

Overview/ Progress ISO/IDMP 19844 Substance Implementation Guide to be used in the Global Ingredient Archival System GInAS

Januari - September, 2015
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COLLEGE
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C B G
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M E B

MEDICINES
EVALUATION
BOARD

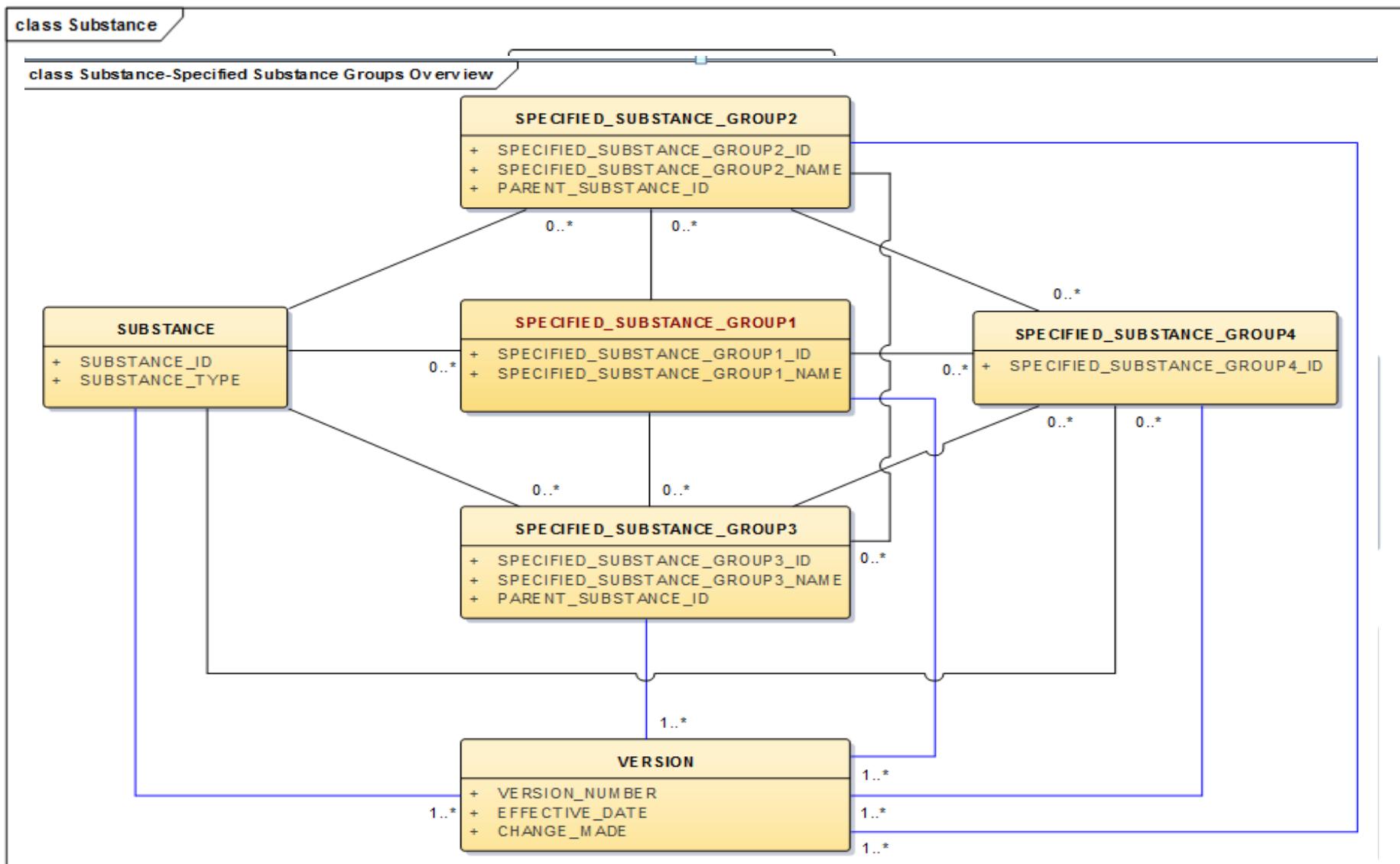


Overview Substance models, new developments

- **General overview and construct of Models**
(Herman Diederik, Thomas Balzer, Larry Callahan, Panagiotis Telenis, Rik Smithies)
- **Discussion Chemical Substances**
(Editor Annex Herman Diederik, Ciska Matai and Frank Switzer, Larry Callahan, review Andrew Marr)
Relationship ISO 11238 with ISO 11616/ ISO/DTS 20451 PhPID Implementation Guide
- **Discussion Protein Substances**
(Editor Annex Larry Callahan, Herman Diederik; Editor Larry Callahan Annex Nucleic acids, review Philipp Weyermann including Main Body Document)
- **Discussion Structurally Diverse Substances for the following domains:**
 - **Herbal substance/ Herbal preparation**
(Editor Annex Herman Diederik and Elizabeth Dauncey (Kew Garden), in cooperation with Frank Switzer, Barry Hammond, Ciska Matai, Burt Kroes)
 - **Blood/ Plasma-derived Substances**
(Editor Annex Marja van de Bovenkamp, Marcel Hoefnagel, Herman Diederik, Larry Callahan)
- **Annexes under development:**
Polymer Substance: Tyler Peryea, Larry Callahan, Peter Jongen
Cell products: Marcel Hoefnagel, Herman Diederik, Fouad Atouf, Judy Arcidiacono
Vaccines: Frank Switzer, Larry Callahan, Ton van der Stappen, Marcel Hoefnagel
Homeopathic Substances: Emiel van Galen, Herman Diederik
Allergens: Vada Perkins, Ilaria del Seppio, Herman Diederik, Marcel Hoefnagel
- **Software development:** NCACTS; Noel Southall and Tyler Peryea
- **Project Lead:** Vada Perkins

Substance_Types Overview

Diagram: Substance

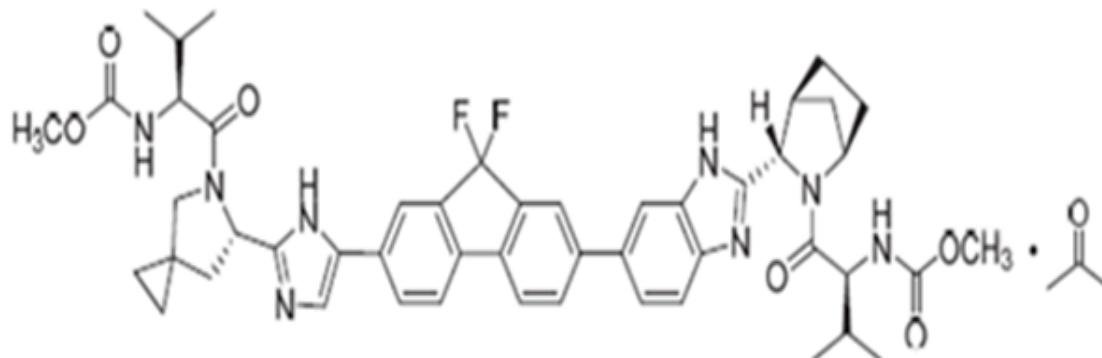


Substance_Type: Chemical Substance

class Chemical Substance

The molecular formula of Amlodipine besilate will be presented by both

2. Lepidasivir acetone solvate [$C_{49}H_{54}F_2N_8O_6 \cdot C_3H_6O$] will have a separate Substance ID from the parent substance Lepidasivir [$C_{49}H_{54}F_2N_8O_6$].



Molecular formula: $C_{52}H_{60}F_2N_8O_7$ ($C_{49}H_{54}F_2N_8O_6 \cdot C_3H_6O$)

Molecular weight: 946,46 g/mol.

Systematic name (INN): methyl [(1S)-1-{(1R,3S,4S)-3-[5-(9,9-difluoro-7-{2-[(6S)-5-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-azaspiro[2.4]hept-6-yl]-1H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzimidazol-2-yl]-2-azabicyclo[2.2.1]heptane-2-carbonyl}-2-methylpropyl]carbamate.

Figure 3 - Illustrative representation of Lepidasivir acetone solvate

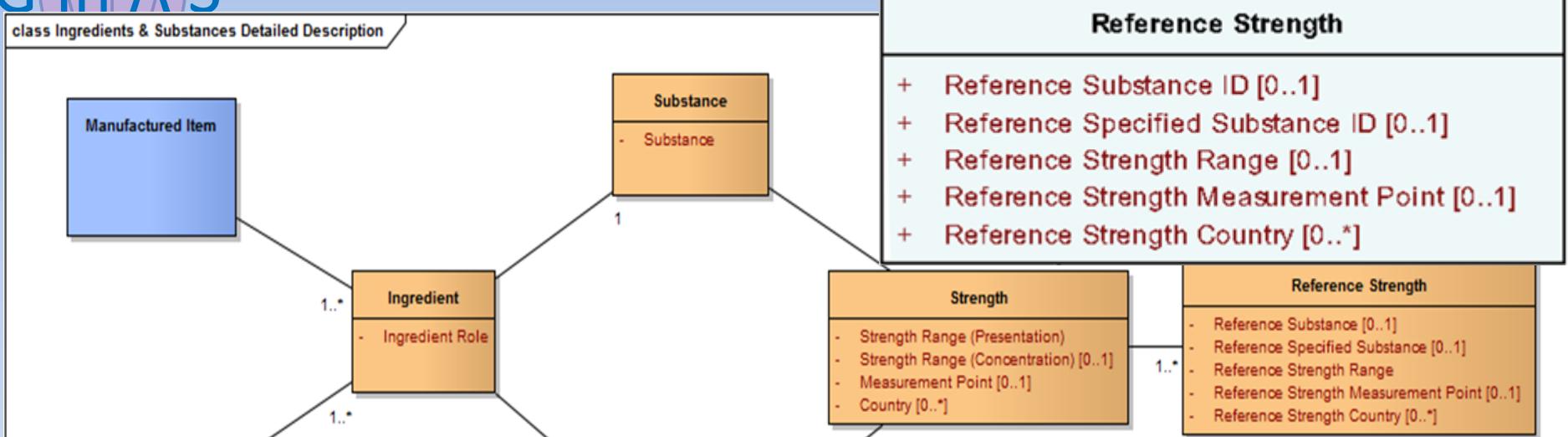
Four Stratum Levels of Pharmaceutical Product and PhPID-Set in relation to Substance moieties

