* systems
4 - Process-Related Impurities	Media Component	4.1	Undesirable impurities deriving from those intentionally used in the manufacturing process that

			are not volatile components
	Residual Solvent	4.2	Inorganic or organic liquids remaining during the manufacturing process
	Non-Media Component	4.3	Undesirable impurities from those components not intentionally derived from the manufacturing process
	Microbiological or Adventitious	4.4	Undesirable impurities that ultimately originate from the presence of microorganisms/viruses
5 - Material Properties	Appearance	5.1	Visual properties of the material, including drug substance and/or drug product
	General Attributes	5.2	Properties of the material, including drug substance and/or drug product that are not visually evaluated
6 - Formulation	Buffer	6.1	Components of a formulation that serve to control pH
	Surfactant	6.2	Components of a formulation that serve to affect surface tension
	Tonicity	6.3	Components of a formulation that serve to adjust osmolality
	Cryoprotectant	6.4	Components of a formulation intended to prevent damage due to freezing
	Antioxidant	6.5	Components of a formulation that serve to inhibit oxidation
1.1 - Charge	Acidic Variants	1.1.1	Profile content identified as species with a lower isoelectric point in charge variant determination
	Basic Variants	1.1.2	Profile content identified as species with higher isoelectric point in charge variant determination

	Neutral Main Peak	1.1.3	Profile content identified as predominant species close to its pI in charge variant determination
	Profile	1.1.4	The entire pattern of the charge evaluation as measured
	pI	1.1.5	Isoelectric point determination of active ingredient
1.2 – Mass	Intact Molecular Weight	1.2.1	Whole active ingredient molecular mass
	Non-Glycosylated Molecular Weight	1.2.2	Whole active ingredient molecular mass after removing glycosylation
1.3 - Absorbance	Extinction Coefficient	1.3.1	Characteristic that determines how strongly a species absorbs or reflects radiation or light at a particular wavelength
2.1 - Primary Structure	Sequence	2.1.1	Determination of the primary amino acid sequence of the active ingredient
	Sequence Variant	2.1.2	Identification and level of primary sequences that are considered modifications to the active ingredient
	Deamidation	2.1.3	Identification and level of sequence modifications that resulted due to loss of the amide functional group in the side chain of asparagine or glutamine
	Oxidation	2.1.4	Identification and level of sequence modifications that are the covalent modification of a protein induced either by direct reactions with reactive oxygen species (ROS) or indirect reactions with secondary by-products of oxidative stress
	Aspartic Acid Isomerization	2.1.5	Identification and level of primary sequence modifications that are

			intramolecular rearrangements to form a succinimide which subsequently hydrolyzes
	Conjugation Site	2.1.6	Identification of modification location in the sequence where a covalent attachment occurs for a linked non-protein polymer
	C-terminal Proline amidation	2.1.7	Identification and level of primary sequence modifications that are amidation of the C-terminal proline
	N-terminal pyroglutamate	2.1.8	Level of primary sequence modifications that are pyroglutamate formation of the N-terminal Glutamic Acid
	C-terminal Lysine clipping	2.1.9	Level of primary sequences modifications that are cleavage of the C-terminal lysine
	Hydroxylysine	2.1.10	Identification and level of primary sequences modifications that are hydroxylysine formation
	Glycation	2.1.11	Identification and level of primary sequence modifications with bound sugar molecules attached by non-enzymatic reactions
2.2 - Higher Order Structure	Free Thiols	2.2.1	Level of sulfur atom(s) in a cysteine side chain that is (are) unpaired to another sulfur atom from a cysteine
	Disulfide Bond	2.2.2	Evaluation of formation of covalent bonds between the sulfur atoms of two cysteine residues in the active ingredient
	Thioether	2.2.3	Evaluation of cysteine crosslinks other than intended disulfide linkages
	Thermal Stability	2.2.4	Evaluation of denaturing of protein in high temperature condition

	Secondary Structure Profile	2.2.5	The specific three-dimensional folded protein structure that is determined by the hydrogen bonds formed between amino acids in the polypeptide chain and excluding side chain interactions
	Tertiary Structure Profile	2.2.6	The overall three-dimensional protein arrangement resulting from folding of the polypeptide chain to assemble the different secondary structure elements in a particular arrangement
	Alpha Helicity	2.2.7	Evaluation of content of common arrangement (alpha helix) in the secondary structure of protein
2.3 - Size Variants	High Molecular Weight – All	2.3.1	Level of all size variants identified as larger in molecular mass size variants than the main protein component
	High Molecular Weight – Dimer	2.3.2	Level of all size variants reflecting agglomeration of two protein molecules
	Low Molecular Weight – All	2.3.3	Level of all species identified as lower in mass than the main protein component
	Low Molecular Weight – Individual	2.3.4	Level and identification of individual species identified fragments of the protein
	Low Molecular Weight – HHL	2.3.5	Level of individual species of immunoglobulin molecule identified as loss of light chain fragment
	Monomer	2.3.6	Level of individual species identified as intact protein
	Residual Homodimer	2.3.7	Level of monoclonal antibody impurity formed

