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Defining Advanced Therapies (ATMP)

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CBG-MEB

Washington, October 2017

The presentation represents personal views only, meant to initiate further discussion. Does not necessarily reflect current or future view of MEB, EMA, CHMP, or any other regulatory body

Outline

- Regulatory basis and definitions
- Description of Cell-based products: IDMP ISO-11238 Standard (Structurally Diverse Substances)
- Data elements for unique identification of cell products
- Example 1: Tissue-engineered medicinal product: 3 chondrocytes products
- Endeavour to capture Chondrocytes product in database model
- Example 2: Cell-based medicinal product: Active cellular immunotherapy product

Advanced Therapy Medicinal Products

- **Gene therapy products**
  - *contains recombinant nucleic acid …. with a view to regulating, repairing, replacing, adding or deleting a genetic sequence*
- **Cell Based Medicinal Products**
  - *…..cells or tissues subject to **substantial manipulation…***
  - *Or indicated for **heterologous use***

Somatic cell therapy products:

- ***pharmacological, immunological or metabolic action ….***

Tissue Engineered products:

- used with a view to, **regenerating, repairing or replacing a human tissue**

- **Combination products**
  - ATMP containing medical device

Advance Therapy Medicinal Products:
1) Directive 2009/120/EC: Part IV

Somatic cell therapy medicinal product:
a biological medicinal product which has the following characteristics:

a) Contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are *not* intended to be used for the same essential function(s) in the recipient and the donor;

b) Is presented as having properties for, or is used in or administered to human being with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

- The active substance shall be composed of the engineered cells and/or tissues
- Additional substances (e.g. scaffolds, matrices, etc) which are combined with manipulated cells of which they form an integral part shall be considered as starting materials, even if not of biological origin.

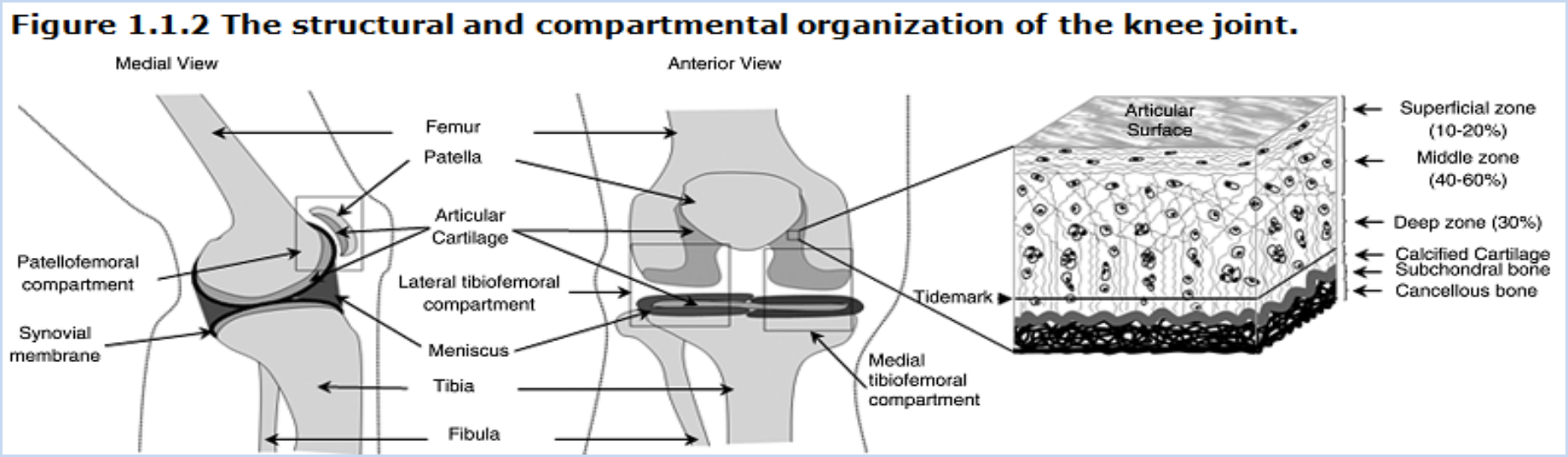
HUMAN CELL-BASED MEDICINAL PRODUCTS

Cells are complex biological systems

- Cells respond to (subtle) external triggers.
- Cells are heterogenic (intra- & inter-batch)
- Quality parameters determined by:
  - Origin & history of starting material
  - Each manufacturing step
    - Dissociation procedure of cells (mechanical/enzymatic/transport conditions)
    - Culture conditions (cytokines, media components, cell-cell contact, etc.)
    - Cell doubling level (de-differentiation)
- QC tests only limited part of Quality parameters

Knee Cartilage damage
Transplanted Autologous Chondrocytes

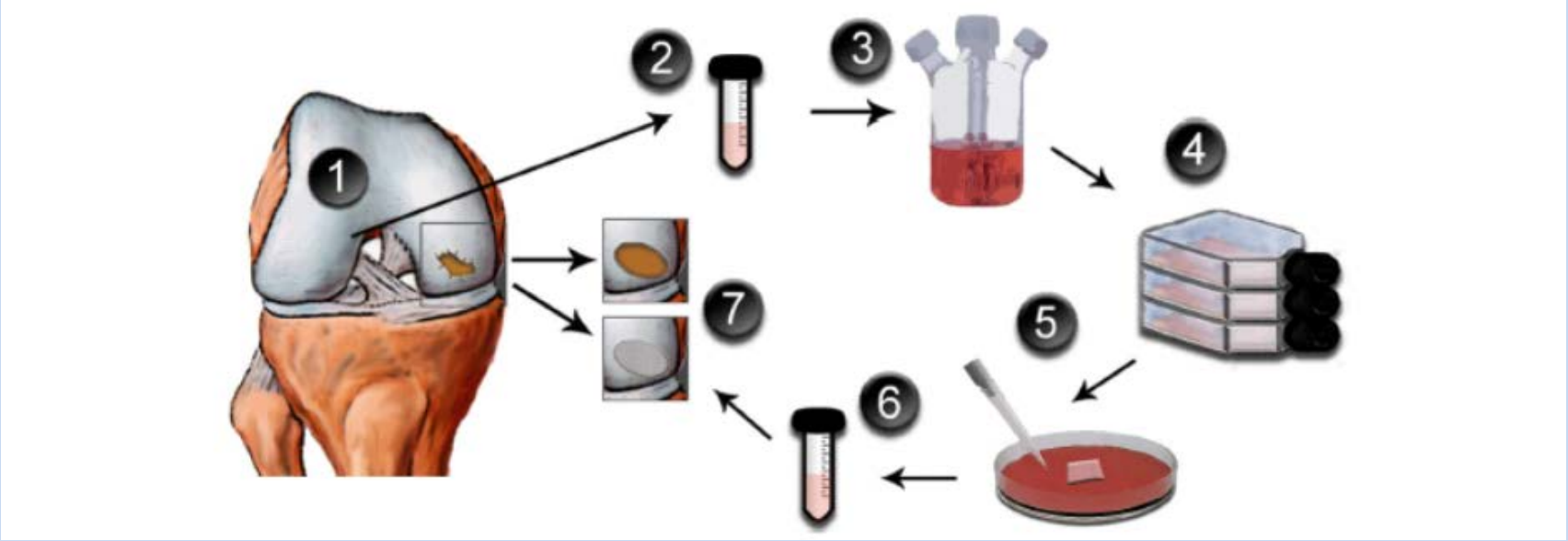
- **Autologous Chondrocytes Implantation (ACI):**
  - Autologous chondrocytes extra-corporally multiplied by cultivation.
  - Cultured chondrocytes transplanted into (larger) lesions.
  - Implanted chondrocytes kept in situ by a cover, (periosteal flap / collagen membrane) to prevent cartilage hypertrophy. *(ChondroCelect)*
- **Autologous Chondrocytes on Matrix:**
  - Autologous chondrocytes multiplied and seeded on collagen /hyaluronan based scaffold prior to transplantation.
  - Facilitate transplantation & more equalized distribution of cells. *(Hyalograft & MACI)*



Advanced Therapy Medicinal Product:
Manufacturing Process, Identification, Characterization

The manufacturing process of the Active Substance consists of the following steps:

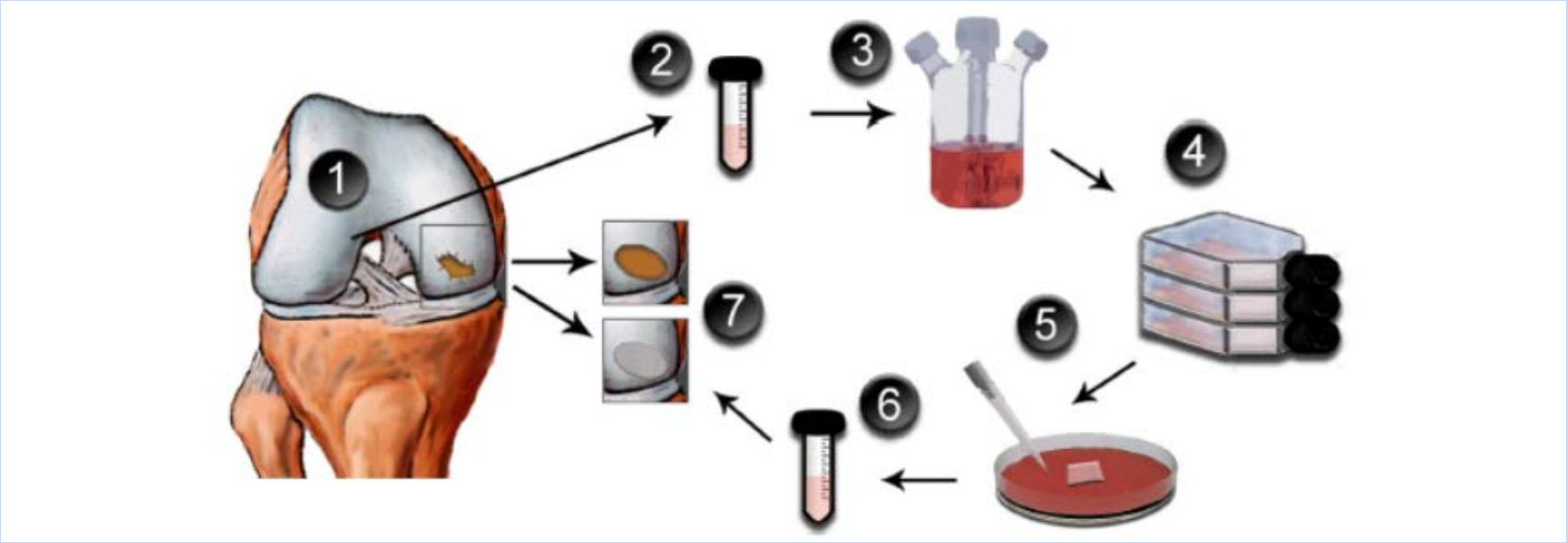
- **Biopsy digestion (mechanical/collagenase)**
- **Expansion culture (growth factors, cell doubling level)**
- **Cell culture harvest (trypsine) and wash**
- **Pooled cell suspension seeded onto membrane / scaffold**
- **Incubation period on membrane**



Advanced Therapy Medicinal Product:
Manufacturing Process, Identification, Characterization

Critical Steps that impact on Substance:

- Total Cell count and viability after biopsy processing/collagenase treatment
- Cell yield, viability, days in culture
- Adhesion of cells to membrane
- Critical quality specifications measured during:
  - expansion phase
  - culture on scaffold



Chondrocyte Products:
Potency, Identification, Characterization

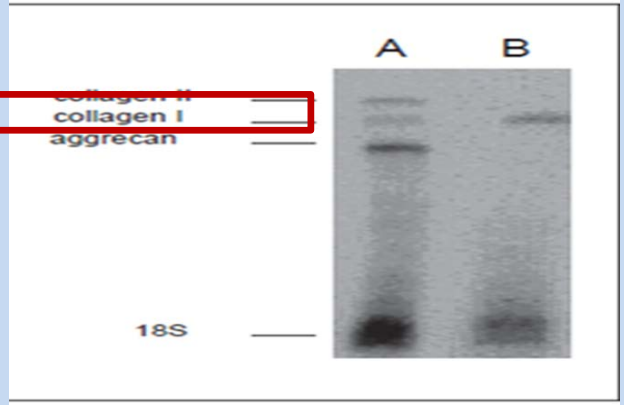
Potency

- ChondroCelect: Cellular expression patterns of genes relevant for cartilage and chondrocyte biology
- MACI: Aggrecan mRNA expression by real-time PCR.
- Hyalograft C: Measurement of COMP protein; Cartilage Oligomeric Matrix Protein (COMP): non-collagenous glycoprotein of articular extracellular matrix.

Identity

- MACI: Quantitative RT-PCR assay expression ratio of:
  HAPLN1 (chondrocytes) **:** MFAP5 (synoviocytes/fibroblasts)
- Hyalograft C: RT-PCR assay of Aggrecan mRNA Expression in Chondrocytes vs. Fibroblast cells

Cellular Impurities: Synoviocytes/fibroblasts



Active substance definition Chondrocyte products

ChondroCelect, Hyalocraft C and MACI

ChondroCelect: Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins.