Table 1 — The four levels of PhPID

PhPID Active Substance Stratum	PhPID_SUB_L1 → Substance(s) Term PhPID_SUB_L2 → Substance Term(s) + Strength + Reference Strength PhPID_SUB_L3 → Substance Term(s) + Administrable Dose Form PhPID_SUB_L4 → Substance(s) Term+ Strength + Reference Strength + Administrable Dose Form
PhPID Specified	PhPID_SpSUB_L1 → Specified Substance(s) Term PhPID_SpSUB_L2 → Specified Substance(s) Term+ Strength + Reference Strength
class PhPID High-Level Conceptual <pre> class PhPID High-Level Conceptual class PhPID_Set { <<Substance Stratum>> <<Specified Substance Stratum>> <<Strengths>> } class PhPID_Sub { <<Substance Stratum>> + ID + Name + Administrable Dose Form [0..1] + Strength (concentration) [0..1] + Strength (presentation) [0..1] + Unit of Presentation [0..1] + Adjuvant [0..*] } class Substance_Set { <<Substance Stratum>> + Substance + Role + Confidentiality Indicator [0..1] } class Reference_Strength { <<Strengths>> + Reference Substance ID [0..1] + Reference Specified Substance ID [0..1] + Reference Substance Range + Reference Substance Measurement Point [0..1] + Reference Substance Country [0..*] } class Specified_Substance_Set { <<Specified Substance Stratum>> + Specified Substance ID [1..3] + Role + Confidentiality Indicator [0..1] } class Medical_Device { <<Specified Substance Stratum>> + ID + Name } class Version { <<Strengths>> 1..* + Effective Date } PhPID_Set --> PhPID_Sub : 4 PhPID_Set --> Medical_Device : 0..* PhPID_Set --> Version : 1..* PhPID_Set --> PhPID_SpSUB : 0..4 PhPID_Sub --> Substance_Set : 1..* PhPID_SpSUB --> Reference_Strength : 0..* PhPID_SpSUB --> Specified_Substance_Set : 1..* Version --> Note : This can either be omitted or has to have all 4. In effect "(0 or 4)". </pre>	

Figure 1 – Pharmaceutical Product Identification (PhPID) High Level Conceptual

Four Stratum Levels of Pharmaceutical Product and PhPID-Set in relation to Substance and Strength (S)



To avoid confusion the <Substance term>+<Strength>, <Unit> ; + <Reference Substance term>+<Strength> , <Unit> should be presented:

PhPID_SUB:

<Amoxicillin Trihydrate>,<287>,<mg> (equivalent to) <Amoxicillin Anhydrous>,<250>,<mg> [ACTIM]

<Metoprolol Succinate>,<95,2>,<mg> (equivalent to) <Metoprolol Tartrate>,<100>,<mg> [ACTIR]

<Metoprolol Succinate>,<95,2>,<mg> (equivalent to) <Metoprolol (ACTIB)>,<78,0>,<mg> [ACTIM]

[Mol. weight: M. Succinate 326,4; Mol. weight: M. Tartrate 342,5; Mol. weight: M. 267,4]

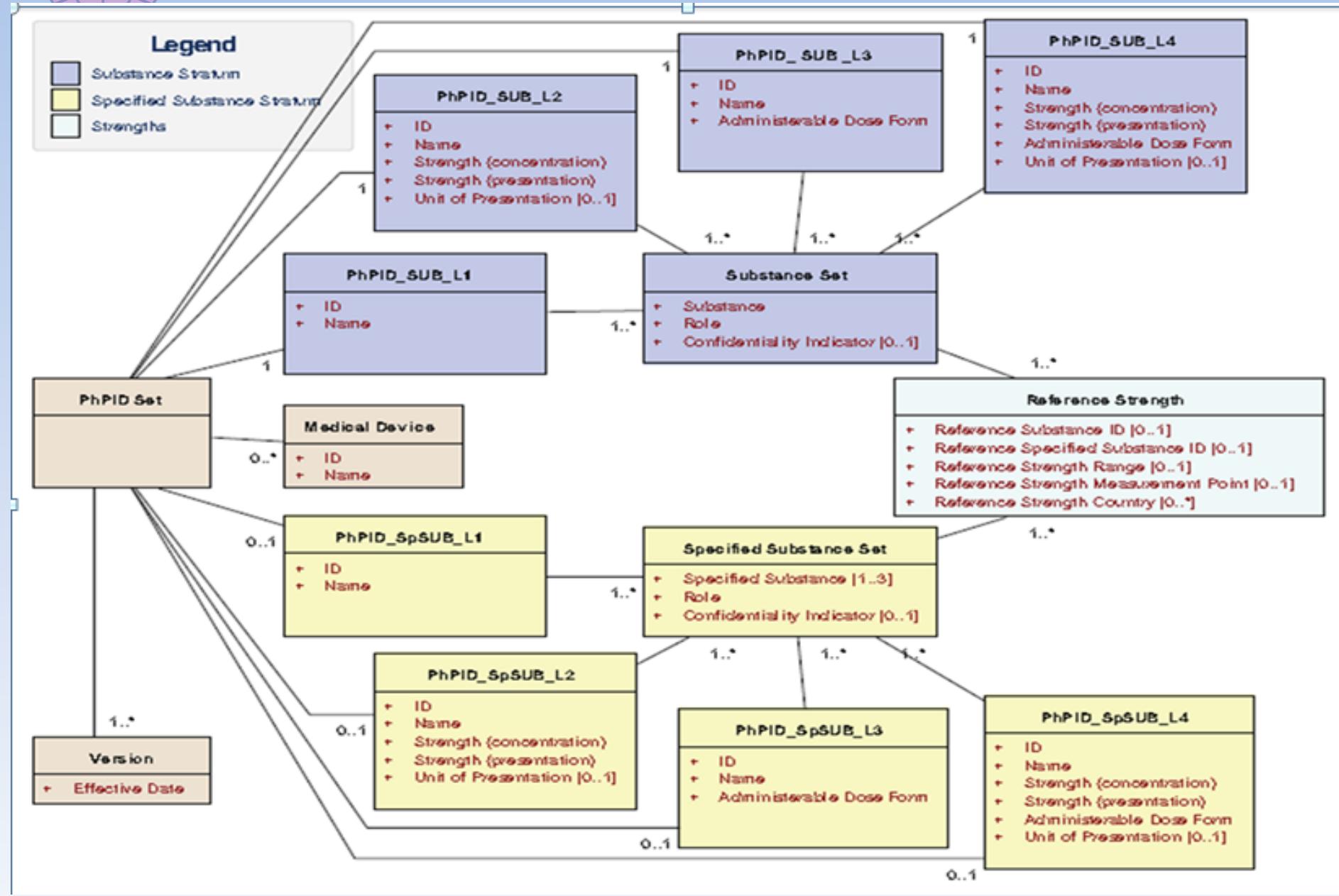
<Xylometazoline hydrochloride>,<0,5>,<mg/ml> [ACTIB] (equivalent to)

<Xylometazoline>,<0,43>,<mg/ml> [ACTIM]

<Lithium Carbonate>,<300>,<mg> (equivalent to) <Lithium ion>,<8>,<mmol> [ACTIR]

NOTE: Strength and Reference Strength are different.

Four Stratum Levels of Pharmaceutical Product and PhPID-Set in relation to Specified Substance Group 1,2,3





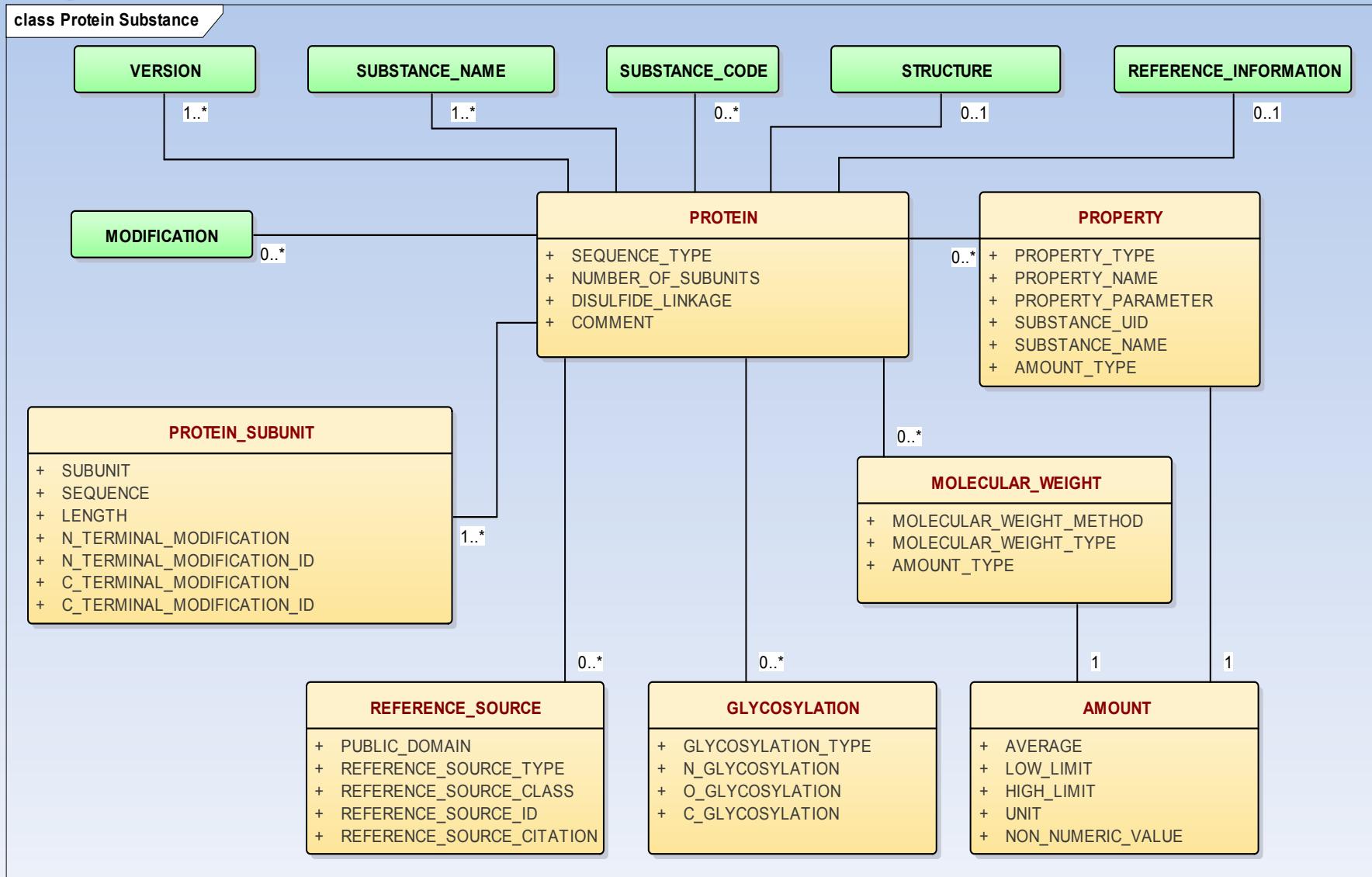
SpPhID Stratum Level_L1 of Pharmaceutical Product and PhPID-Set in relation to Specified Substance Group 1,2,3 _Names and ID's