			with incorrect (i.e., the same) arm pairings
2.4 - Linked Non-Protein Polymer	N-Glycosylation	2.4.1	Carbohydrate attachments to N-terminal amino acids
	O-Glycosylation	2.4.2	Carbohydrate attachments to O-linked amino acids
	Glycosylation Ratio	2.4.3	Ratio of N-Glycosylation to O-Glycosylation content
	Conjugation	2.4.4	Attachment of a non-alpha amino polymer that is not considered glycosylation
3.1 - Cellular Evaluation	Apoptosis	3.1.1	Functional evaluation that reflects measurement of a type of programmed cell death
	ADCC	3.1.2	Functional evaluation that reflects measurement of Antibody Dependent Cellular Cytotoxicity
	CDC	3.1.3	Functional evaluation that reflects measurement of Complement Dependent Cytotoxicity
	ADCP	3.1.4	Functional measurement than reflects Antibody Dependent Cellular Phagocytosis
	Activation	3.1.5	Functional evaluation that reflects measurement of cellular or signaling activity
	Inhibition	3.1.6	Functional evaluation that reflects measurement of cellular or signaling activity reduction
	Neutralization	3.1.7	Functional evaluation that reflects measurement of reduction of function by blocking
	Proliferation	3.1.8	Functional evaluation that reflects measurement of cell multiplication
	Cytotoxicity	3.1.9	Functional evaluation that reflects measurement of cell killing activity
3.2 - Binding	FcγRIa	3.2.1	Evaluation of a binding activity to Fc (crystallizable

			fragment)-gamma receptor Ia
	FcγRIIa	3.2.2	Evaluation of a binding activity to Fc-gamma receptor IIa
	FcγRIIb	3.2.3	Evaluation of a binding activity to Fc-gamma receptor IIb
	FcγRIIIa	3.2.4	Evaluation of a binding activity to Fc-gamma receptor IIIa
	FcRn	3.2.5	Evaluation of a binding activity to neonatal crystallizable fragment receptor
	C1q	3.2.6	Evaluation of a binding activity to Complement component 1q
	Target	3.2.7	Identification and evaluation of a binding activity to the intended specific target
3.3 - Enzymatic Evaluation	Kcat	3.3.1	The maximal number of molecules of substrate converted to product per active site per unit time when the enzyme is saturated with substrate, also referred to as turnover number
	Km	3.3.2	Measure of enzyme efficiency reflecting the concentration of substrate that permits the enzyme to achieve half Vmax, also referred to as the Michaelis constant
	Activity	3.3.3	General measurement of enzyme activity other than 3.3.1 and 3.3.2
	Phosphorylation	3.3.4	Measure of enzymatic addition of phosphate group
3.4 - Animal/Tissue (in vivo)[1]	Survival	3.4.1	Evaluation of effect based on animals alive at endpoint

	Glucose Response	3.4.2	Evaluation of effect based on glucose measurement in tissue or blood
4.1 - Media Component[1]	Antifoam A	4.1.1	Level of process-related impurity for antifoam A
	Methotrexate	4.1.2	Level of process-related impurity for methotrexate
	m-Cresol	4.1.3	Level of process-related impurity for m-Cresol
	Trehalose	4.1.4	Level of process-related impurity for trehalose
	Kanamycin	4.1.5	Level of process-related impurity for kanamycin
	Zinc	4.1.6	Level of process-related impurity for Zinc
4.2 - Residual Solvent[1]	Methanol	4.2.1	Level of residual solvent for methanol
	Acetonitrile	4.2.2	Level of residual solvent for acetonitrile
	Ethyl Acetate	4.2.3	Level of residual solvent for ethyl acetate
4.3 - Non-Media Component [1]	Host Cell Protein	4.3.1	Level and identity (optional) of residual unintended proteins originated from production cells
	Residual Protein A	4.3.2	Level of remaining leached Protein A
	Host Cell DNA	4.3.3	Level of residual DNA from production cells
	Free Drug	4.3.4	Level of drug-linker that is not conjugated in an antibody-drug conjugate
	Unconjugated Impurity	4.3.5	Level and identity of small molecule process-related impurities that are not conjugated in an antibody-drug conjugate
4.4 - Microbiological or Adventitious	Bioburden	4.4.1	Level of bacteria or other microorganisms observed – could be either in drug substance or drug product
	Mycoplasma	4.4.2	Presence of mycoplasma – could be either in drug substance or drug product

[1] Examples provided in these sections are not considered all-inclusive.