Hyalograft C: characterized viable autologous chondrocytes expanded *in vitro* seeded and cultured on a *hyaluronan based scaffold.*

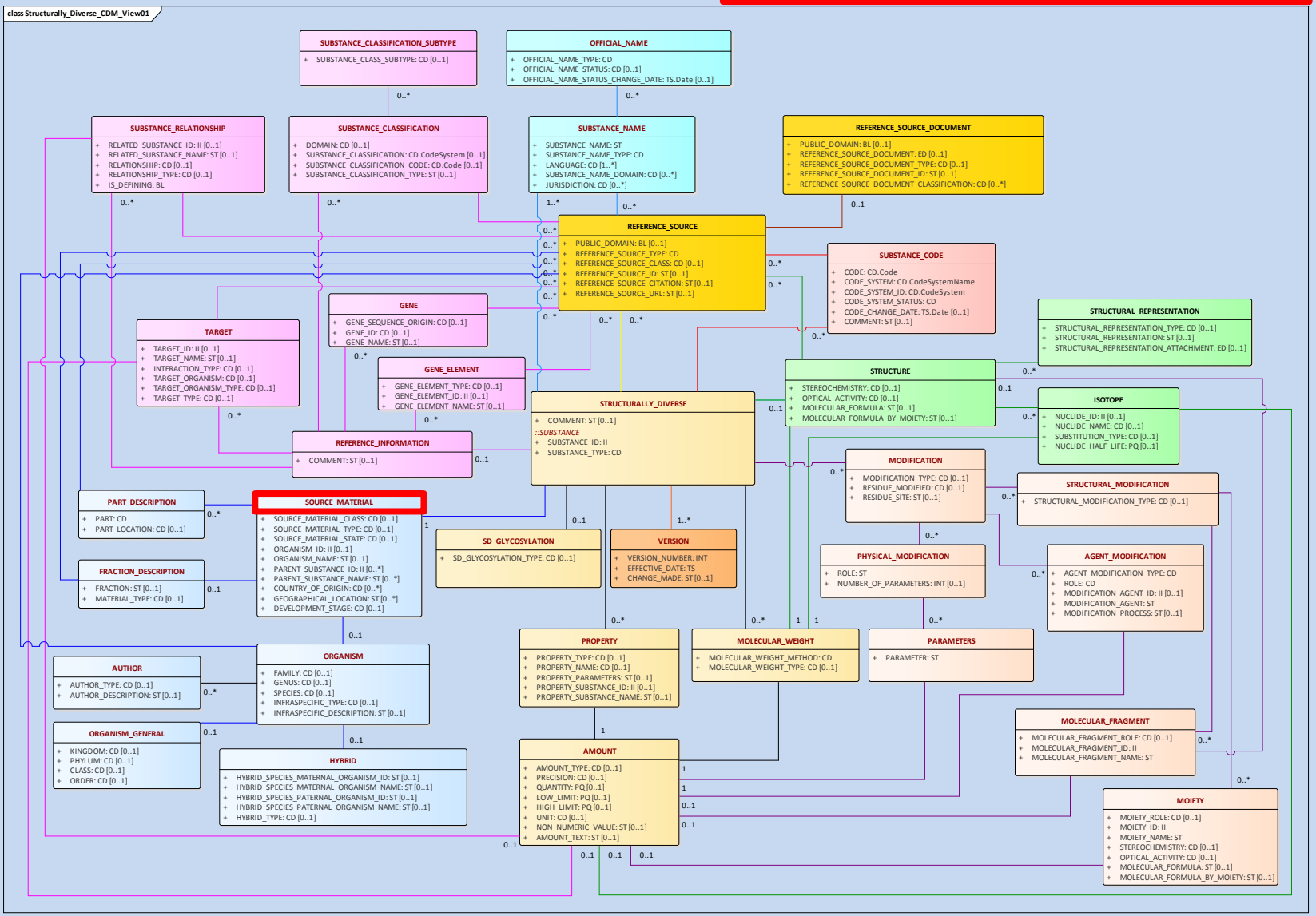
- **Autologous chondrocytes (from cartilage biopsy) expanded on monolayer**
- **Scaffold: non-woven pad composed of hyaluronic acid benzyl ester polymer; class III Medical Device (CE marked)**

MACI: human autologous cartilage-derived cultured chondrocytes combined with a CE marked purified, resorbable porcine-derived, collagen type I/III membrane

- **Cultured autologous chondrocytes**
- **Membrane: purified resorbable porcine peritonium collagen scaffold held in place with fibrin sealant. Class III Medical Device (CE marked)**

GInAS

Autologous_Cultured chondrocytes
CHON12345 (Artificial ID)



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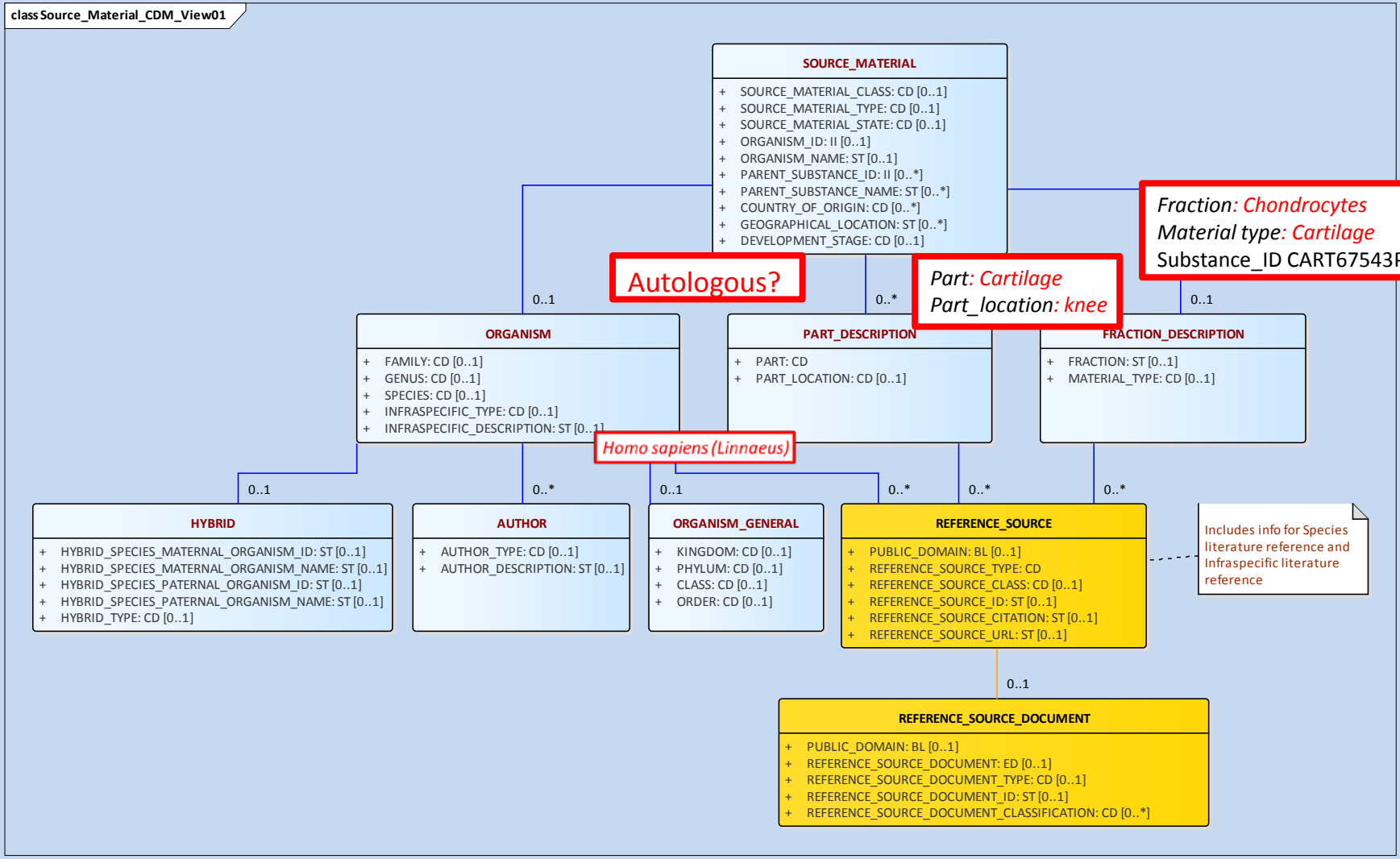

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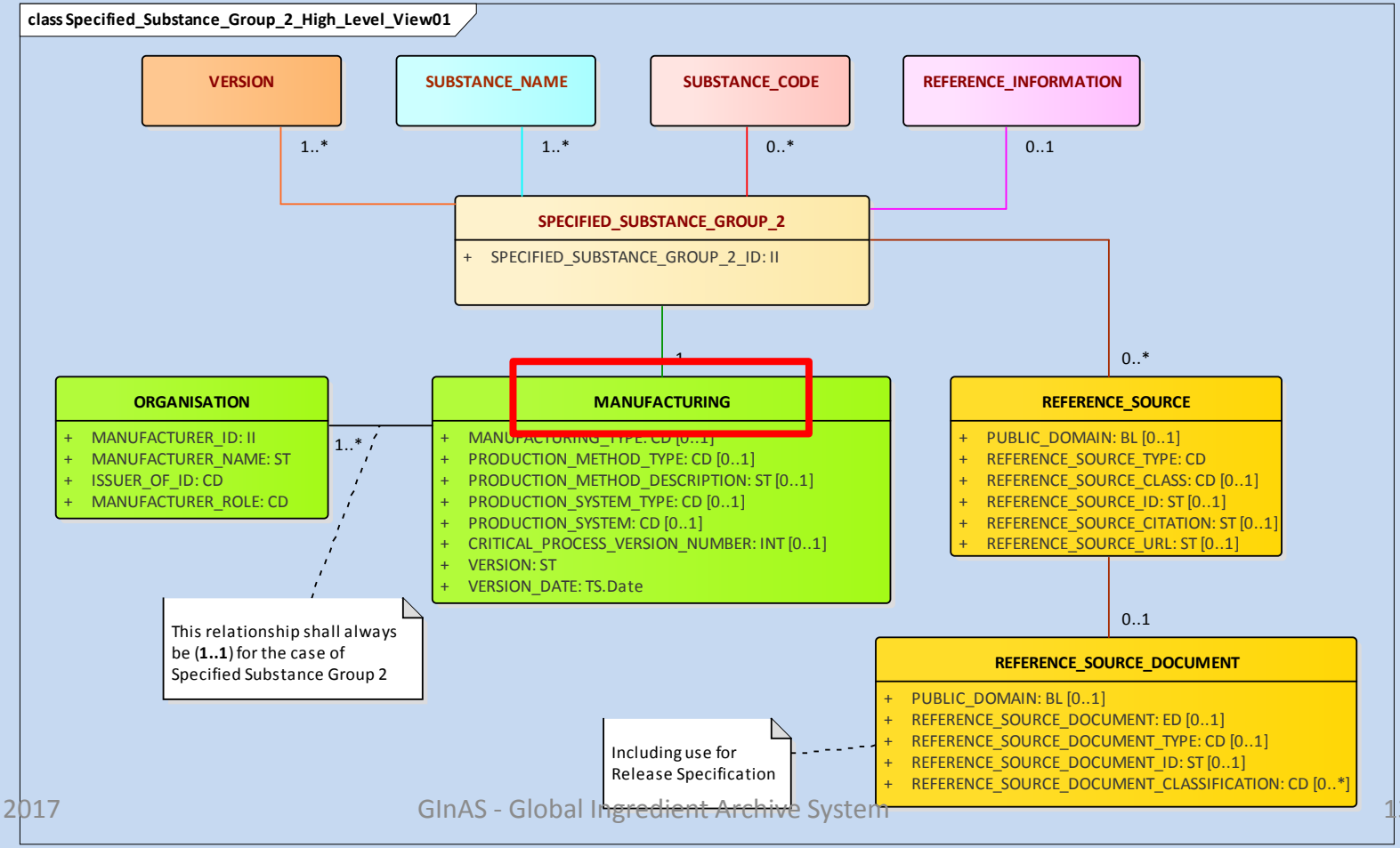