TRACEABILITY of Substance Manufacturer

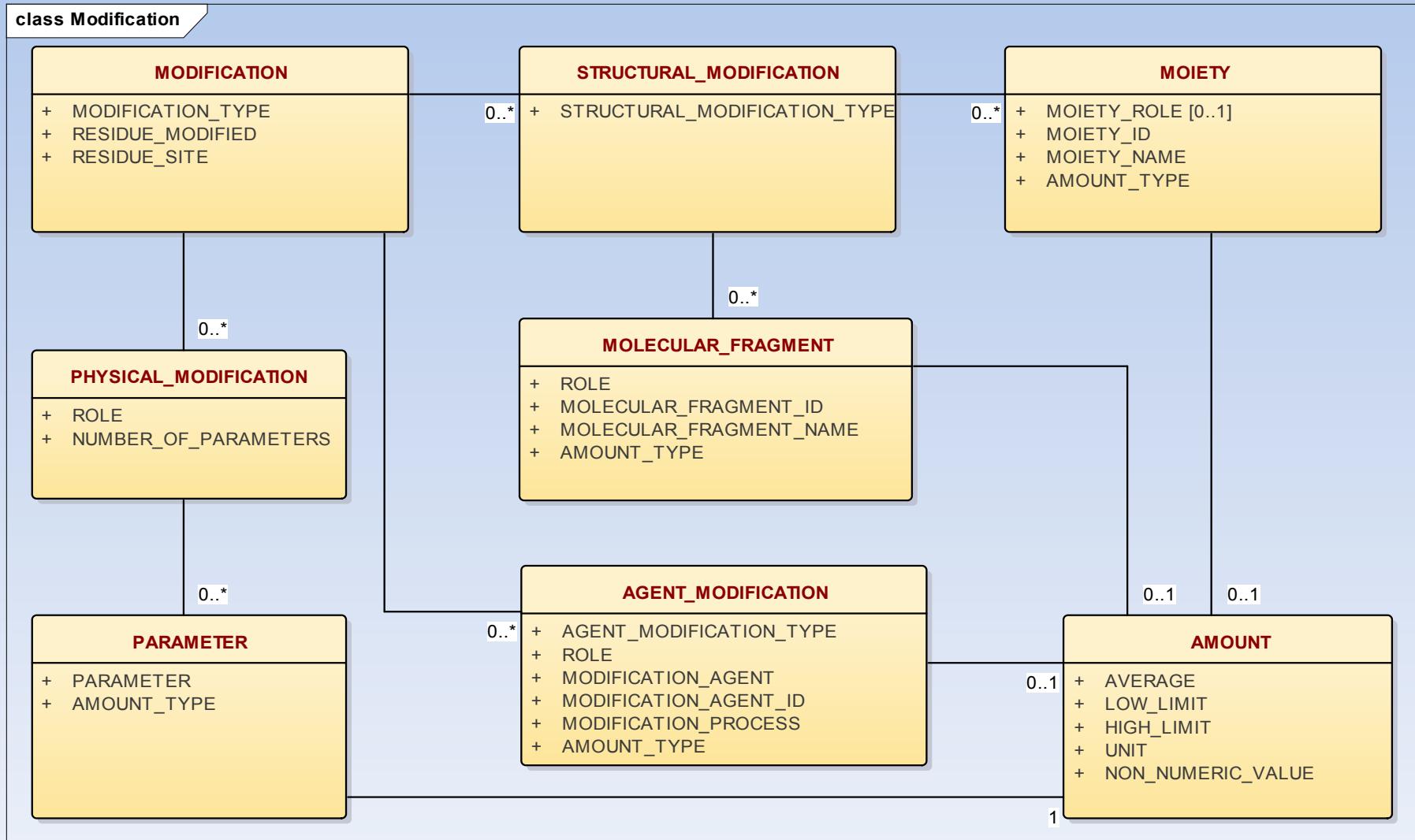
PhPID Active Substance Stratum	PhPID_SUB_L1: Substance Term; Id: 1ZK20VI6TY (UNII) PhPID_SUB_L1: Term(s) (=Name); Triamcinolone
Ingredient Composition of the Manufactured Item/ Pharmaceutical Product	Medicinal Product: Triamcinolone Pharmachem 1 mg/ g Ointment Manufacturing organisation: Pharmachem Manufacturing_Type: Manufacturing operation Manufacturing_Type: Batch release: Pharmaceutical Product Quantity: Ointment, 30 g (in aluminium tube) Ingredient composition: Substance Role: <ACTIB> Specified Substance Group 1_ID: T56342HGS0: 30;
PhF Specified Substance Stratum (Optional?, NO)	----- PhPID_SpSUB_L1: Specified Substance(s) Term (=Name); SSG1_Name Triamcinolone, micronized PhPID_SpSUB_L1: Specified Substance(s) Term; SSG2_ID: HIS4CHEM67; PhPID_SpSUB_L1: Specified Substance(s) Term (=Name); SSG2_Name : Triamcinolone, micronized –Histo Chemicals Note: Coupling SSG1 with Manufacturer (Sp) Substance PhPID_SpSUB_L1: Specified Substance(s) Term; SSG3_ID: EPHGY75643; PhPID_SpSUB_L1: Specified Substance(s) Term (=Name); SSG3_Name : Triamcinolone EP Note: Coupling SSG3 with the Grade PhPID_SpSUB_L2: Specified Substance Term(s) / Strength/ Reference Strength: Triamcinolone micronized; 30 mg/30 g; 1 mg/g; PhPID_SpSUB_L3: Specified Substance Term(s) / Administrable Dose Form: Triamcinolone, micronized; Ointment;



Substance_Type: Protein Substance



Substance_Type: Protein Substance; Element group Modification



Brentuximab Vedotin

Brentuximab

Element Group: Protein Subunit

Element Group: Structural Modification (Repeat)

Fragment
Attachment

Cysteine-VC-MMAE Structure

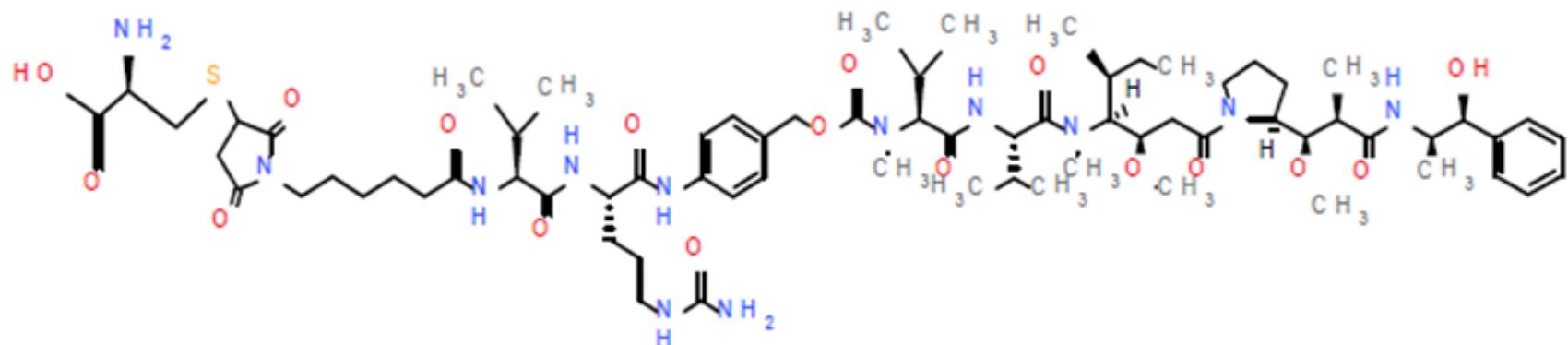
Green
Black
indicates

Figure 12

Element Group: Amount

Average	4.5	PQ
High Limit	3	PQ
Low Limit	5	PQ

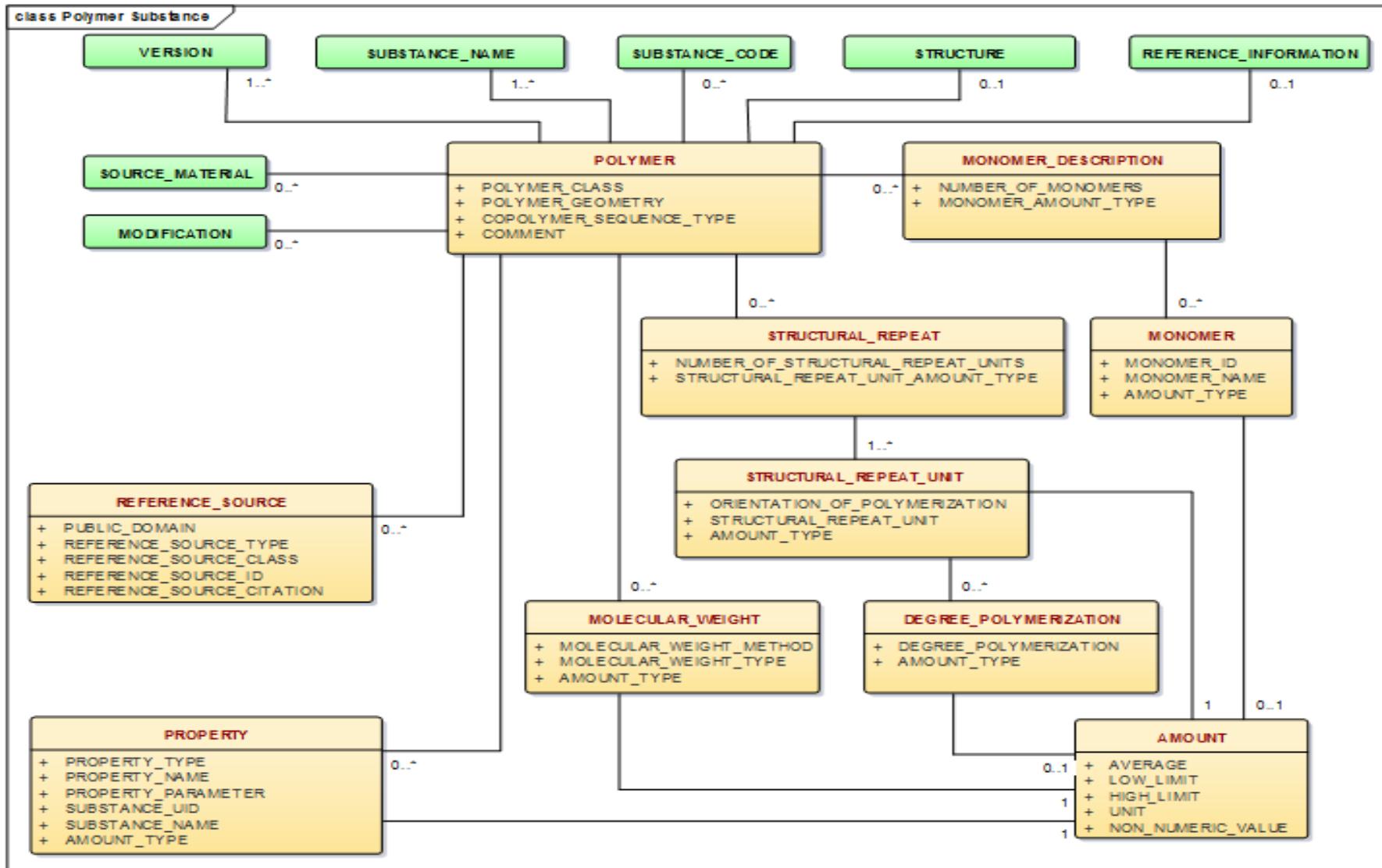
Molecular Fragment ID	6603LUTWVUR (UNII)	CD	
Molecular Fragment Name	Cysteine-VC-MMAE	CD	
Amount Type	Average Mole Ratio Toxin to Antibody	CD	