	Endotoxin	4.4.3	Level of bacterial lipopoly-saccharide detected – could be either in drug substance or drug product
	Virus Specific	4.4.4	Level of a specific virus – could be either in drug substance or drug product
5.1 - Appearance	Color of Solution	5.1.1	The use of visual perception to indicate purity and/or a means to identify contamination
	Color of Solid	5.1.2	Description (could or could not include a standard) for the color of a drug substance or drug product in a non-liquid form (e.g., powder, capsule, etc.)
	Clarity of Solution	5.1.3	Measurement of the turbidity of the solution or qualitative or quantitative measurement of degree of opalescence of a solution, including instrumental measurement of the light reflected by the solution
	Opalescence	5.1.4	Description (could or could not include a standard) for visual opalescence of drug substance or drug product
	Turbidity	5.1.5	Measurement of the clarity and degree of opalescence of liquids by comparison of the solutions in diffused daylight after preparation of the reference suspension
	Visible Particles	5.1.6	Level and description of particles visible by naked eye
	Description/Appearance	5.1.7	Visual inspection of the drug substance or product to assess the physical state and color
5.2 – General Attributes[2]	Sterility	5.2.1	Result of tests done under aseptic conditions to

[2] Examples provided in these sections are not considered all-inclusive.

			ensure that there are no contaminating micro-organisms present in the sample
	Osmolality	5.2.2	Measurement of the solute concentration of a solution expressed in terms of the weight of the solvent
	pH	5.2.3	The measure of the acidity or alkalinity of either drug substance or drug product
	Identity	5.2.4	Evaluation of identification of either drug substance or drug product
	Reconstitution Time	5.2.5	Measurement of how long it takes to dissolve a solid product in a diluent
	Protein Concentration	5.2.6	Level of protein amount in a unit volume observed
	Water Content	5.2.7	Level of residual water observed in solid product
	Sub-Visible particles	5.2.8	Level and size threshold of small particles not observable to the unaided eye
	Content Uniformity	5.2.9	Degree of uniformity in the amount of the drug substance among dosage units
	Particle Size Distribution	5.2.10	Level and size threshold of material particles evaluated for that is not based on appearance
6.1 - Buffer[2]	Histidine	6.1.1	Level of histidine in formulation
	Arginine	6.1.2	Level of arginine in formulation
	Citrate	6.1.3	Level of citrate in formulation
6.2 - Surfactant[2]	Polysorbate 80	6.2.1	Level of Polysorbate 80 as a surfactant in formulation
	Polysorbate 20	6.2.2	Level of Polysorbate 20 as a surfactant in formulation
	Poloxamer 188	6.2.3	Level of Poloxamer 188 as a surfactant in formulation

6.3 - Tonicity[2]	Sucrose	6.3.1	Level of sucrose as a tonicity agent in formulation
6.4 - Cryoprotectant[2]	D-Trehalose	6.4.1	Level of D-trehalose as a cytoprotectant in formulation
6.5 - Antioxidant[2]	EDTA	6.5.1	Level of ethylenediaminetetraacetic acid as an antioxidant agent in formulation
2.4.1 - N-Glycosylation	Afucosylation	2.4.1.1	Level of glycoforms possessing Man3GlcNAc2Asn lacking a core fucose, this excludes levels of high mannose from value
	Afucosylation including Mannosylation	2.4.1.2	Level of glycoforms possessing Man3GlcNAc2Asn lacking a core fucose, this also should include levels of high mannose within value
	Galactosylation	2.4.1.3	Level of glycoforms including both complex and hybrid that include galactose
	Mannosylation	2.4.1.4	Level of glycoforms possessing Man3GlcNAc2Asn structure with 5–9 mannose residues and possesses only mannose attachments to the core
	Sialyation	2.4.1.5	Level of glycoforms including both complex and hybrid that include sialic acid residues
	Non-Glycosylated Heavy Chain	2.4.1.6	Level of immunoglobulin heavy chain that do not have glycosylation
2.4.4 - Conjugation	Unconjugated Protein	2.4.4.1	Content of protein that is not conjugated to the intended non-protein component (e.g., drug-linker in antibody-drug conjugate product)

	Drug to Protein Ratio	2.4.4.2	Ratio of drug molecules conjugated to a protein molecule in a conjugate (e.g., antibody-drug conjugate)
	Drug Load Distribution	2.4.4.3	Fractional distribution of number of drug molecules per protein in a conjugate (e.g., antibody-drug conjugate)
	Main Peak Purity	2.4.4.4	Level of purity for active component of a conjugate
	Conjugated Impurity – Total	2.4.4.5	Level of total impurities conjugated to the active protein component
	Conjugated Impurity – Individual	2.4.4.6	Level and identification of individual impurity conjugated to the active protein component

Draft Pharmaceutical Quality/Chemistry Manufacturing and Controls (PQ/CMC) Data Elements and Terminology

Figure 1. Visual Representation of CQA Controlled Terminology