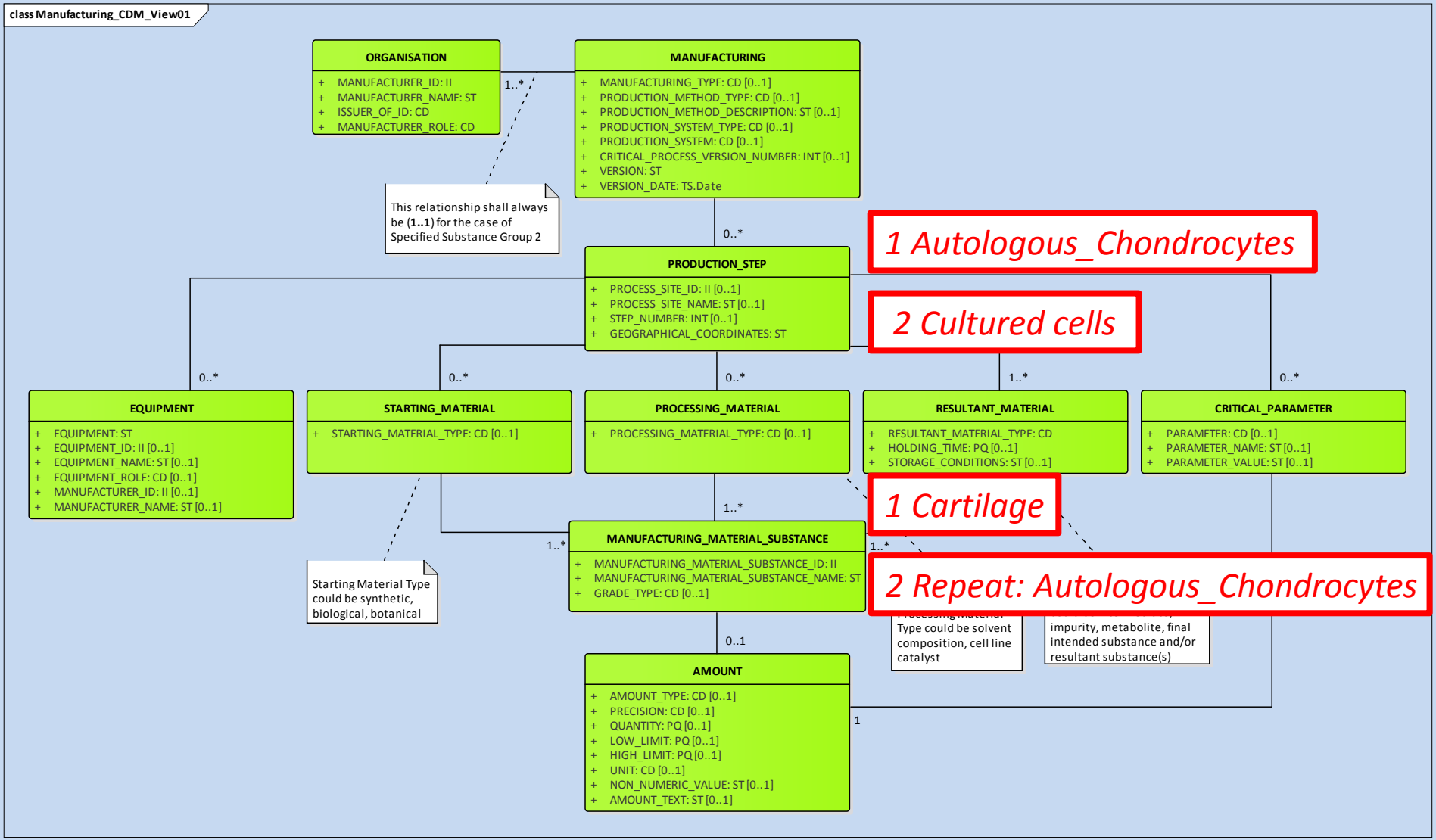
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2 Cultured cells
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impurity, metabolite, final intended substance and/or resultant substance(s)
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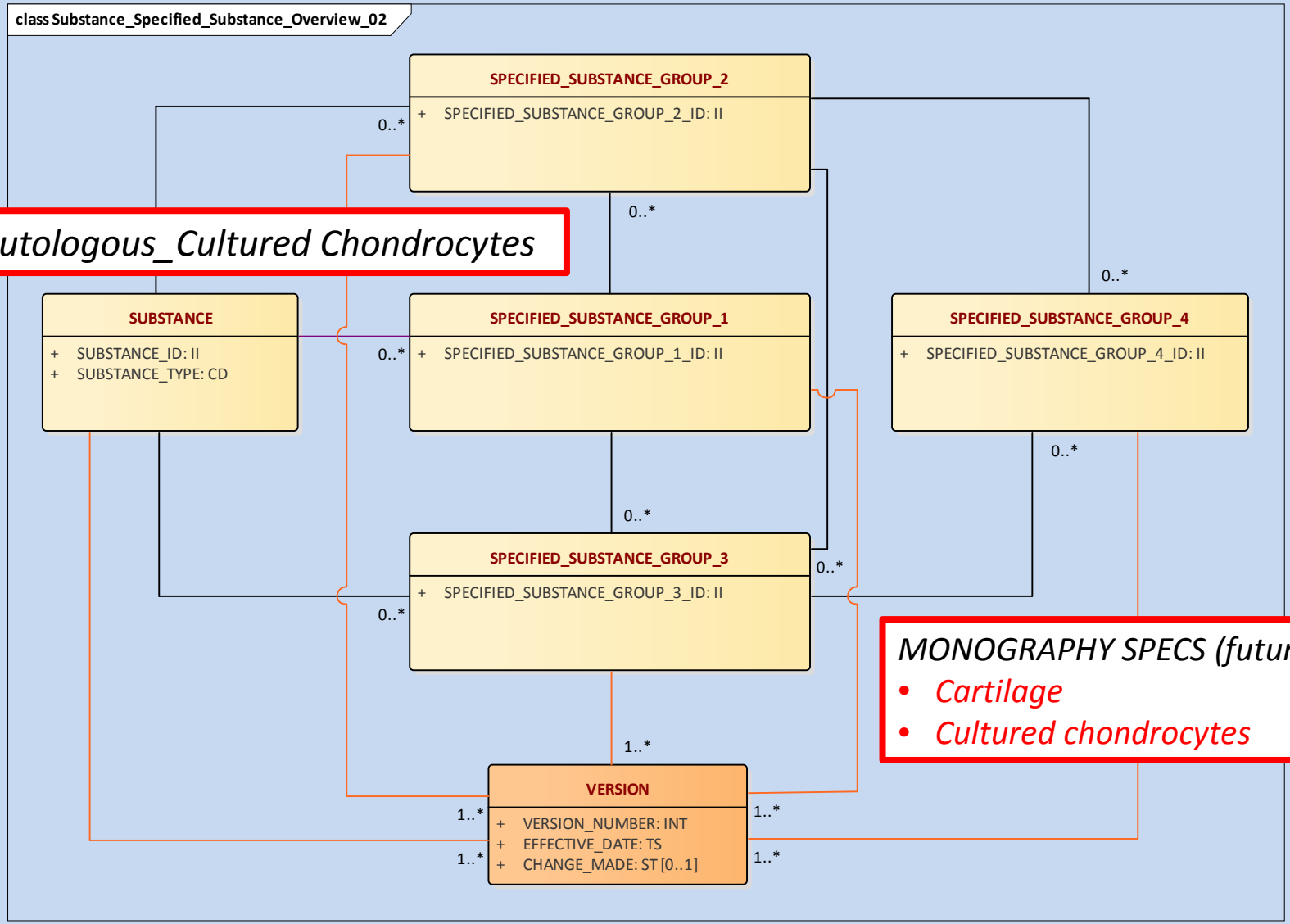
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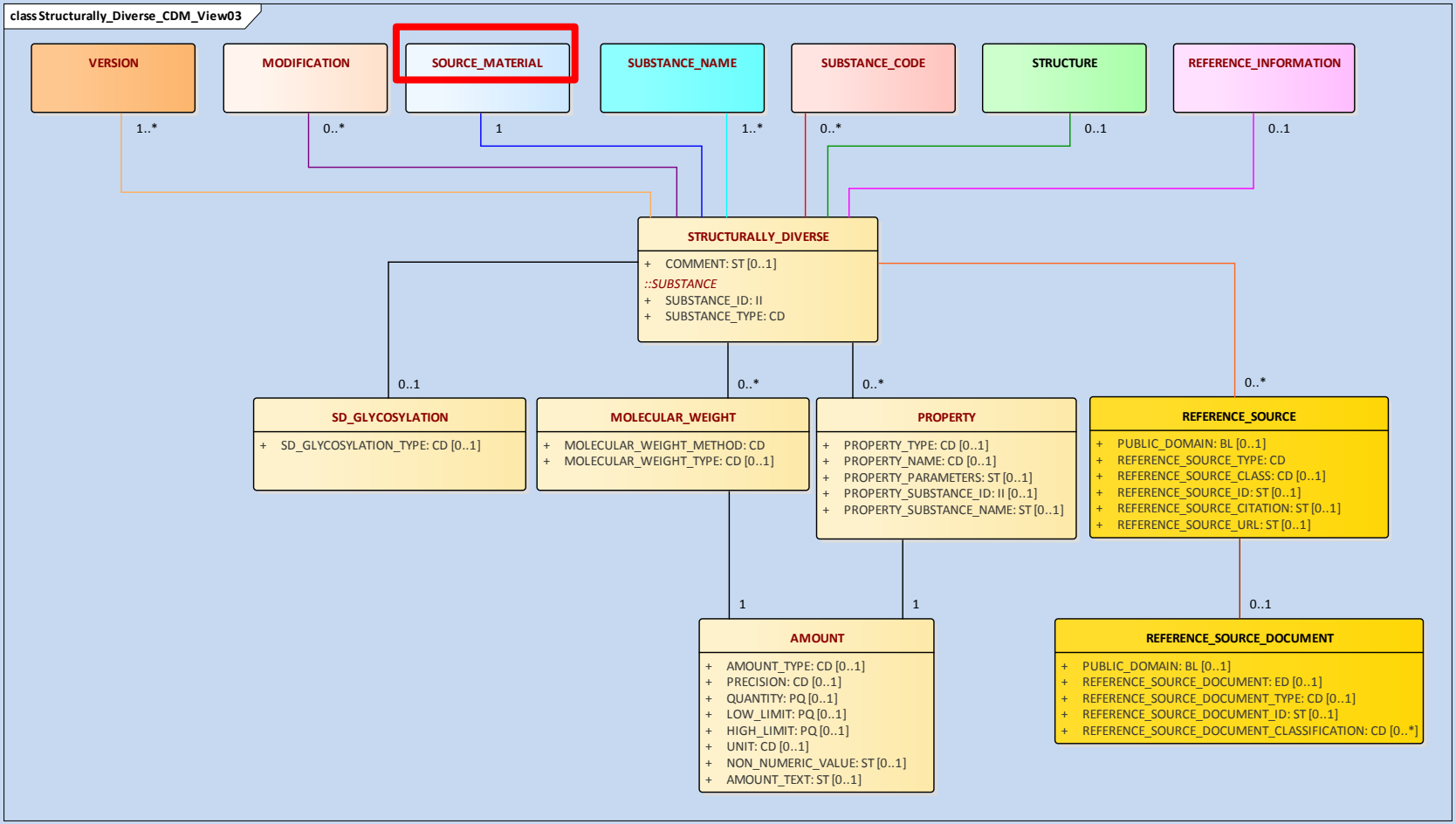
MONOGRAPHY SPECS (future)
• Cartilage
• Cultured chondrocytes

Autologous_Cultured chondrocytes on Matrix

CHONM12345 (Artificial ID)



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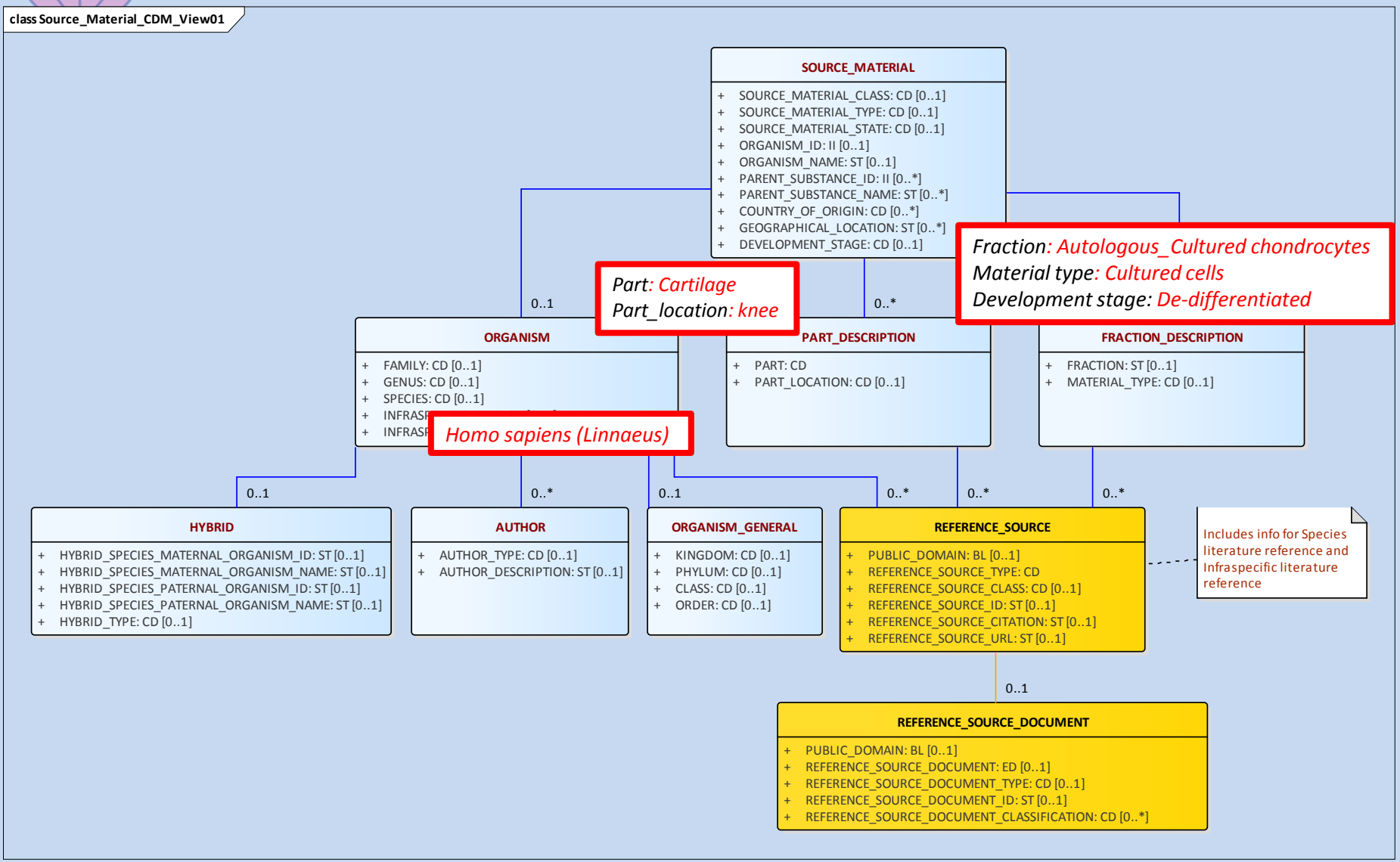

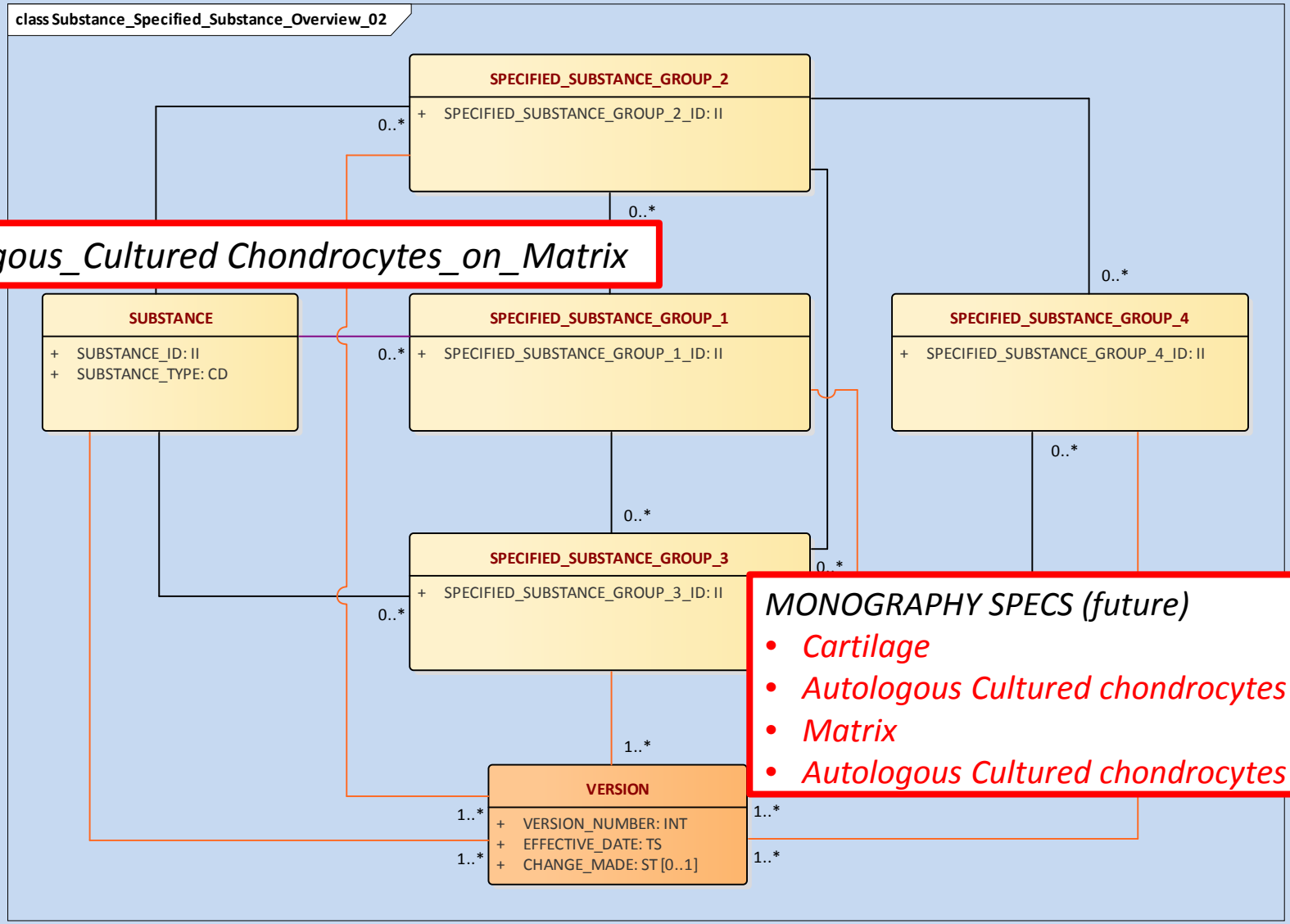

Autologous_Cultured Chondrocytes_on_Matrix

MONOGRAPHY SPECS (future)