Element Group: Structure



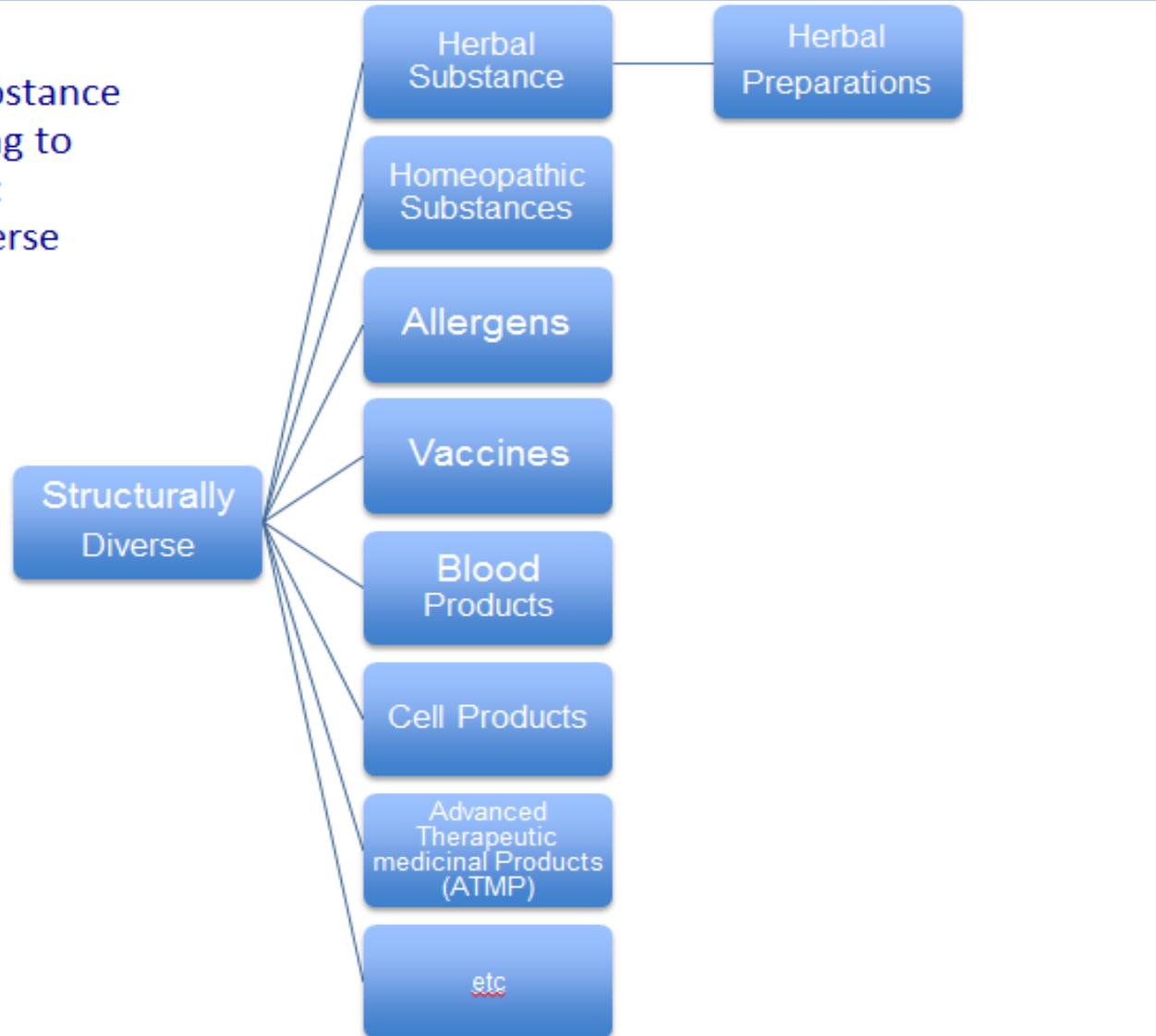
GInAS Substance_Type: Structurally Diverse Substance

Diagram: Polymer Substance



Substance_Type: Structurally Diverse, Substances intended for the following classes/ medicinal products

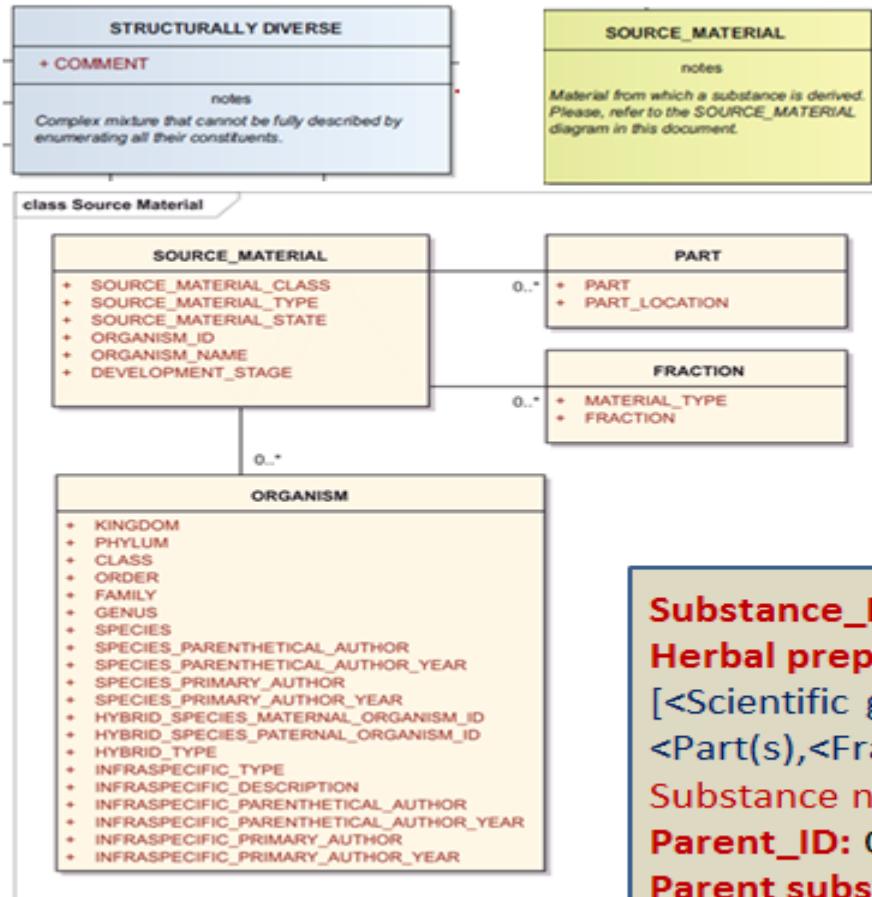
Examples of Substance classes belonging to Substance Type: Structurally Diverse





Substance_Type: Structurally Diverse, Herbal Substance (fresh), Herbal Preparation (1)

ISO/DTS 11238 Information model for the unique identification of the Substance_Type:
Structurally Diverse, Substance (fresh) / Herbal preparation



Substance_ID: OLIJF5643S

Substance_Name:

[<Scientific genus/binomial/trinomial
with Author>,<Part(s)>] :

Olea europaea L., Fruit

Substance Name_Type: Other

Substance Information Level:

Herbal Preparation_Type: Oil, Exudate, Juice

Substance_ID: HJTE78543

Herbal preparation_Name:

[<Scientific genus/binomial/trinomial without Author>,
<Part(s),<Fraction>] : *Olea europaea*, Fruit, Oil

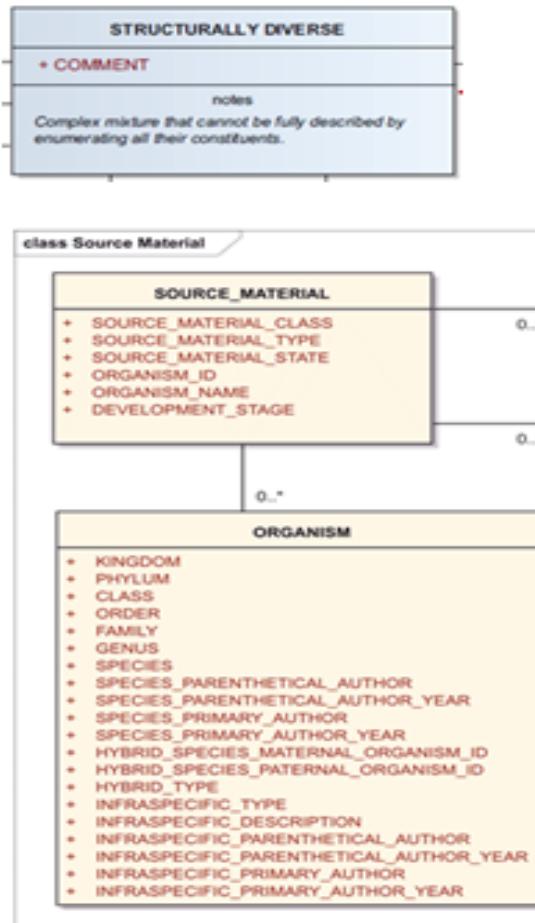
Substance name_Type: Other

Parent_ID: OLIJF5643S

Parent substance_Name: *Olea europaea* L., Fruit

Substance_Type: Structurally Diverse, Herbal Substance (fresh), Herbal Preparation (2)

ISO/DTS 11238 Information model for the unique identification of the Substance Type:
Structurally Diverse, Herbal Substance/ Herbal preparation



Substance Information Level: **Herbal Substance**

Herbal Substance_ID: OLIJF5643S

Herbal Substance_Name:

[<Scientific genus/binomial/trinomial with Author>, <Part(s)>]

Substance Information Level: **Herbal Preparation: Oil, Exudate**

Herbal preparation_ID: HPR852369P

Herbal preparation_Name:

[<Scientific genus/binomial/trinomial with Author>, <Part(s)>, <Fraction>]

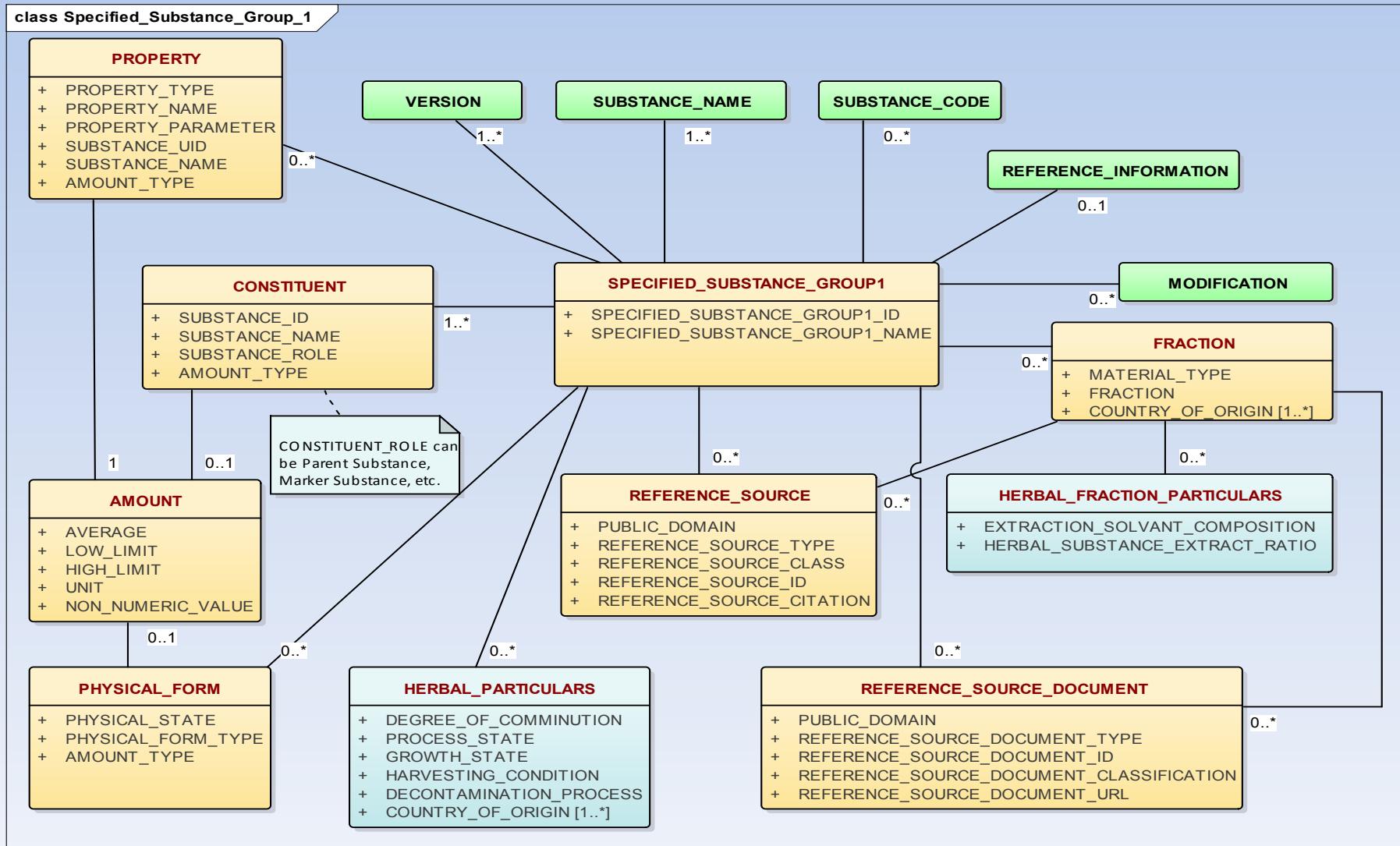
Substance Information Level: **Herbal Preparation: Extract**