- *Cartilage*
- *Autologous Cultured chondrocytes*
- *Matrix*
- *Autologous Cultured chondrocytes on matrix*

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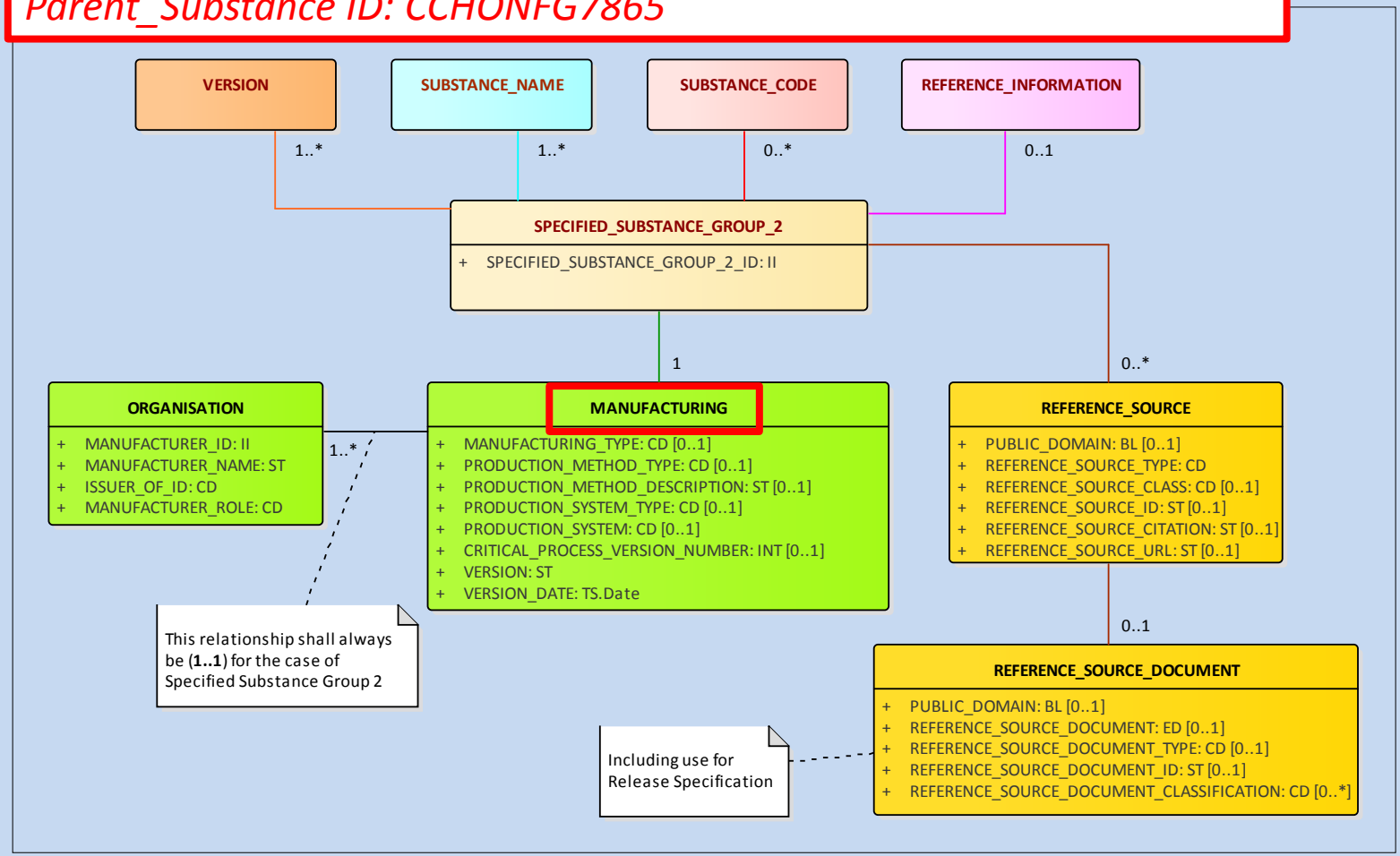

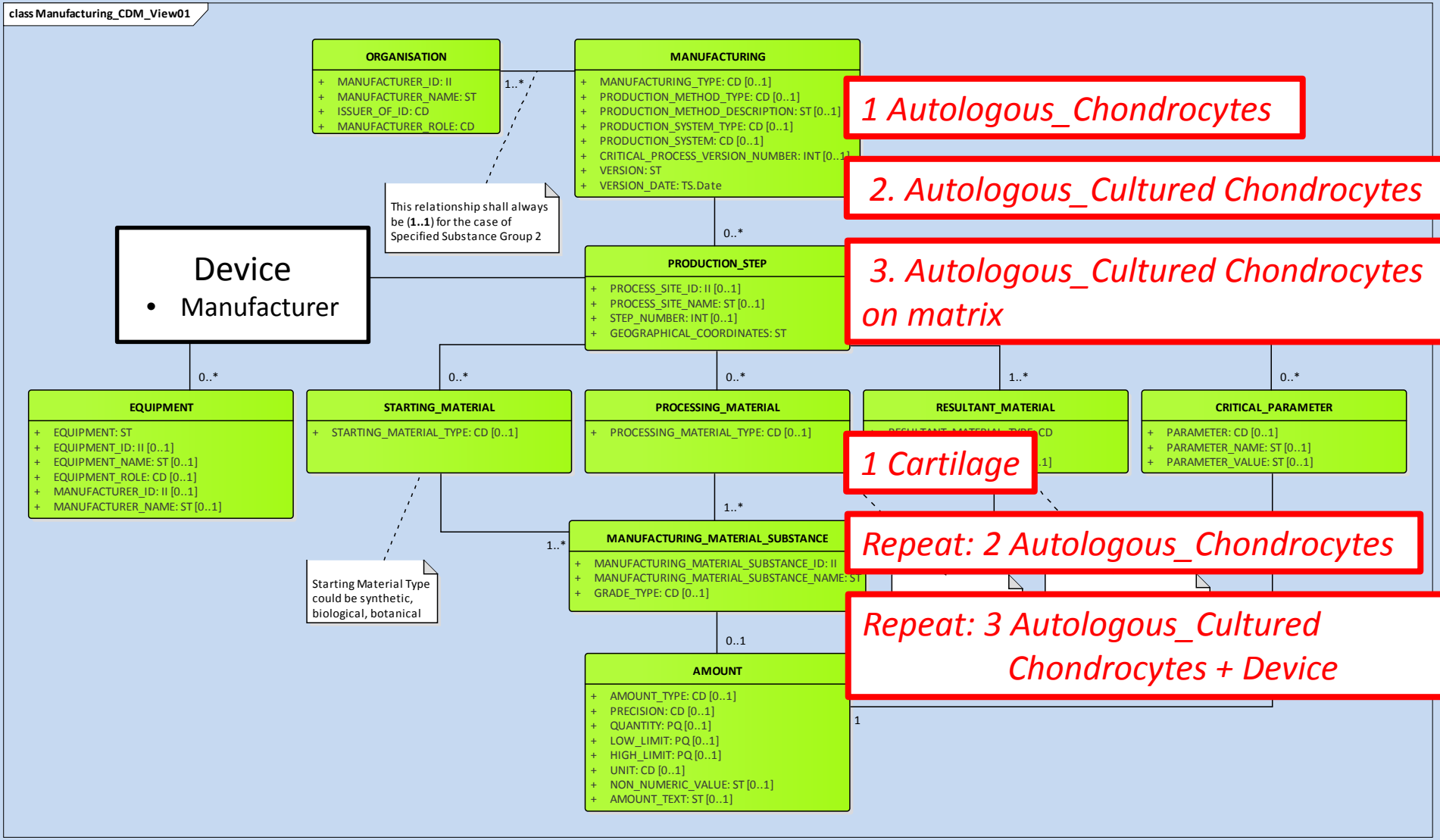
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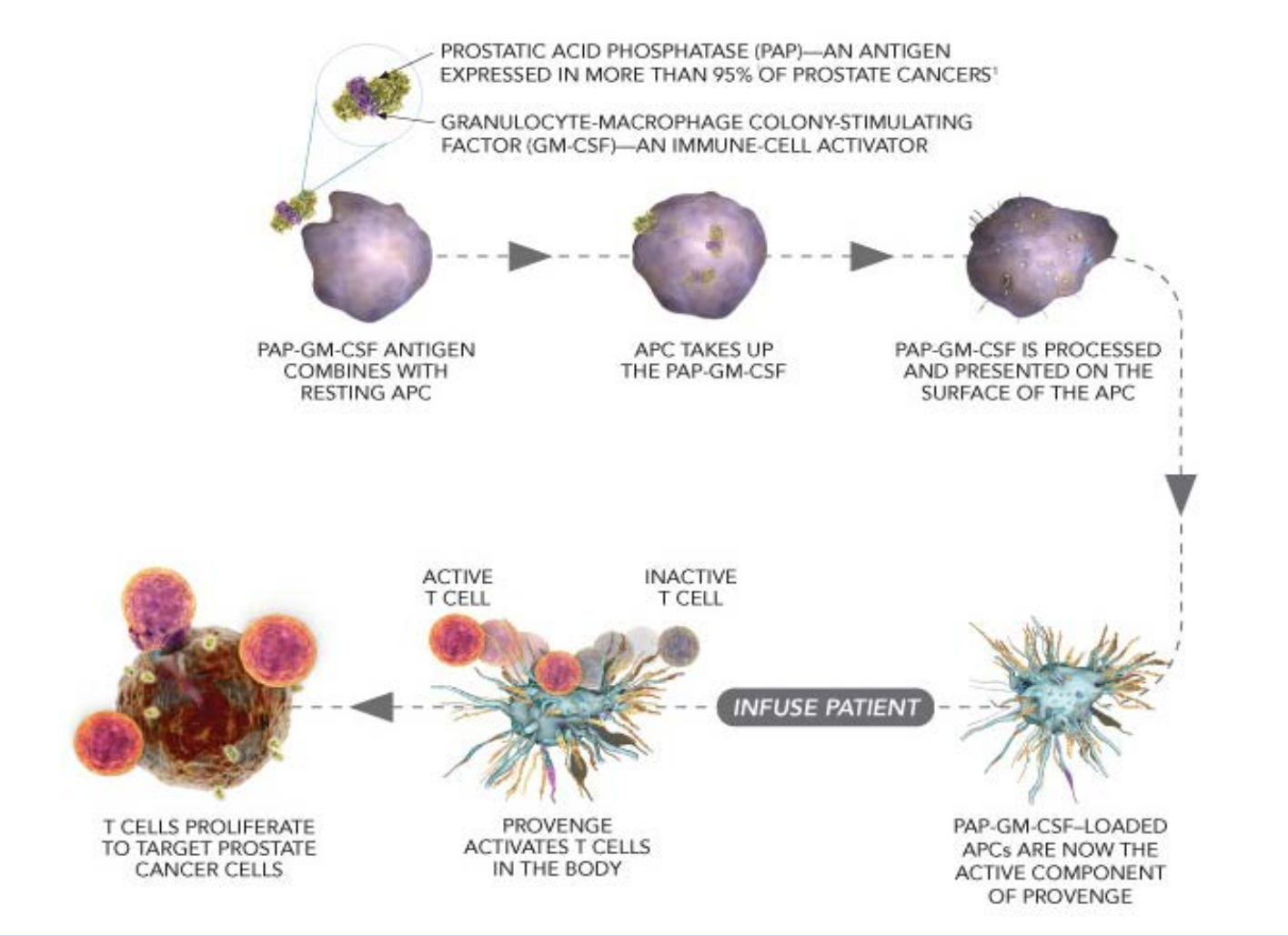
1 Autologous_Chondrocytes
2. Autologous_Cultured Chondrocytes
3. Autologous_Cultured Chondrocytes on matrix
1 Cartilage
Repeat: 2 Autologous_Chondrocytes
Repeat: 3 Autologous_Cultured Chondrocytes + Device

Advanced Therapy Medicinal Products

Cellular immunotherapy product: Provenge

INN: Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (sipuleucel-T)



Cellular immunotherapy product: Provenge
Active substance

- Active substance (Sipuleucel-T): autologous **PBMCs** activated ex vivo with recombinant fusion protein PA2024

- **PBMCs** (periferal blood mononuclear cells) include:
  - ➔ T cells, B cells, Natural Killer (NK) cells and
  - ➔ APCs (incl. monocytes & dendritic cells (DCs))

- Activated APCs: CD54+ cell population
- DCs (most effective APCs) represent a small percentage
- CD54+ cells: potency measure of Provenge

Cellular immunotherapy product: Provenge

Fusion Protein

- Recombinant fusion glycoprotein is starting material
- Prostatic acid phosphatase (354 AA) linked to GM-CSF (127 AA) by glycine-serine dipeptide.
- Potential glycosylation sites: 5 N-sites & 1 O site.
- Molecular mass about 132 kDa (exists as dimer).

Figure 1: Schematic of Precursor Form of PA2024 Fusion Protein

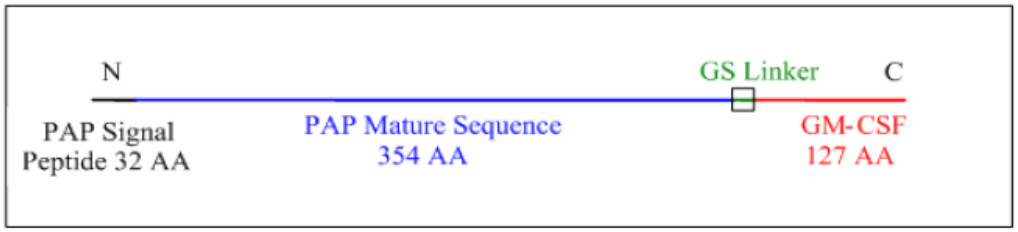


Figure 2: PA2024 Amino Acid Sequence (Precursor Protein)

```
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 51 DTFPTDPIKE SSWPQGFGQL TQLGMEQHYE LGEYIRKRYR KFLNESYKHE 100
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501 FLLVIPFDCW EPVQE                                     515
```
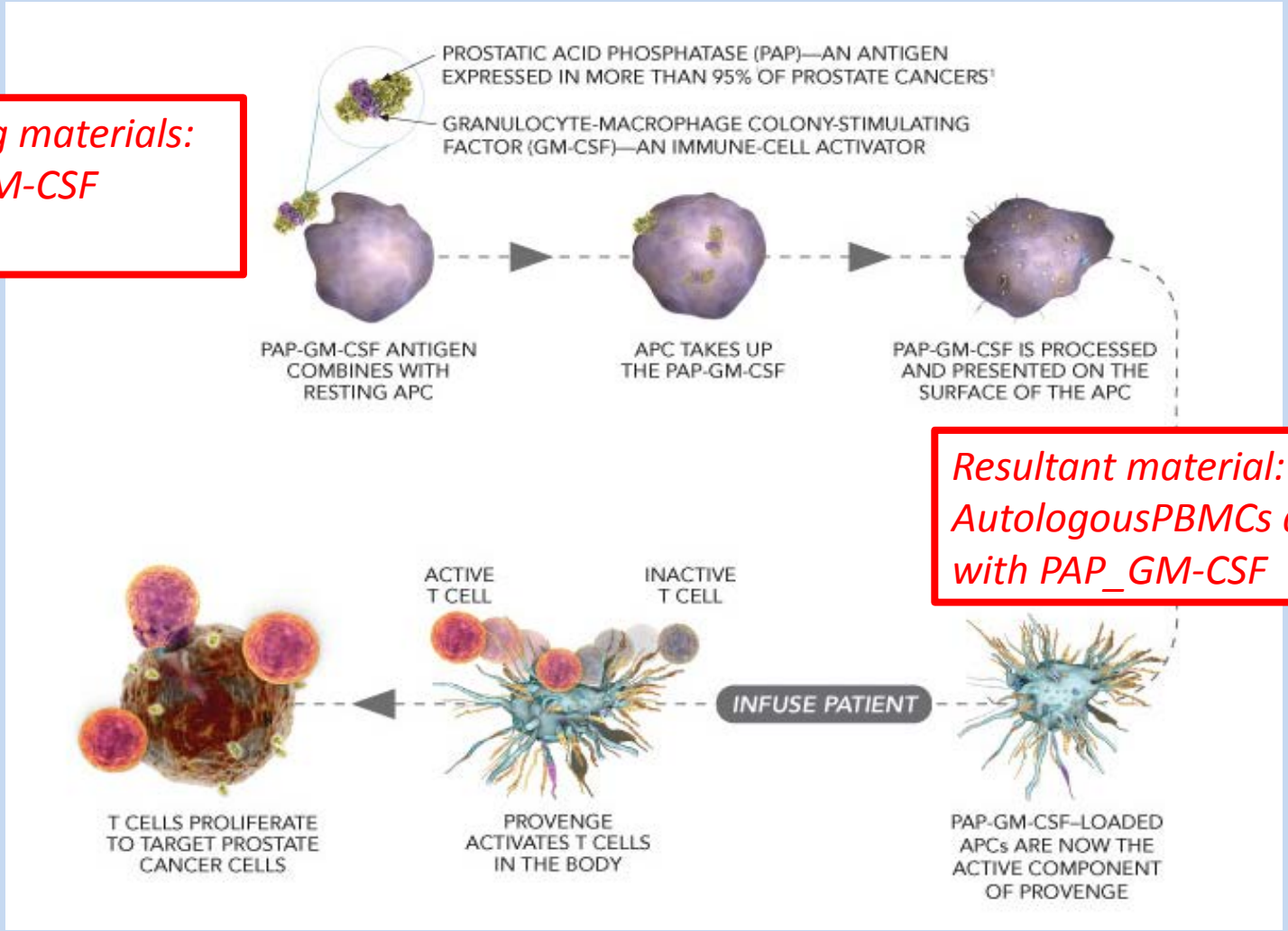

∇—Potential glycosylation sites
Cyan—PAP signal peptide, 32 amino acids
Dark blue—PAP mature protein, 354 amino acids
Orange—Amino acid substitutions
Green—Glycine/serine dipeptide synthetic linker
Pink—GM-CSF mature protein127 amino acids

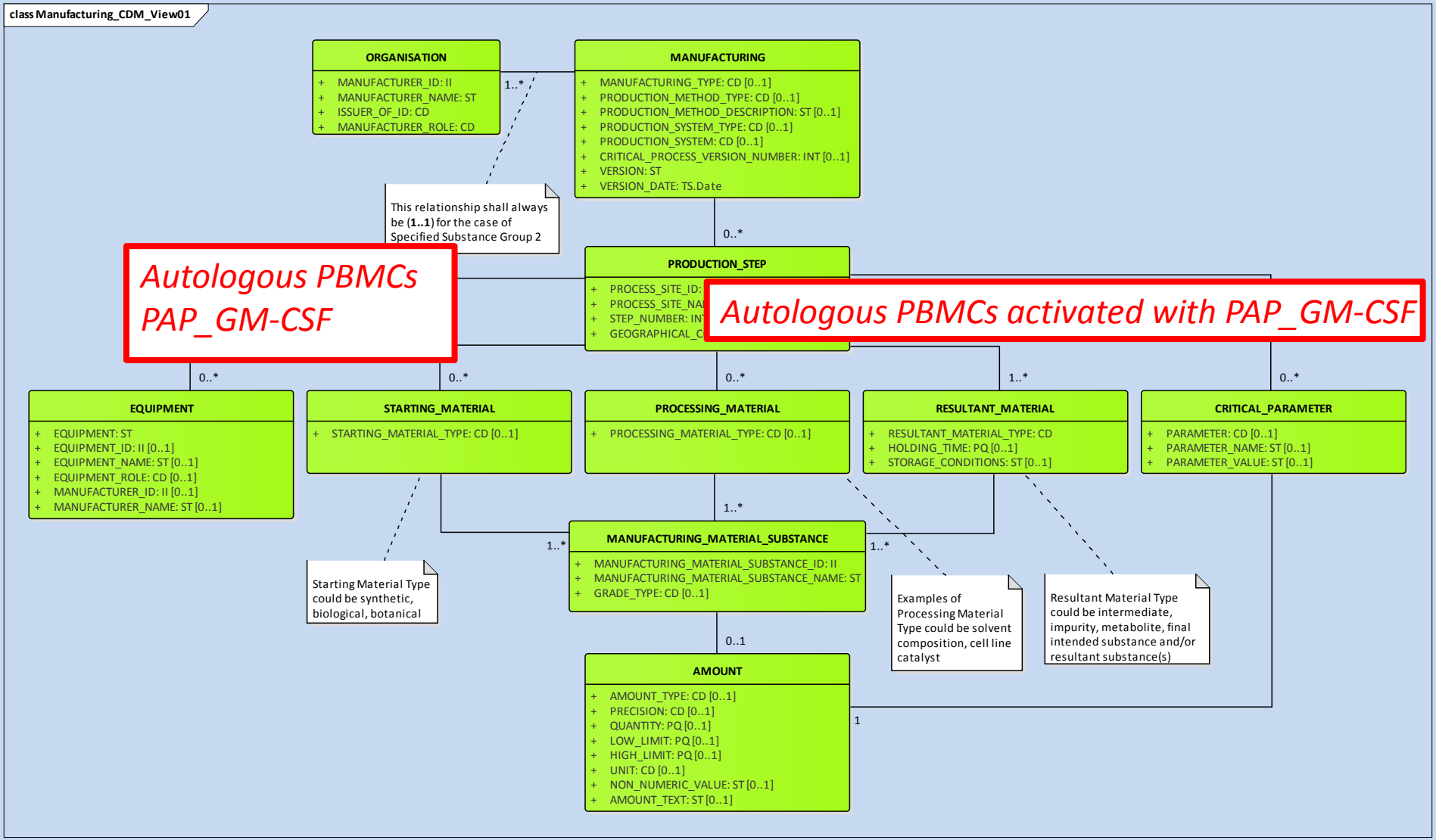
Advanced Therapy Medicinal Products
Cellular immunotherapy product: Provenge

INN: Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (sipuleucel-T)

Starting materials:
PAP_GM-CSF
PBMCs



Resultant material:
AutologousPBMCs activated with PAP_GM-CSF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Autologous PBMCs PAP_GM-CSF
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Autologous PBMCs activated with PAP_GM-CSF
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1..*
1..*
Starting Material Type could be synthetic, biological, botanical
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Examples of Processing Material Type could be solvent composition, cell line catalyst
Resultant Material Type could be intermediate, impurity, metabolite, final intended substance and/or resultant substance(s)
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Advanced Therapy Medicinal Products
Cellular immunotherapy product: CAR-T cells

NOVARTIS

Our Work About Us News Investors Careers

Novartis CAR-T cell therapy CTL019 unanimously (10-0) recommended for approval by FDA advisory committee to treat pediatric, young adult r/r B-cell ALL

JUL 13, 2017

- *Recommendation based on review of CTL019 r/r B-cell ALL development program, inclua pivotal Phase II global ELIANA trial*
- *A Biologics License Application (BLA) for this indication is under FDA priority review; if CTL019 could become first CAR-T cell therapy available*
- *Positive ODAC recommendation is latest milestone for CTL019 program that started throu collaboration with the University of Pennsylvania*

Basel, July 12, 2017 - Novartis announced today that the US Food and Drug Administratior Oncologic Drugs Advisory Committee (ODAC) unanimously (10-0) recommended approva (tisagenlecleucel), an investigational chimeric antigen receptor T cell (CAR-T) therapy, for t of relapsed or refractory (r/r) pediatric and young adult patients with B-cell acute lymphobl leukemia (ALL).

"The panel's unanimous recommendation in favor of CTL019 moves us closer to potentially the first-ever commercially approved CAR-T cell therapy to patients in need," said Bruno Strigini, CEO, Novartis Oncology. "We're very proud to be expanding new frontiers in cancer treatment by advancing immunocellular therapy for children and young adults with r/r B-cell ALL and other critically ill patients who have limited options. We look forward to working with the FDA as they complete their review."

NIH Center for Cancer Research

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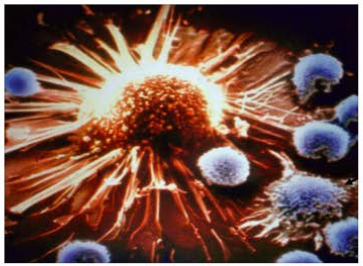
T-Cell Warriors—Equipped to Kill Cancer Cells



Cytotoxic T cells (blue) can be genetically reprogrammed to recognize an antigenic marker (e.g., CD19) on a cancer cell and mount an attack on that cell.

When the body recognizes tumor cells as foreign, a natural immune response arises to attack them. Unfortunately, tumors have ways to evade immune surveillance systems and antitumor responses are often too weak to defeat the disease. Rather than relying on the body's natural response, scientists can now manipulate a patient's own immune cells so that they latch on to tumor cells by recognizing specific proteins on their surface. A type of immune cell that has been explored for this purpose is the killer (cytotoxic) T cell, which eliminates cells infected by viruses, damaged cells, and tumor cells.

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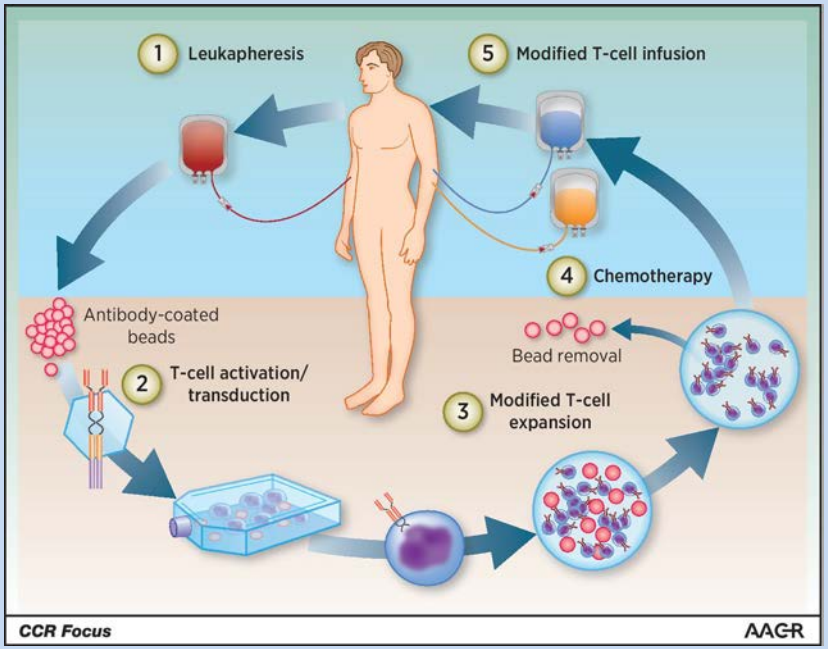
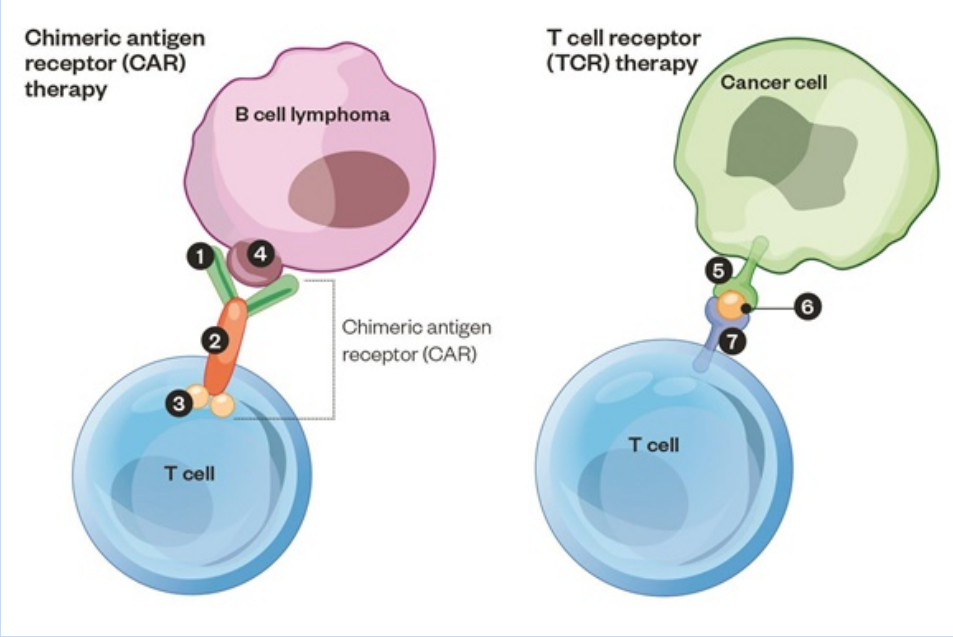
Advanced Therapy Medicinal Products