Herbal preparation Extract_ID: XYZ123456E

Herbal preparation Extract_Name:

[<Scientific genus/binomial/trinomial **without Author**>,
<Part(s)>, <Extract_Type>, <Extraction solvent_Composition>,
<Unit>, <Herbal Drug (substance)-Extract-Ratio>, <Unit>] e.g.
[Ginkgo biloba, Leaf, Dry Extract Acetone-Water (60-40 w,w)
(65-37=1 w,w)]

Substance_Type: Structurally Diverse, Herbal Substance (fresh), Herbal Preparation, Specified Substance Group 1 Information level



Formulation of a Traditional Herbal Medicinal Product, e.g. Danshen Capsule

Herbal Substance: [Nomenclature based on the CFDA (China Food and Drug Administration)]

Scientific Name: *Salvia miltiorrhiza* Bunge; Family: *Labiatae* (Lamiaceae)

Parts of the plant: Dried, fragmented root and rhizome, cut pieces NMT 5 cm.

Supplier of Herbal Substance: e.g. Tasly Plant Pharmaceutical, Shaanxi province, China

Harvest time, Cultivated plants: In the autumn of the next year after seeding when the aerial parts of the plants are wilting (Shaanxi province of China). The harvested material is dried at 50°C – 60°C as soon as possible after harvesting (loss on drying ≤13%) and stored in closed PP bags under low relative humidity conditions.

Marker Substance for specification:

- Salvianolic acid B (Mol. Form.: C₃₆H₃₀O₁₆; Mol. Weight: 718,6 Da); NLT 3,0 %
- Tanshinone IIA (Mol. Form.: C₁₉H₁₈O₃; Mol. Weight: 294,3 Da) ; NLT 0,12 %

Analytical marker: Rosmarinic acid (Mol. Form.: C₁₈H₁₆O₈; Mol. Weight: 360,3 Da);

BP-spec.:NLT 0,17 %



Salvia miltiorrhiza, also known as red sage, tan shen, or danshen, is a perennial plant of the genus *Salvia*, highly valued for its roots in traditional Chinese medicine.

Native to China and Japan, it grows at 90 to 1,200 m (300 to 3,900 ft) elevation, preferring grassy places in forests, hillsides, and along stream banks.

Sample of the Root and Rhizoma. Cylindrical, slightly curved segments, 5 cm long. The external surface is reddish brown, rough with longitudinal striations.



CAS Registry Name:

Benzene propanoic acid, .alpha.-[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]-3,4-dihydroxy-, (.alpha.R)-

CAS No.: 20283-92-5

SALVIA MILTIORRHIZA ROOT AND RHIZOME

Salviae miltiorrhizae radix et rhizoma

DEFINITION

Dried, whole or fragmented rhizome and root of *Salvia miltiorrhiza* Bunge, collected in spring or autumn.

Content:

- salvianolic acid B (C₃₆H₃₀O₁₆; M_r 719): minimum 3.0 per cent (dried drug);
- tanshinone II_A (C₁₉H₁₈O₃; M_r 294.3): minimum 0.12 per cent (dried drug).

EP monograph no.: 2663



Formulation of a Traditional Herbal Medicinal Product, e.g. Danshen Capsule (Cont. *Salvia miltiorrhiza* Radix Extr.))

Herbal Preparation:

Extract: Danshen extract is a brown to dark brown soft (semi-solid) extract, made through the process of extraction and concentration ($4,5 - 6 = 1$).

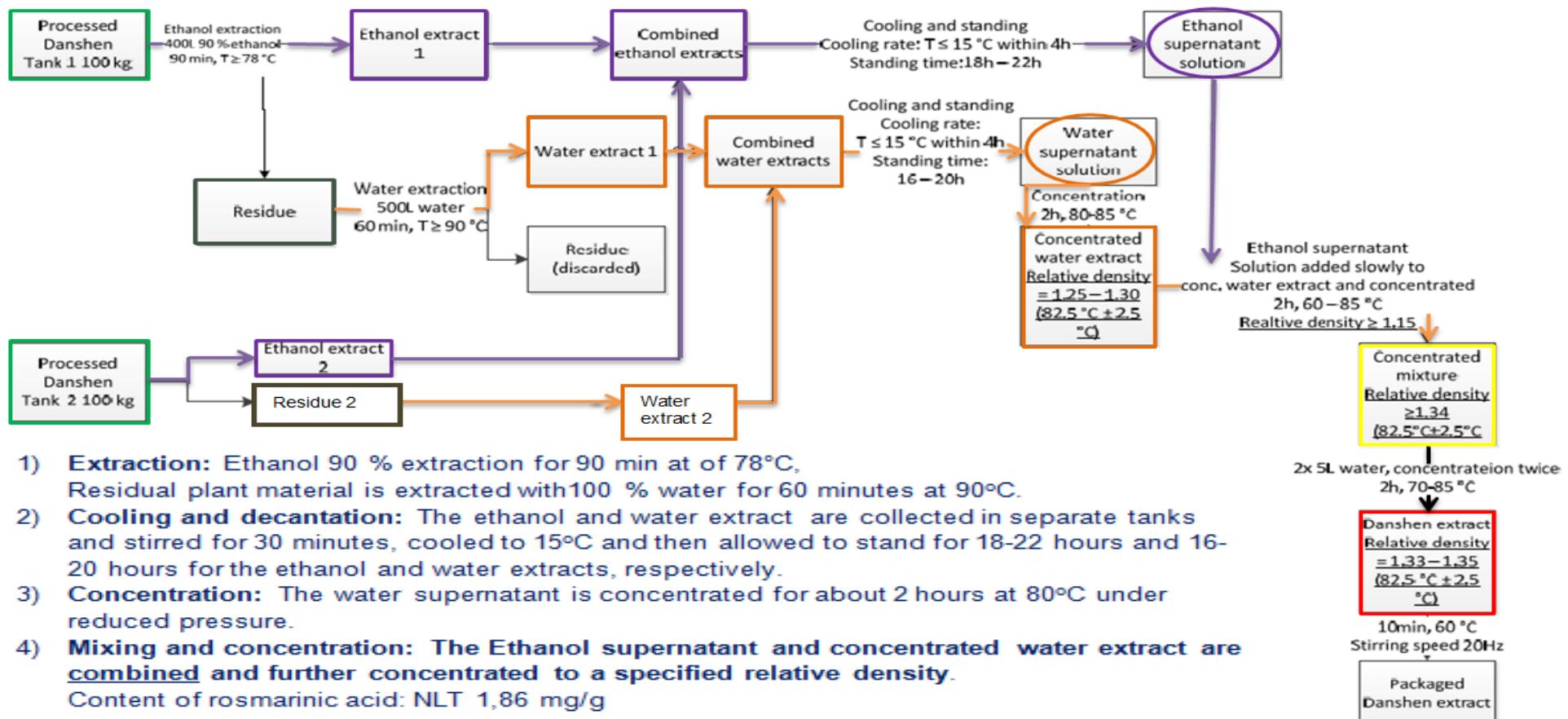
Name: **Salvia miltiorrhiza root and rhizome Ethanolic (90 pCt.)-water liquid extract ($4,5 - 6 = 1$)**.

Dutch Name: Salvia miltiorrhiza wortel en wortelstok ethanolisch (90 pCt.) en waterig droog extract ($4,5 - 6 = 1$);

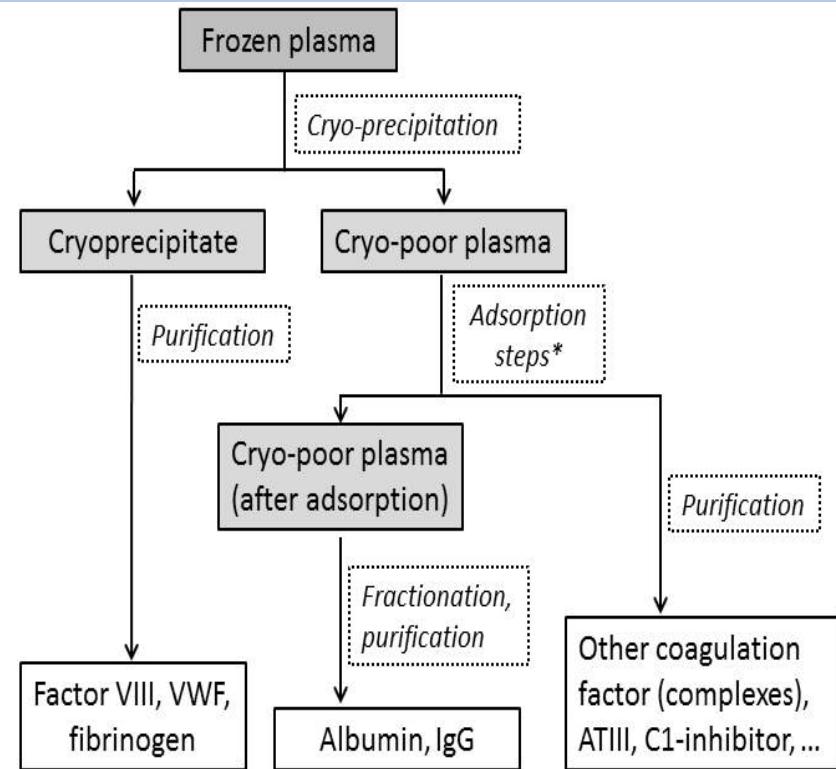
DER: 4,5 – 6 Parts Herbal Substance = 1,0 Part Extract;

Extraction solvent: Ethanol (90) – Water (10) = Ethanol 90 pCt.