Cellular immunotherapy product: CAR-T cells

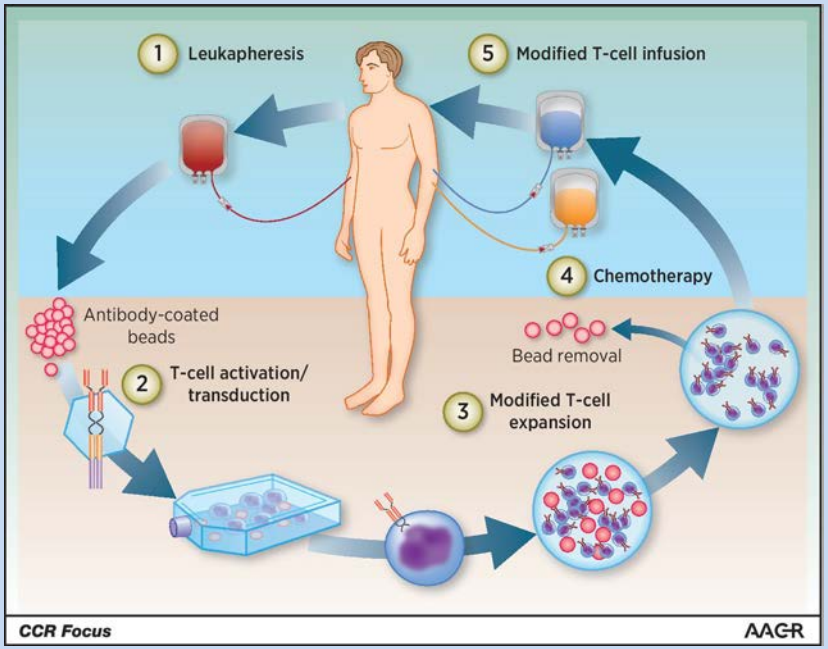
INN: Tisagenlecleucel

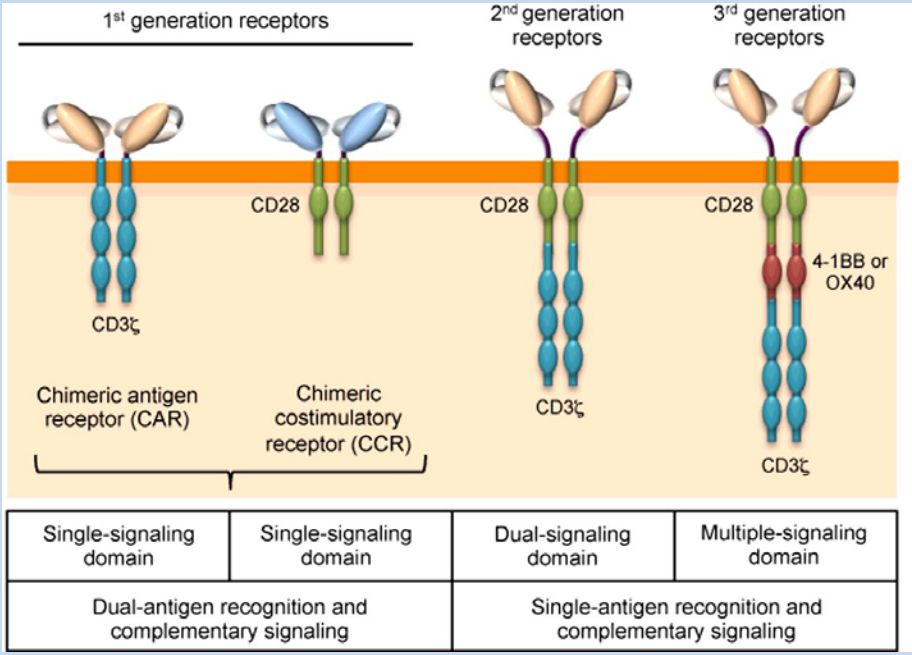


From: Maus & June (2016) Clin Cancer Res 22



Advanced Therapy Medicinal Products
Cellular immunotherapy product: CAR-T cells



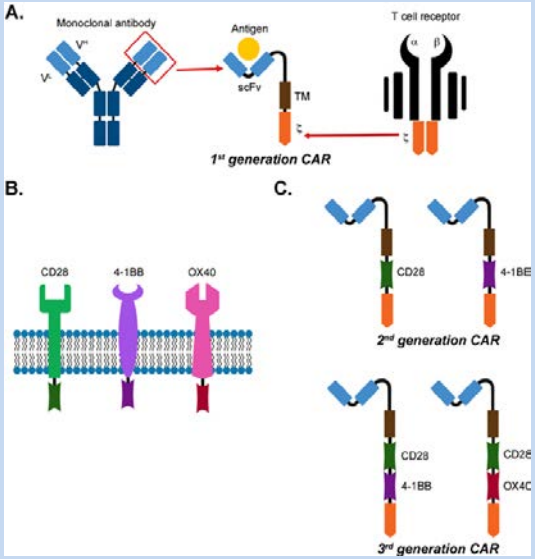


From Alonso-Camino et al. (2016), Biochem.Soc.Trans. 44

CAR-T CELLS

Which elements to include?

- Autologous T cells
- Vector
- Genetic construct:
  - Chimeric Antigen Receptor (CAR; Fv fragment)
  - Costimulatory domain CD28
  - Costimulatory domain OX40 or 4-1BB
- Target of CAR (e.g. CD19)
- Transduced T cells



Conclusion and Challenges

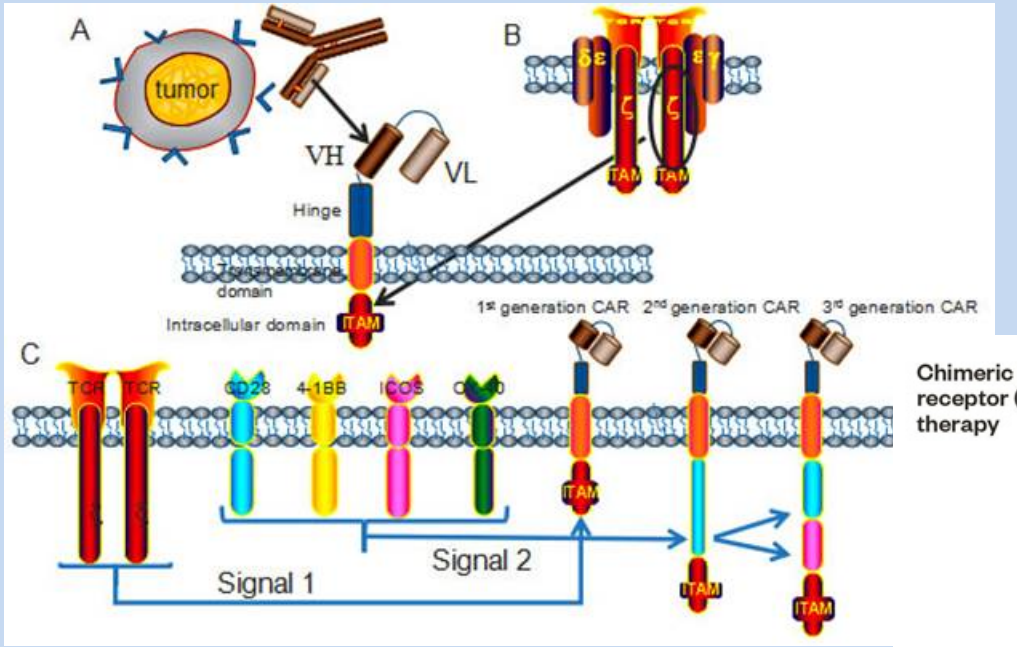
- Cell based medicinal products (CBMP) can be captured
- Substances for CBMP can be defined
- Complete range of CBMP not yet considered
- Gene therapy medicinal products (GTMP) to be tackled
- Gene editing tools/techniques (e.g. CRISPR-Cas9) may prove challenging

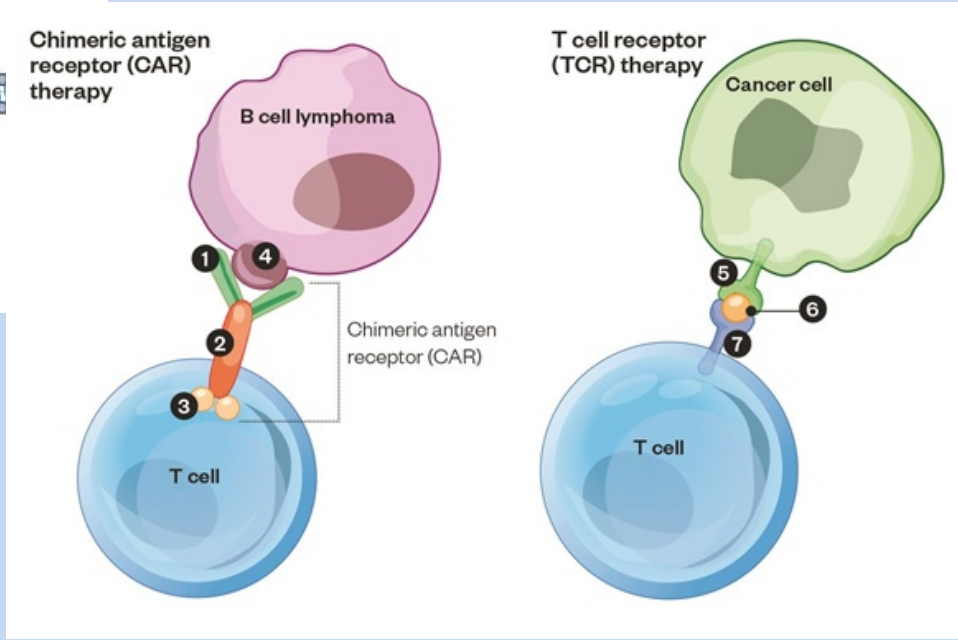
Thanks to:
Panagiotis Telonis (EMA)
Herman Diederik (EMA)

mh.hoefnagel@cbg-meb.nl

Advanced Therapy Medicinal Products

Cellular immunotherapy product: CAR-T cells





ISO 11238 TOC

Contents

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ISO/TS 19844 TOC (2)

ISO/TS 19844:2017

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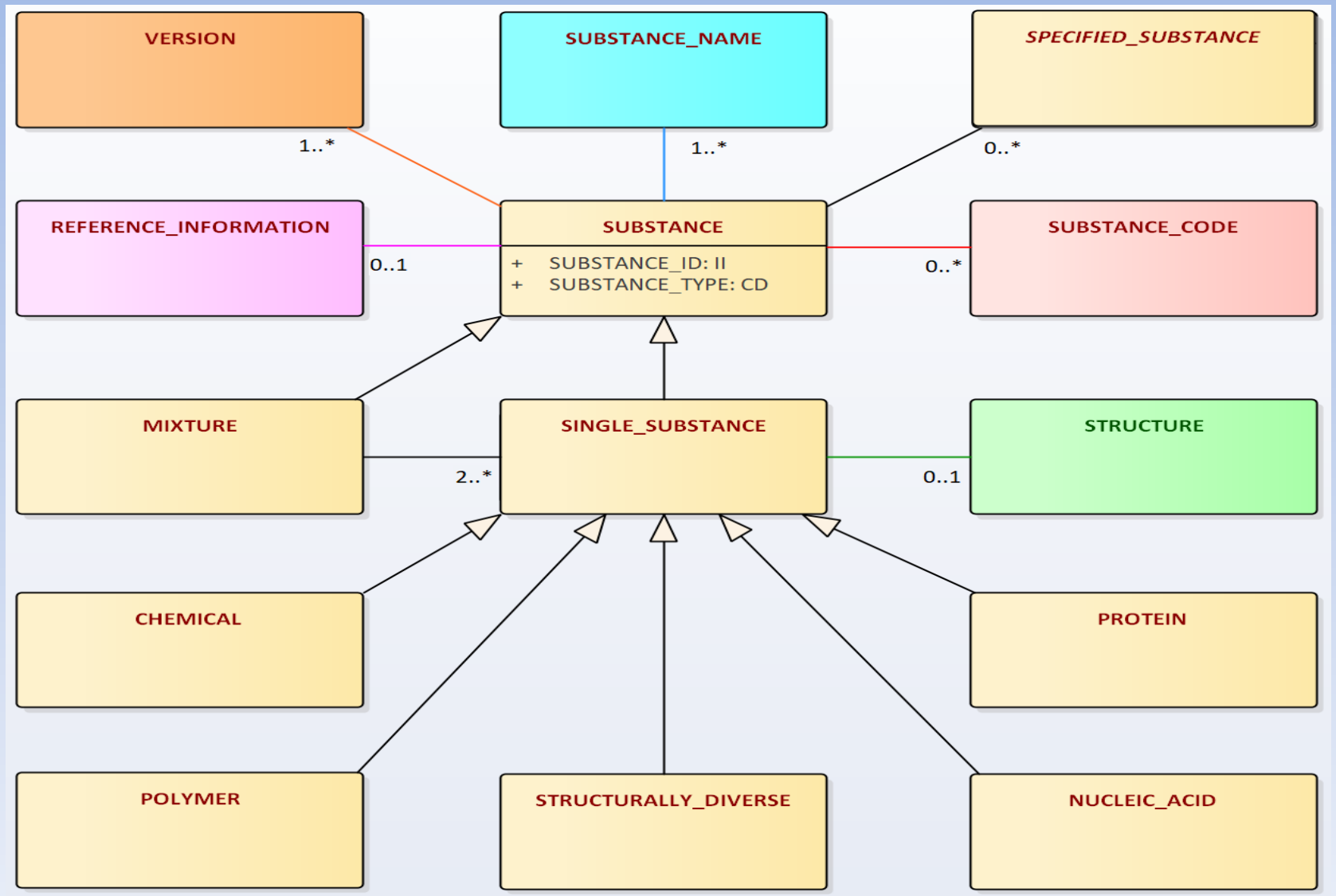
ISO 11238/19844 Substance (high-level)



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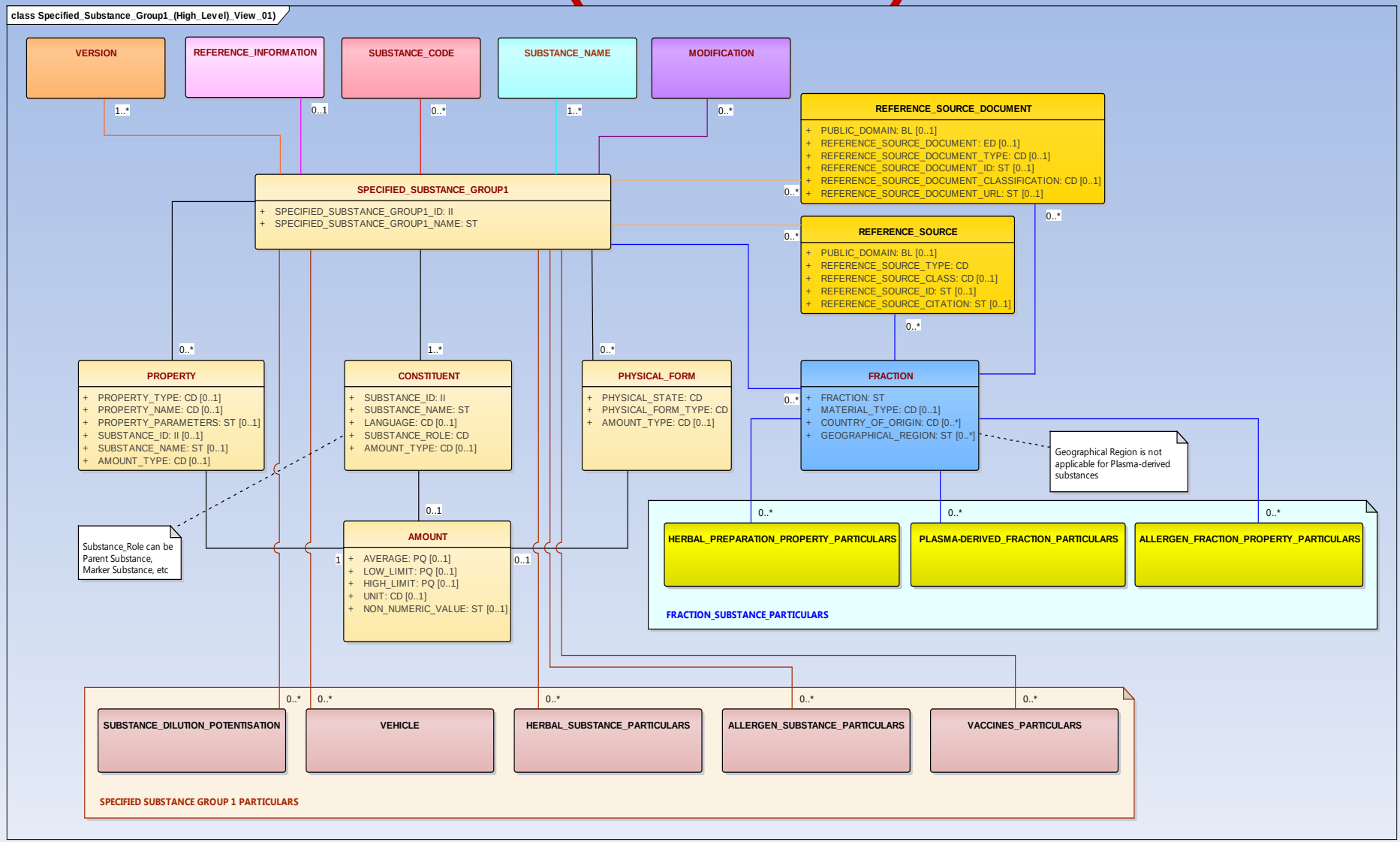
ISO 11238/19844 Specified Substance Group 1 (Iteration 2)



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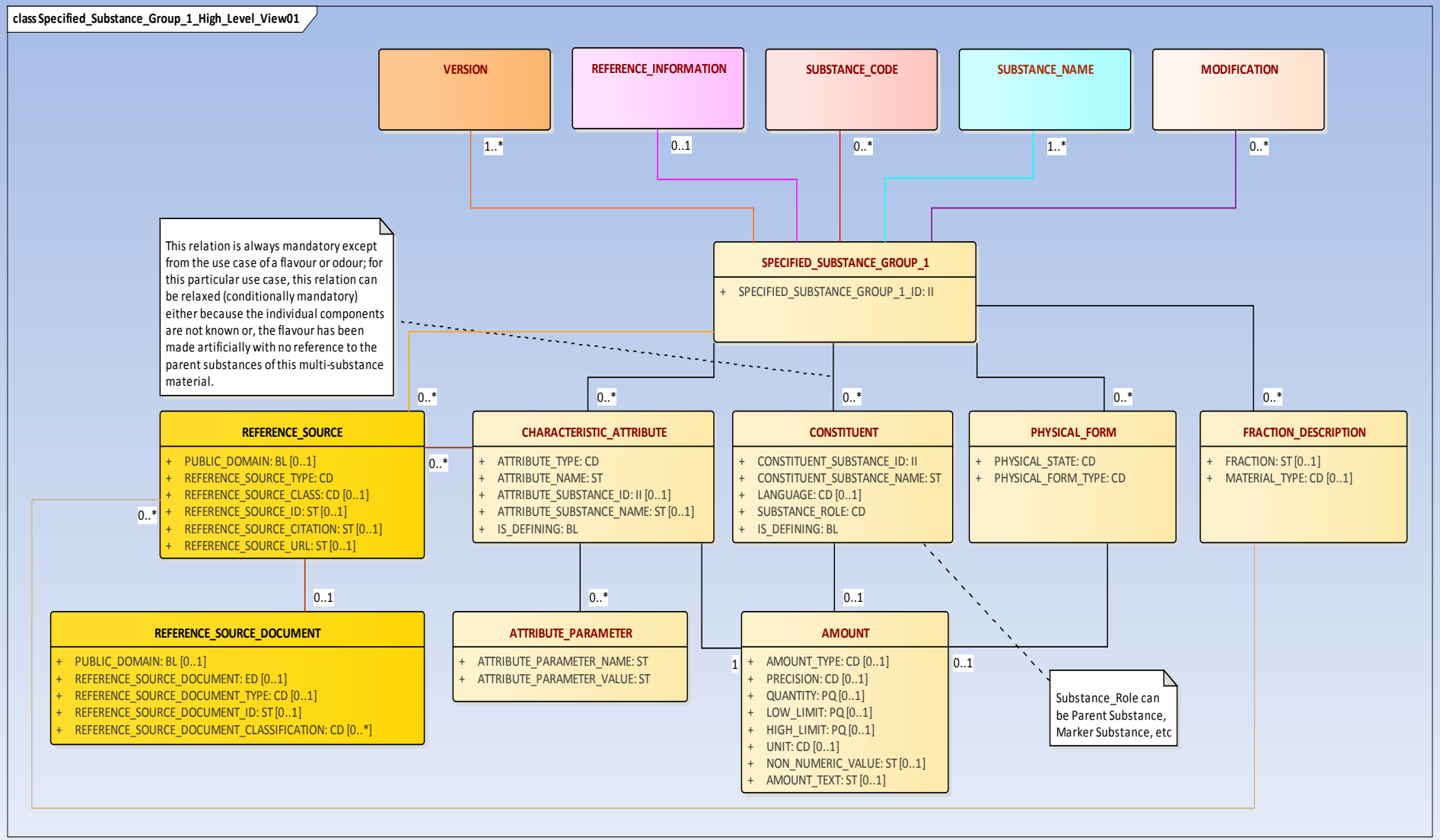
ISO 11238/19844 Specified Substance Group 1 (Iteration 3)



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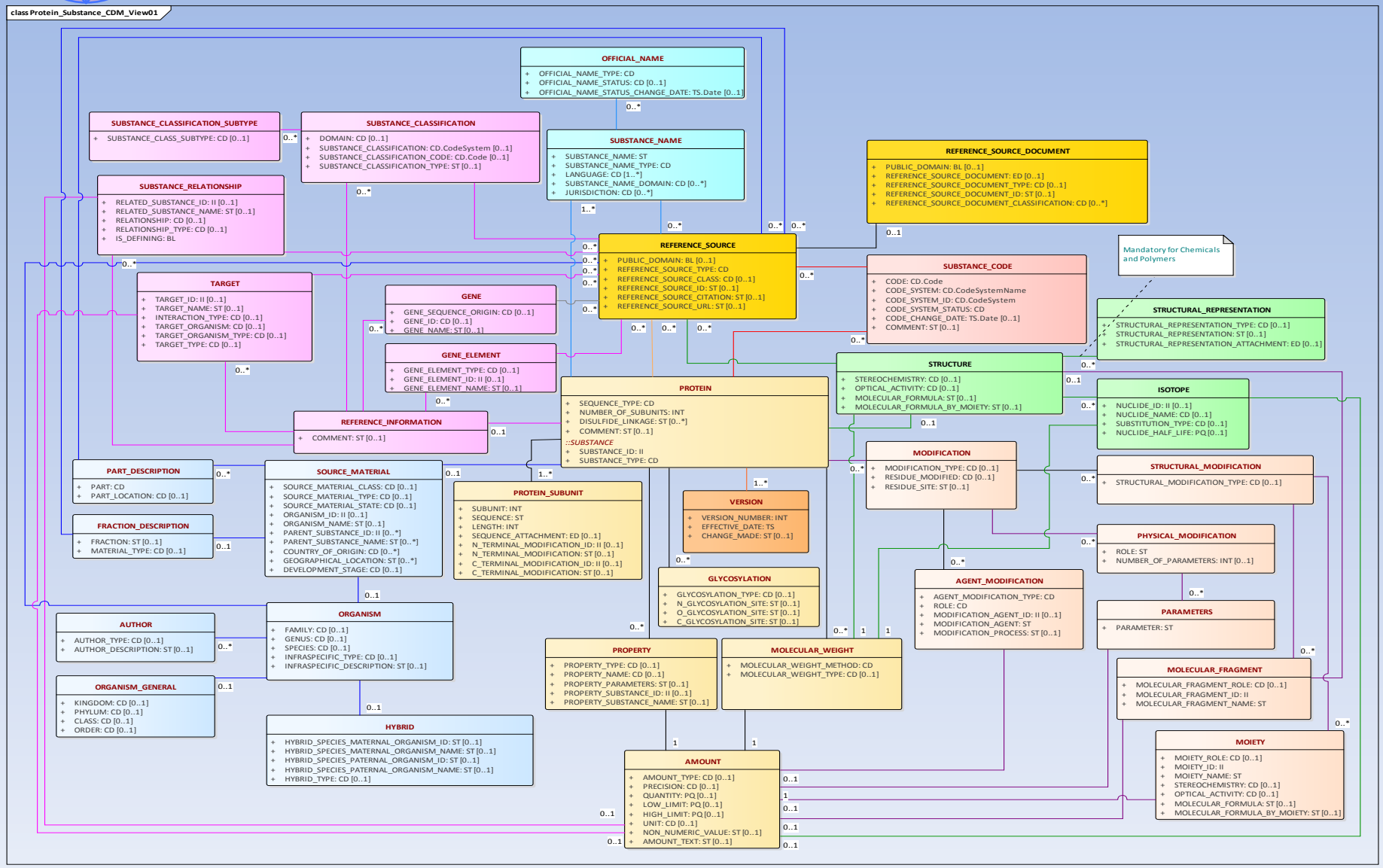
Protein CMD, Substance Information level



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MAB, Brentuximab Vedotin

Characterising elements at the Substance info level:

AMOUNT
- + AMOUNT_TYPE: CD [0..1]
- + PRECISION: CD [0..1]
- + QUANTITY: PQ [0..1]
- + LOW_LIMIT: PQ [0..1]
- + HIGH_LIMIT: PQ [0..1]
- + UNIT: CD [0..1]
- + NON_NUMERIC_VALUE: ST [0..1]
- + AMOUNT_TEXT: ST [0..1]

PROTEIN
- + SEQUENCE_TYPE: CD
- + NUMBER_OF_SUBUNITS: INT
- + DISULFIDE_LINKAGE: ST [0..*]
- + COMMENT: ST [0..1]

::SUBSTANCE
- + SUBSTANCE_ID: II
- + SUBSTANCE_TYPE: CD

PROTEIN_SUBUNIT
- + SUBUNIT: INT
- + SEQUENCE: ST
- + LENGTH: INT
- + SEQUENCE_ATTACHMENT: ED [0..1]
- + N_TERMINAL_MODIFICATION_ID: II [0..1]
- + N_TERMINAL_MODIFICATION: ST [0..1]
- + C_TERMINAL_MODIFICATION_ID: II [0..1]
- + C_TERMINAL_MODIFICATION: ST [0..1]