Manufacturer of Herbal Preparation: e.g. Tasly Pharmaceutical Group Co., Ltd, China

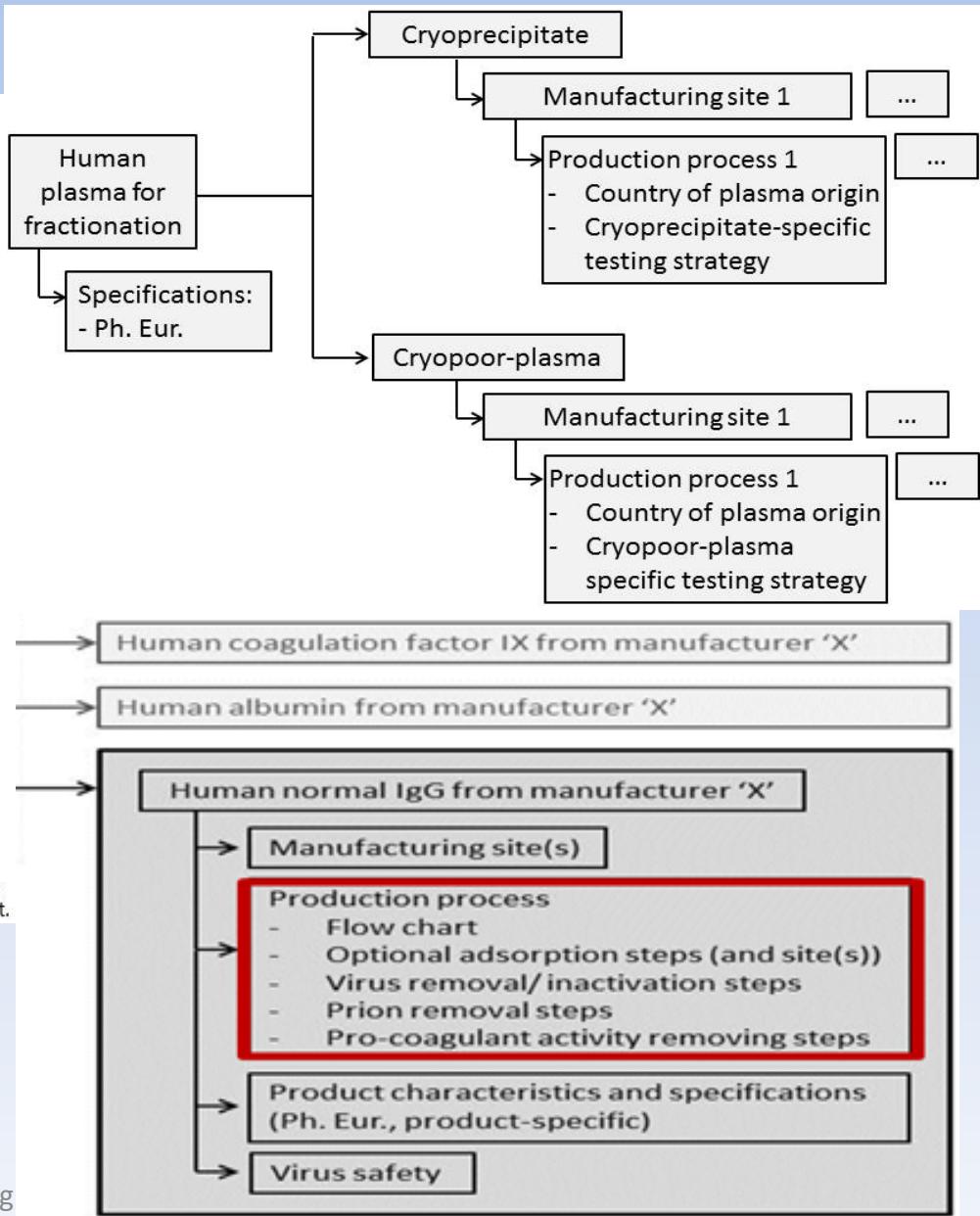


Part and Fraction described for Plasma derived products, Substance level description

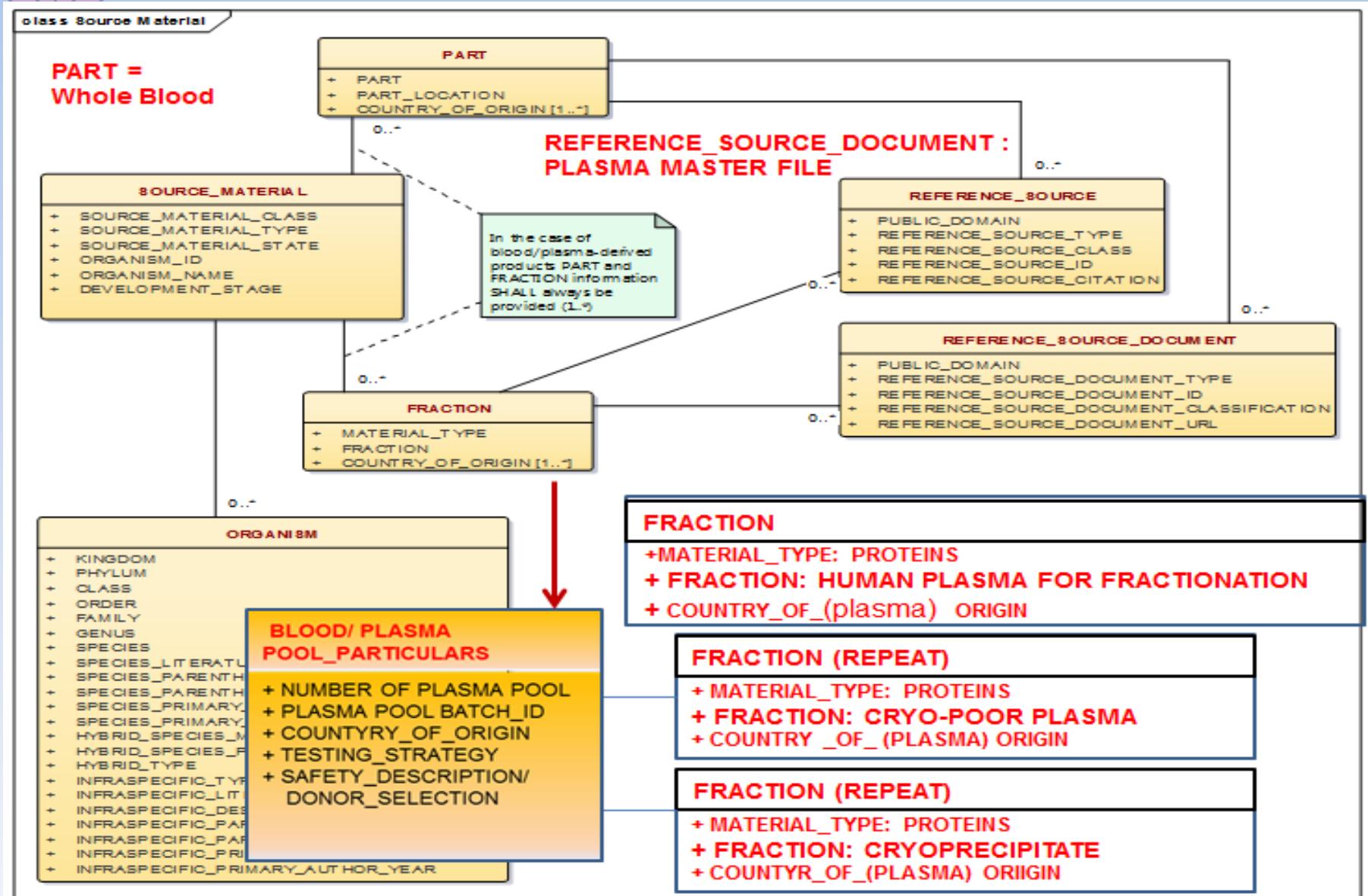


* Adsorption (chromatography) steps may be mandatory or optional steps in the manufacturing process. Optional adsorption steps are not directly aimed at adsorption or purification of the substance of interest.

High level simplified representation of manufacturing process of different types of plasma-derived products (substances)

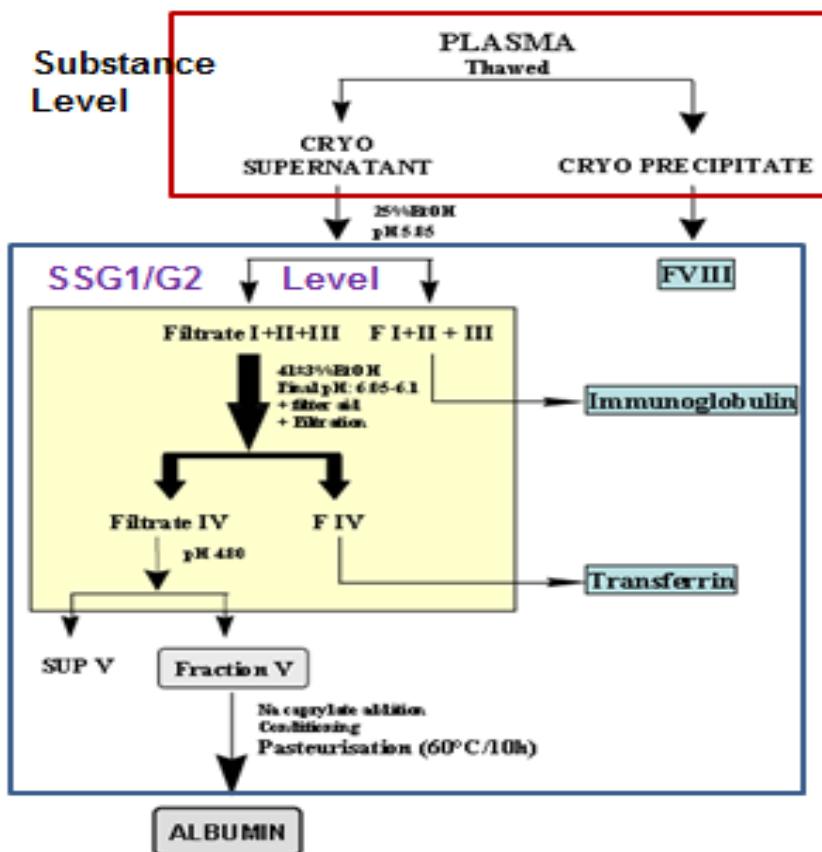


Information Model at the Substance Level for Plasma-derived Substance



Information flow for Albumin, Plasma derived

Scheme 1: Flow-chart Albumin.



Human Albumin, Plasma derived described at the Substance level

Substance Information level:

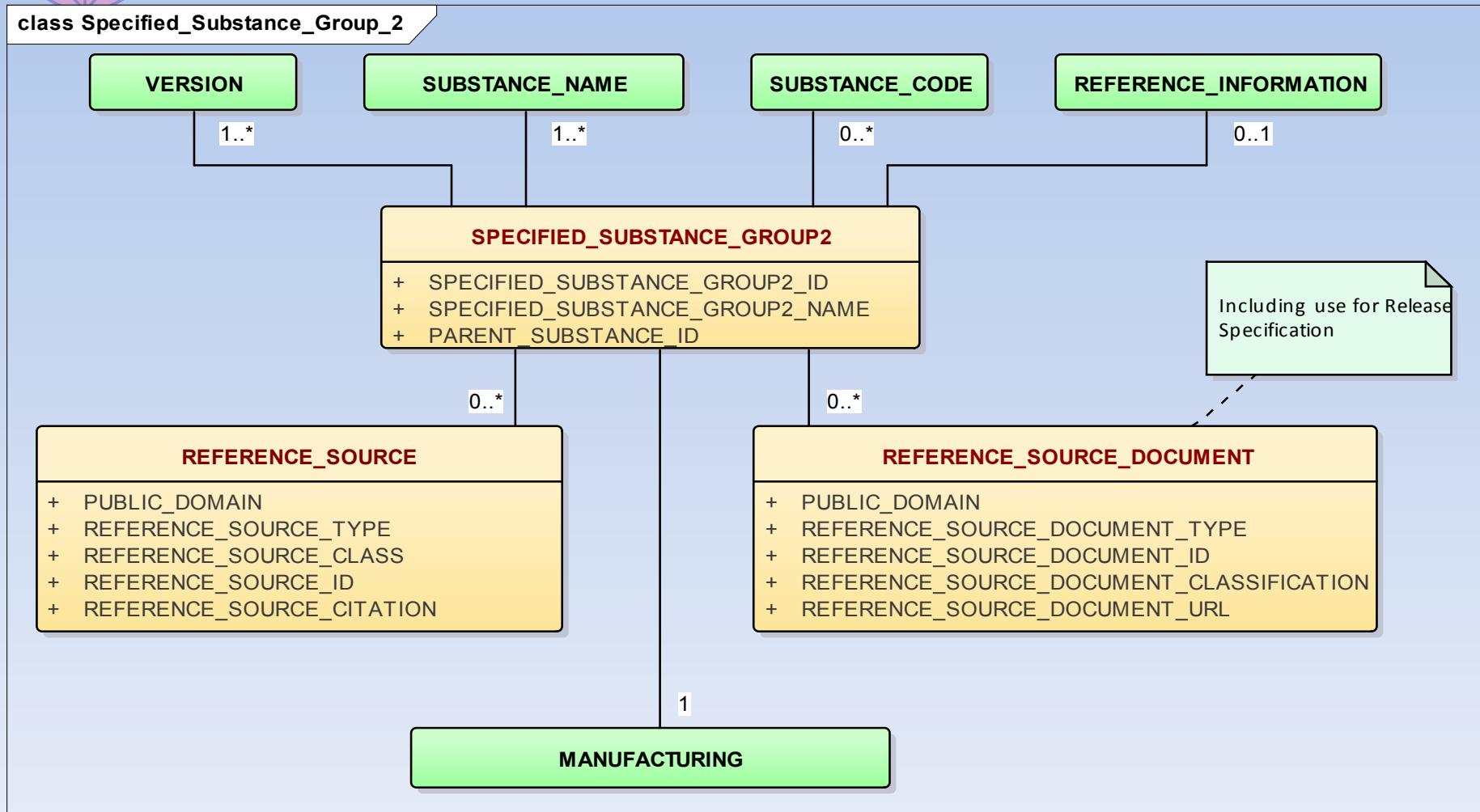
Source material < Part > Whole Blood < Fraction >
Human Plasma for Fractionation

[“Plasma Thawed”] Substance_ID: HUMPLAS6543

- **Source Material <Fraction (Repeat):**
 <Fraction> Cryopoer-Plasma
 Substance_ID: PLAS785643
 <Fraction> Cryoprecipitate
- <Fraction> Cryopoer-Plasma to be further described at the Specified Substance Group 1 Information level:
 <Fraction> Cryopoer-Plasma process flow N
 SSG1_ID: PLASN46245Q
SSG1_Name: Cryopoer-Plasma process flow N
Parent_ID: PLAS785643
- Tied to Manufacturer AA, Site, Country, GPS, Code, Manufacturing Process, Critical version No;
- **SSG2_ID: PLASMrt8564**
SSG2_Name: Cryopoer-Plasma process flow N-Manufacturer AA;
- **Element Group Consituent :**
 Substance_ID: ALBU896754
Substance_Name: Human Albumin, Plasma-derived; This substance will be tied to ManufacturerAA at the SSG2-Level.
- Element Group: Protein
 Characterization in Accordance with the Substance_Type: Protein

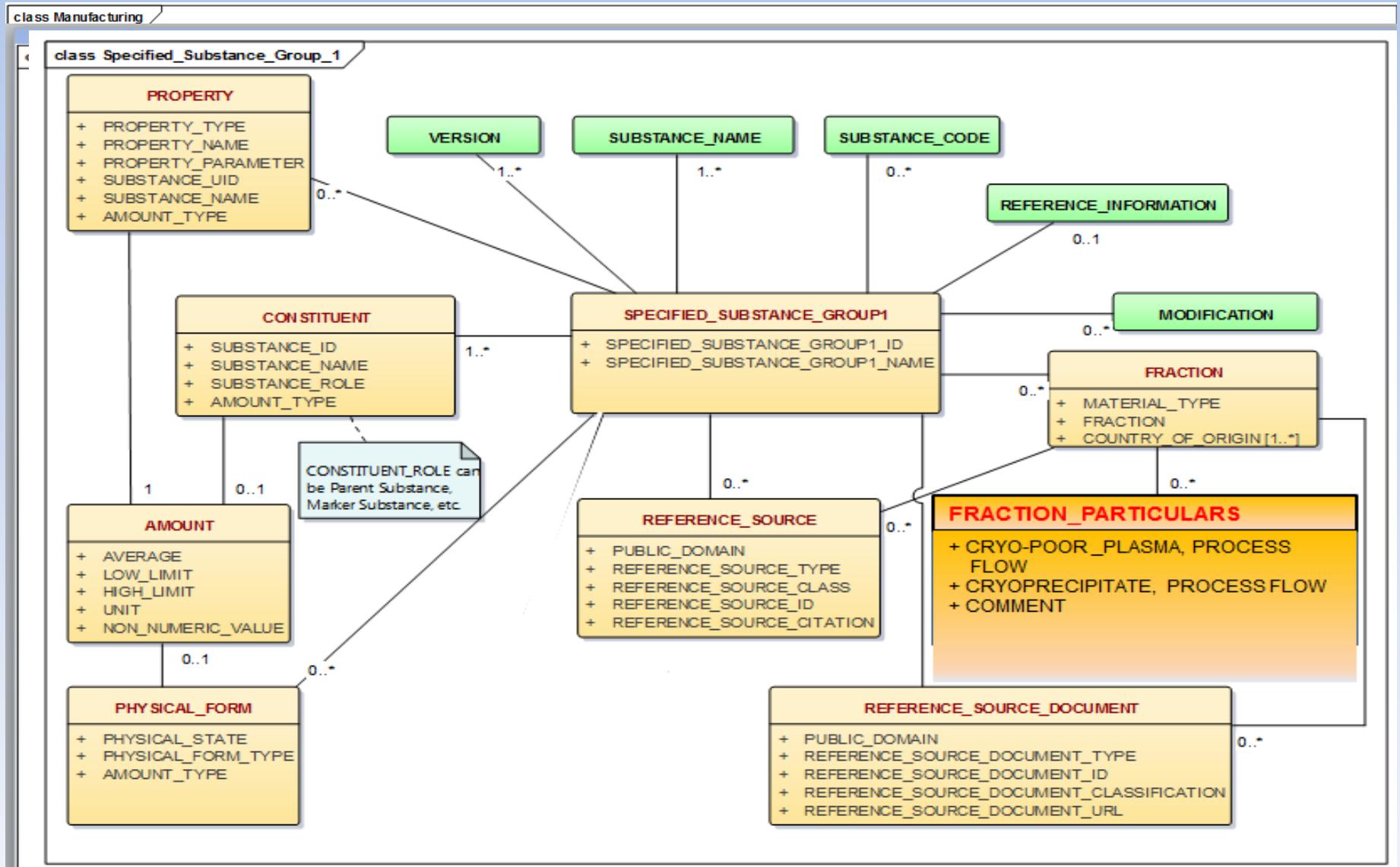


Manufacturing at SSG2-Level Plasma derived Albumin





Manufacturing at SSG2-Level Plasma derived Albumin Extended Model



Bacterial vaccine; live (attenuated)

Example: BCG Vaccine, freeze-dried

(BCG (Bacillus Calmette Guérin) bacteria seed RIVM derived from seed 1173-P2, RVG 26876)

Active substance: live bacteria derived from a culture of the bacillus of Calmette and Guérin
(Mycobacterium bovis BCG)

Organism_Name: *Mycobacterium bovis*, Calmette and Guérin, derived from 1173-P2

Substance Name:

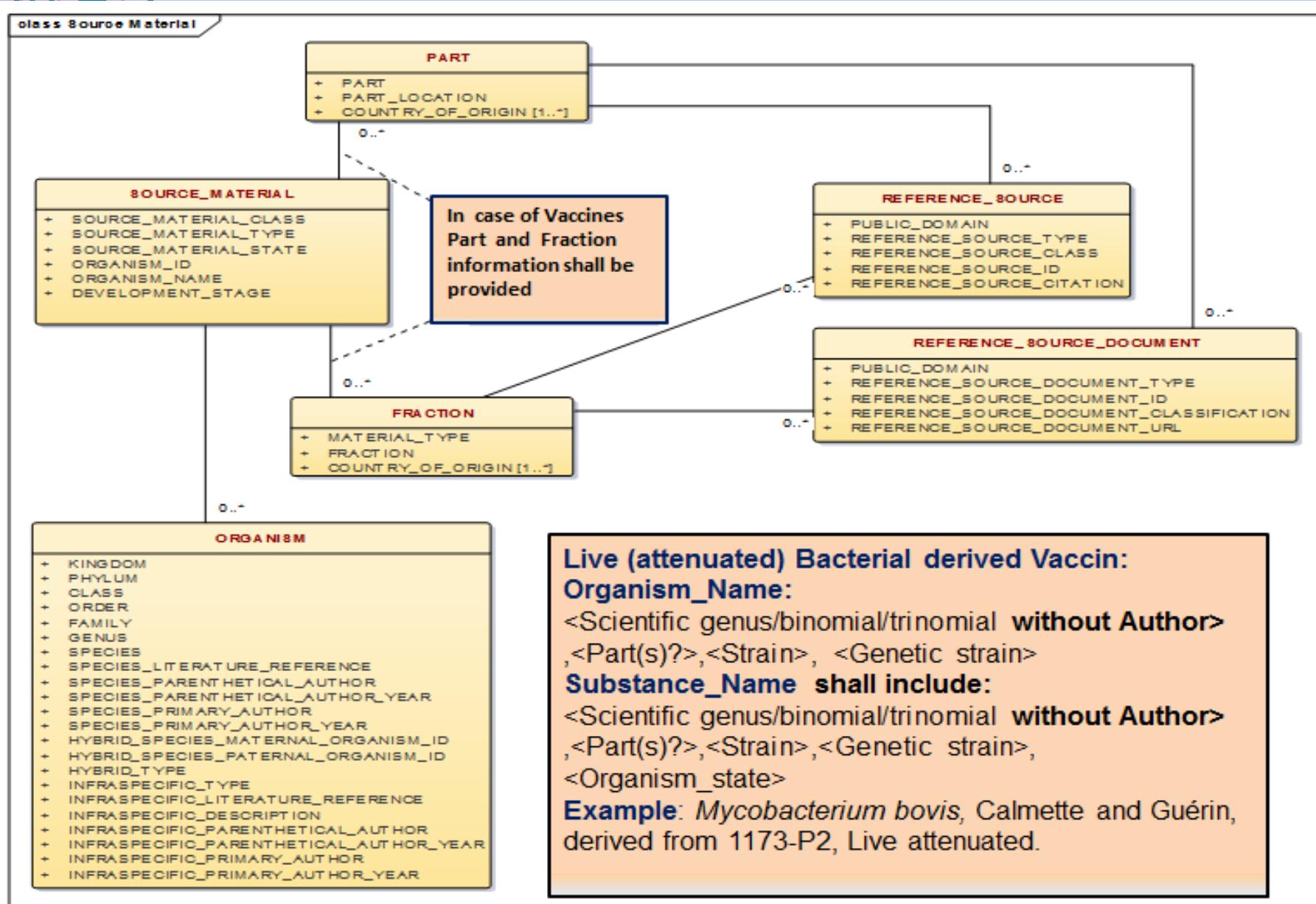
<Scientific genus/binomial/trinomial without Author>, <Part(s)?>, <Strain>, <Genetic strain<Organism_state>

<Organism_state>: Live (attenuated) or Inactivated (data type BL)

Full Taxonomy should be provided: Kindom: Bacteria; Class: Actinobacteria; Order: Actinomycetales; Sub-Order: Cornyebacterineae; Family: Mycobacteriaceae; Genus: *Mycobacterium*

Substance_Name: *Mycobacterium bovis*, Bacillus Calmette and Guérin, derived from 1173-P2, Live Attenuated.