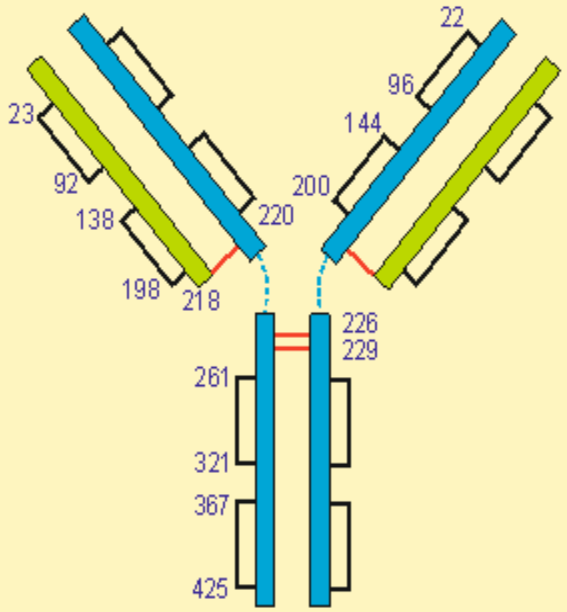
MOLECULAR_WEIGHT
- + MOLECULAR_WEIGHT_METHOD: CD
- + MOLECULAR_WEIGHT_TYPE: CD [0..1]

GLYCOSYLATION
- + GLYCOSYLATION_TYPE: CD [0..1]
- + N_GLYCOSYLATION_SITE: ST [0..1]
- + O_GLYCOSYLATION_SITE: ST [0..1]
- + C_GLYCOSYLATION_SITE: ST [0..1]

STRUCTURE
- + STEREOCHEMISTRY: CD [0..1]
- + OPTICAL_ACTIVITY: CD [0..1]
- + MOLECULAR_FORMULA: ST [0..1]
- + MOLECULAR_FORMULA_BY_MOIETY: ST [0..1]

STRUCTURAL_REPRESENTATION
- + STRUCTURAL_REPRESENTATION_TYPE: CD [0..1]
- + STRUCTURAL_REPRESENTATION: ST [0..1]
- + STRUCTURAL_REPRESENTATION_ATTACHMENT: ED [0..1]

MODIFICATION
- + MODIFICATION_TYPE: CD [0..1]
- + RESIDUE_MODIFIED: CD [0..1]
- + RESIDUE_SITE: ST [0..1]



1. Green bars denote light chain
2. Blue bars represent heavy chain
3. Dashed blue line represents hinge region
4. Black lines represent intra-chain disulfide bonds
5. Red lines represent inter-chain disulfibe bonds
6. Numbers indicate cysteine associated with disulfide bonds

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Sequence and Sequence Attachment of Protein Subunit

1) Sequence and Length of Heavy Chain after Post Translational Modification
2) Sequence Attachment before PTM
3) Sequence and Length of Light Chain; 4) Modifications and Glycosylation

Element Group		
Sequence Type	Complete	
Sequence attachment	QIQLQQSGPEVVKPG KPGQGLEWIGWIYPG TAFMQLSSLTSEDTA VSAASTKGPSVFPLAP TVSWNSGALTSGVHT TQTYICNVNHKPSNT ELLGGPSVFLFPPKPK EVKFNWYVDGVEVH HQDWLNGKEYKCKV VYTLPPSRDELTKNQ PENNYKTTPPVLDSDGSFFLYS CSVMHEALHNHYTQKSLSLSPG	Subunit Sequen Length
Element Group: Protein		
	TVSWNSGALTSGVHTFPAVLQS TQTYICNVNHKPSNTKVDKKVE ELLGGPSVFLFPPKPKDTLMISR EVKFNWYVDGVEVHNAKTKPR HQDWLNGKEYKCKVSNKALPAI VYTLPPSRDELTKNQVSLTCLVK PENNYKTTPPVLDSDGSFFLYSK CSVMHEALHNHYTQKSLSLSPG	
Length	446	

N-Glycosylation	1_297; 2_297	ST
Element Group: Modification (N-Terminal modification)		
Modification Type	Structural Modification	CD
Residue Modified	Glutamine (Q)	CD
Residue Site	1_1; 2-1	ST
Element Group: Structural Modification		
Structural Modification Type	Amino Acid Substitution	CD
Element Group: Molecular Fragment		
Molecular Fragment Role	N-Terminal Pyroglu Formation	CD
Molecular Fragment ID	PYROG45321 (Artificial ID); [SZB8301W42 (UNII)]	II
Molecular Fragment Name	Pyroglutamic acid (pE)	ST
Element Group: Modification (Repeat) (C-Terminal Modification)		
Modification Type	Structural Modification	CD
Residue Modified	Lysine (K)	CD
Residue Site	1-447; 2-447	ST
Element Group: Structural Modification		
Structural Modification Type	Amino Acid Removal	CD
Element Group: Molecular Fragment		
Molecular Fragment Role	C-Terminal Lysine removal	CD

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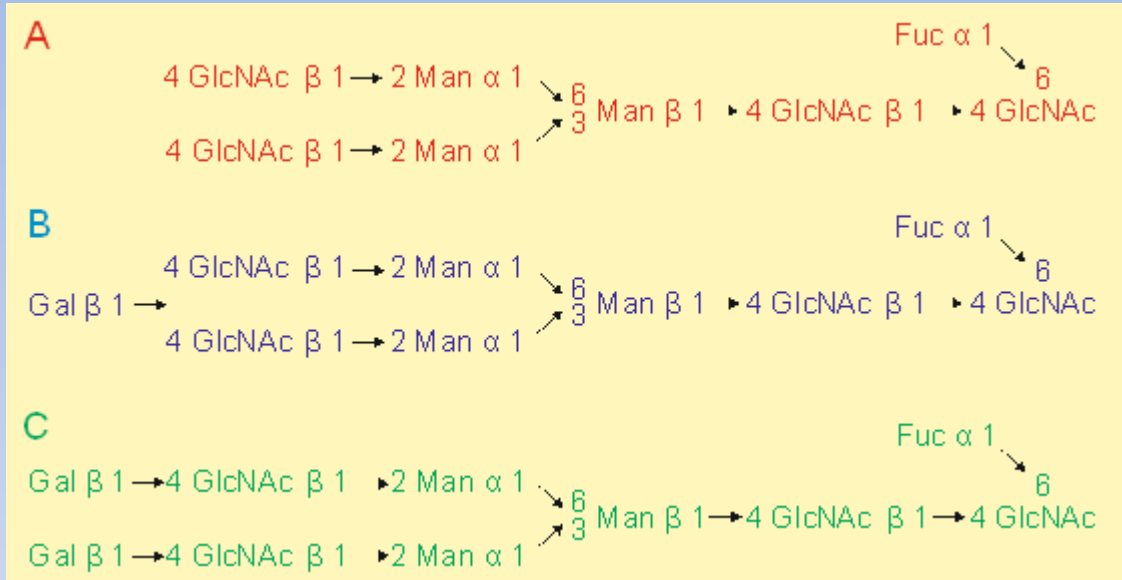
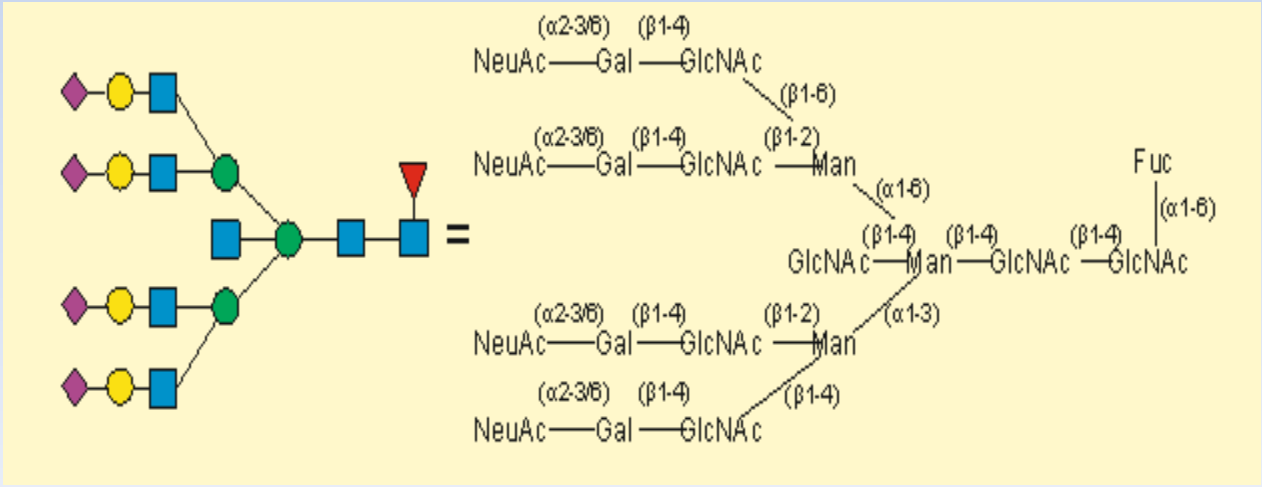
MAB, Brentuximab Vedotin

Characterising elements at the Specified Substance Group 1 info level: Glycan Information: Structural representation of common Glycans





- N-Acetylneuraminic acid (NANA)
- Galactose (Gall)
- N-Acetylglucosamine (GlcNAc)
- Mannose (Man)
- Fucose (Fuc)

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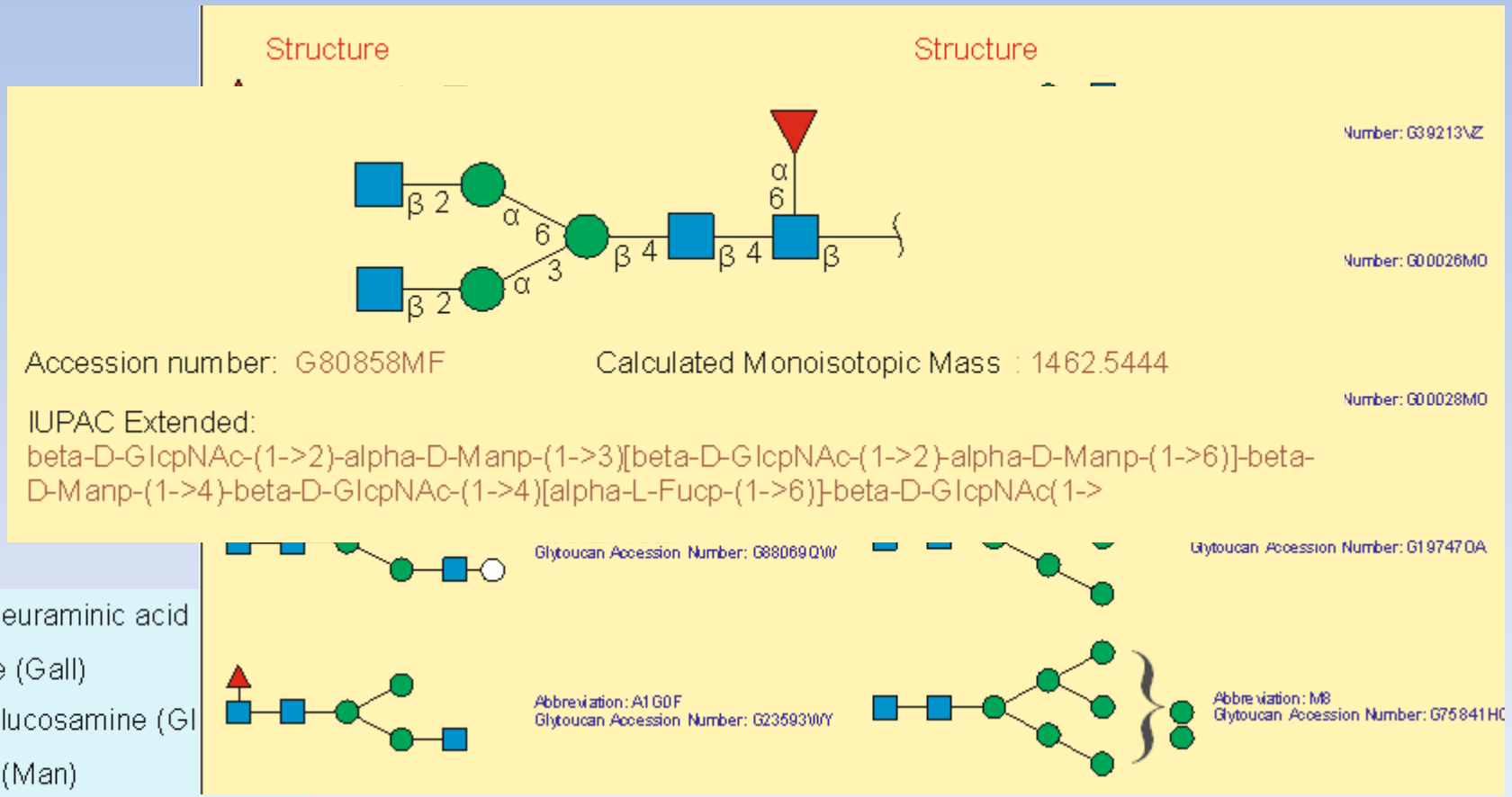
MAB, Brentuximab Vedotin Glycans (1)

Characterising elements at the Specified Substance Group 1 info level:

1) Structural representation of Brentuximab Glycans and GlyTouCan data base Accession Number

2) Display of GlyTouCan Accession Number G80858MF Fragment, IUPAC Extended Name and Calculated Monoisotopic Mass (1462.54)



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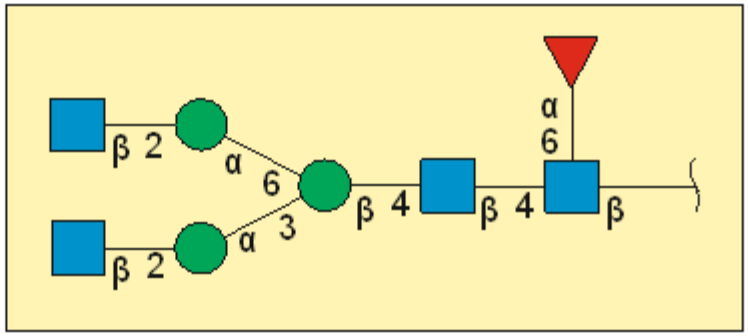
MAB, Brentuximab Vedotin Glycans (1)

Structuring Glycan info at the Specified Substance Group 1 level:

1) Element Group Constituent: Relationship with the Parent Substance

2) Element Group Characteristic Attribute: Type/ Name; Attribute

Element Group: Structure		
Structural Representation Attachment	 **Figure C.23 — Structural representation of the molecular fragment beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->3)[beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->6)]-beta-D-Manp-(1->4)-beta-D-GlcpNAc-(1->4)[alpha-L-Fucp-(1->6)]-beta-D-GlcpNAc(1->)**	ED
Structural Representation Type	Representative beta-D-GlcpNAc-(1->4)[alpha-L-Fucp-(1->6)]-beta-D-GlcpNAc(1->)	CD

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