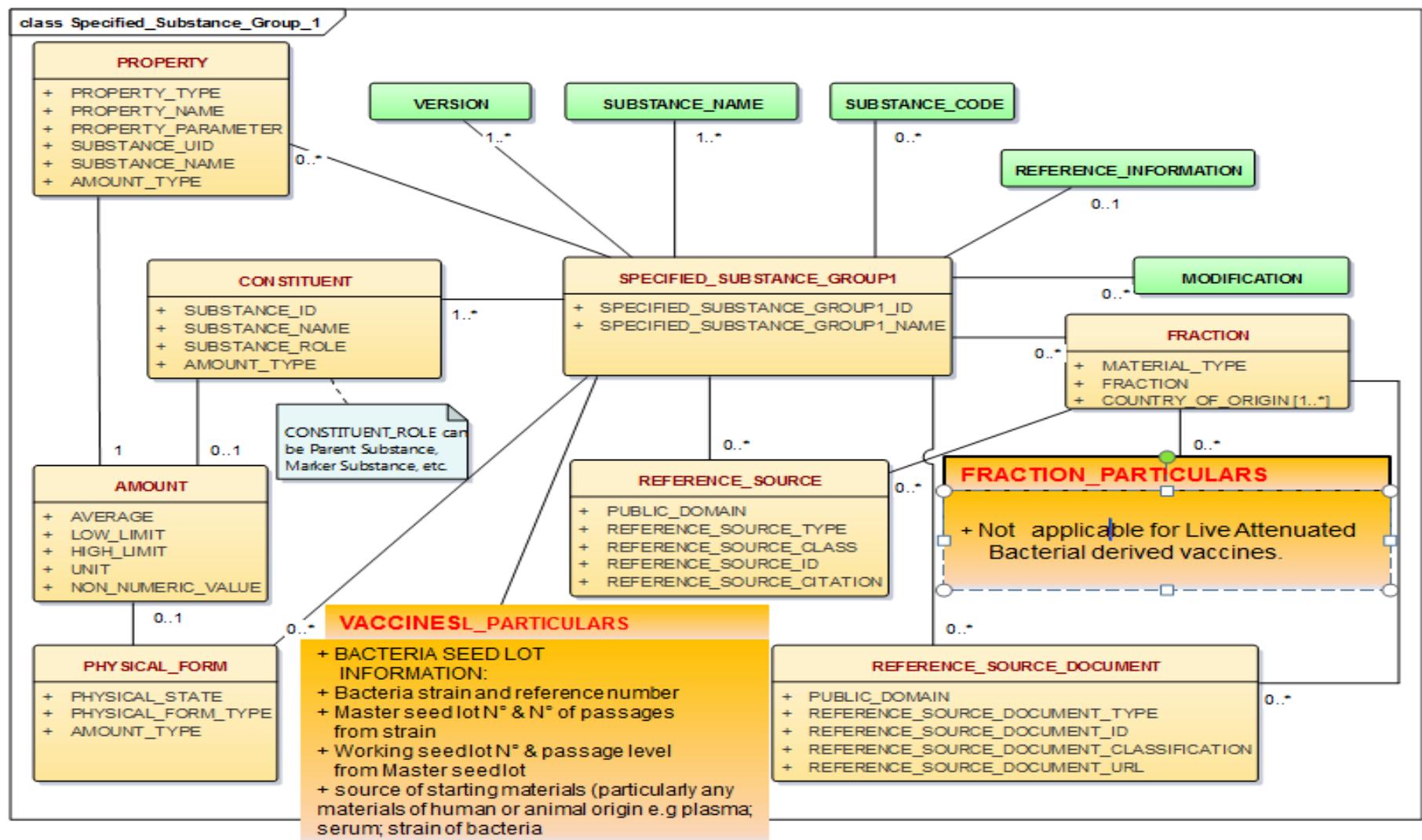
(Dutch Name: Levend verzwakt *Mycobacterium bovis*, BCG, afgeleid van 1173-P2)





VACCINES

SPECIFIED SUBSTANCE GROUP 1 INFORMATION LEVEL



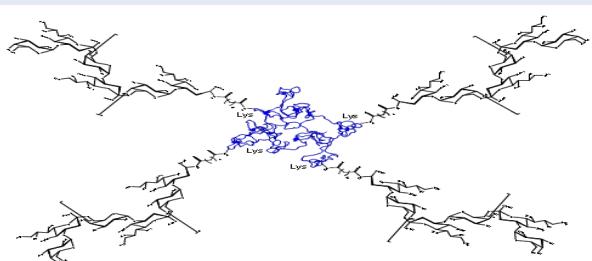


High Level Overview to model Substances in the Vaccine Domain (Meningococcal vaccine)

- 1) Substance_Type Structurally divers; Organism/ Bacteria defining elements
- 2) Fraction: Subunits to be described as Polymers for the sugar units [The Polymer_type and repeating units are depended on the organism by which they are produced]
- 3) Substitution/ Modification: Conjugation to CRM-197 or Tetanus Toxoid, which can be described as a protein
- 4) Agent modification at the Substance or Specified Substance level for the inactivated Vaccines by formaldehyde or an other modification agent
- 5) At the Specified Substance Group 1 extended information of the Organism in the Element Group <Organism Particulars> and Specific Fraction information in the Element Group < Fraction Particulars>

Introduction:

- The Meningococcal ACWY conjugate vaccine (MenACWY) is a tetravalent conjugated meningococcal vaccine that contains sized oligosaccharides from *Neisseria meningitidis* serogroups A, C, W-135, and Y conjugated to CRM197 protein (a non-toxic mutant of *Corynebacterium diphtheriae* toxin, termed Cross-Reacting Material 197).
- CRM197 is the carrier protein resulting from fermentation and purification of *C. diphtheriae* C7 (β 197) M8 strain.
CRM197 is a non-toxic, immunologically cross-reactive mutant protein of diphtheria toxin which is produced as a 58 kDa protein. CRM197 contains a Glycine (Gly) to Glutamine (Glu) substitution at position 52 in the catalytic domain. This change drastically reduces the toxicity of the protein while retaining the majority of the toxin's structure and immunochemistry.
- Polysaccharides utilized alone as antigens usually fail to generate adequate immunological responses, especially in younger age groups. CRM197 is being produced for use as a protein carrier for activated oligosaccharide in order to improve a T-cell dependent antibody.
- In the manufacture of MenACWY vaccine, CRM197 is a process intermediate, which is then conjugated to MenA, MenC, MenW and MenY activated and sized oligosaccharides to give the drug substances: MenA-CRM, MenC-CRM, MenW-CRM, and MenY-CRM.



(Diagram of the Structure of MenW-CRM Conjugate)

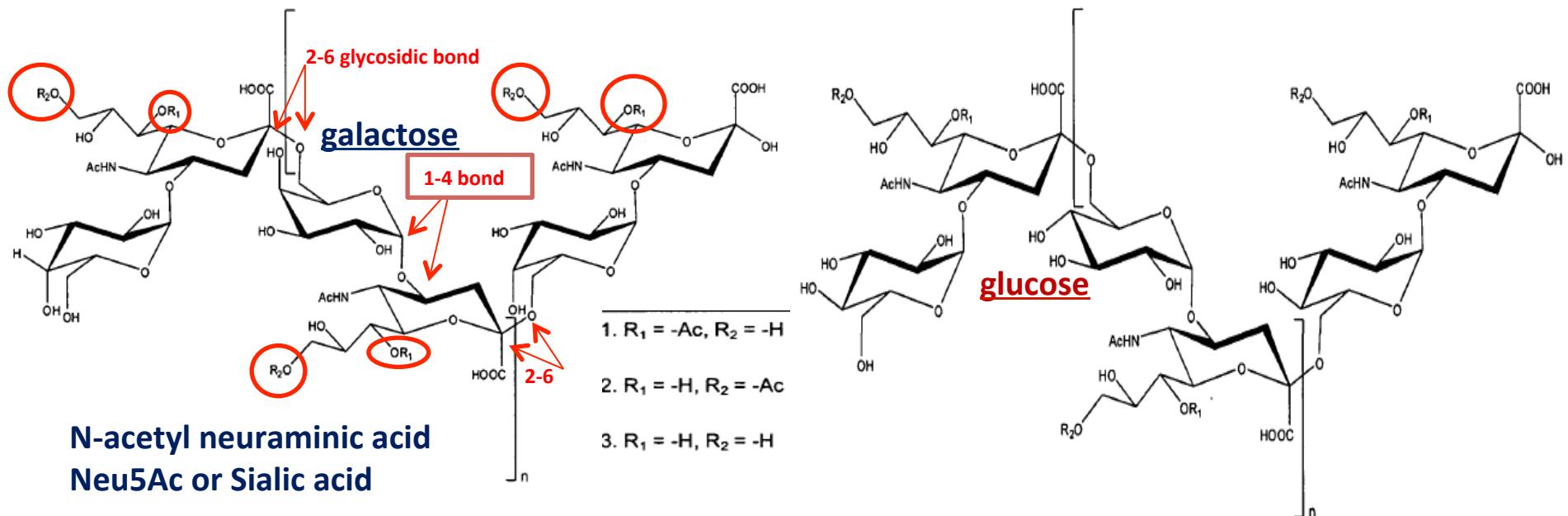
Biopolymers, Structural representation, Glycosidic Bond Structures of MenW and MenY Polysaccharide of Meningococcal ACWY conjugate vaccine (MenACWY)

The structure of MenW and MenY polysaccharide is a heteropolymer whose repeating unit is composed of N-acetylneuraminic acid and galactose and of N-acetyl neuraminic acid and glucose respectively.

MenW: The partly O-acetylated structure is - 6)- α -D-Gal(1 \rightarrow 4)- α -D-NeupNAc-(2 \rightarrow).

MenY: The partly O-acetylated structure is: -6)- α -D-Glc(1 \rightarrow 4)- α -D-Neup5NAc-(2 \rightarrow).

For both structures a portion of the 7- or 9-hydroxyl groups are O-acetylated.



[Men W, SRU: —»4)-D-Neup5NAc(7/9 OAc)- α -(2 \rightarrow 6) -D-Gal- α -(1 \rightarrow ,].

[MenY, SRU: —»4)-D-Neup5NAc(7/9 OAc)- α -(2 \rightarrow 6) -D-Glc- α -(1 \rightarrow ,].



Thank You

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