Identification of substances in: Advanced Therapy Medicinal Products

(ATMP)

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Uppsala, September 2015

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MEDICINES
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Outline of the presentation

- Regulatory basis and definitions in accordance with EU Directive and Guidelines;
- Description of Cell-based products in view of IDMP ISO- 11238 Standard (Structurally Diverse Substances)
- Important data elements for unique identification of cell products
- Example cell-based medicinal product: 3 chondrocytes products
- Endeavour to capture Chondrocytes product in database model
- Example: 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:

Somatic cell therapy medicinal product means 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.

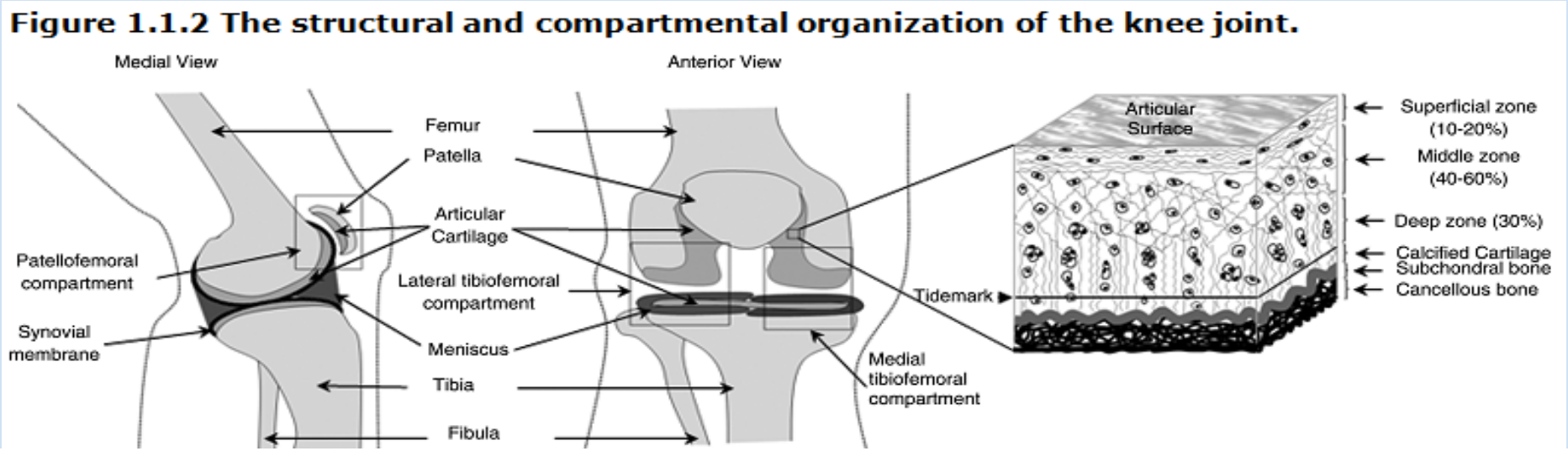
HUMAN CELL-BASED MEDICINAL PRODUCTS

Cells are complex biological systems

- Cells respond to (subtle) external triggers.
- Cells are heterogenic (intra- & inter-batch)
- Quality parameters determined by:
  - –Origin and 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 only limited part of Quality parameters

Knee Cartilage damage
Transplanted Autologous Chondrocytes

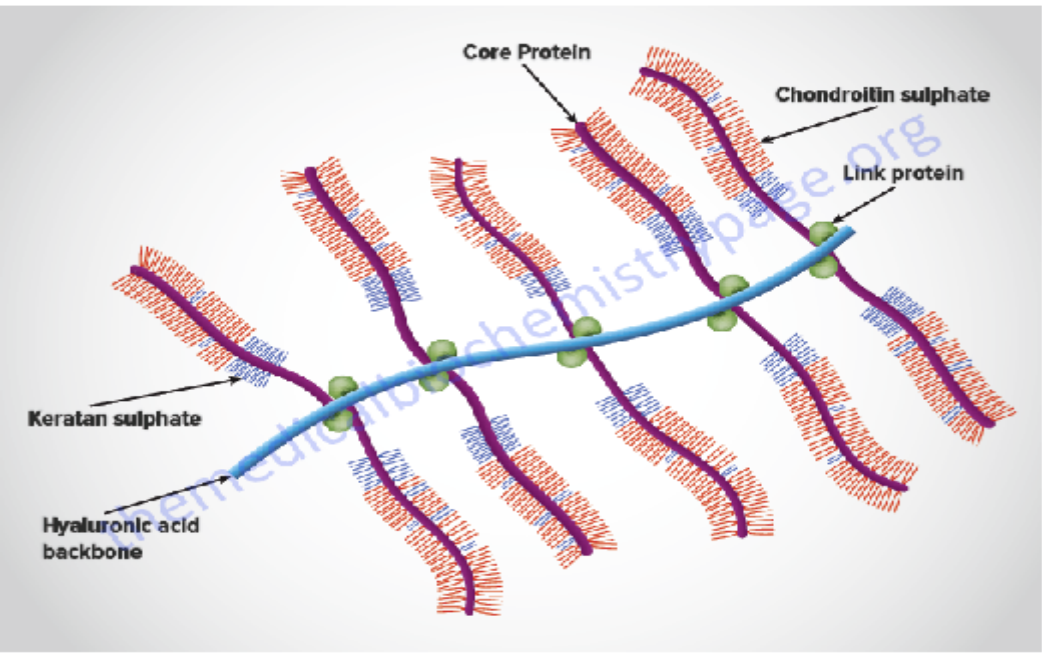
- **Autologous Osteochondral-graft Transplantation (AOT) :**
  - Fragments of healthy cartilage (contains chondrocytes) harvested from non-bearing site directly transplanted into (small) lesion. **(no ATMP!)**
- **Autologous Chondrocytes Implantation (ACI):**
  - Autologous chondrocytes extra-corporally 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 and MACI)*



Advanced Therapy: Articular Cartilage

Proteoglycans (Aggrecan), Chondrocyte Marker

Aggrecan : cartilage-specific proteoglycan core protein (CSPCP)
Encoded by ACAN gene.
Protein is an integral part of extracellular matrix in cartilagenous tissue (withstands compression)
Proteoglycan (protein modified with large number of carbohydrates)



Structure of an aggrecan-type complex proteoglycan

- **2316 Amino acids**
- **4 domains:**

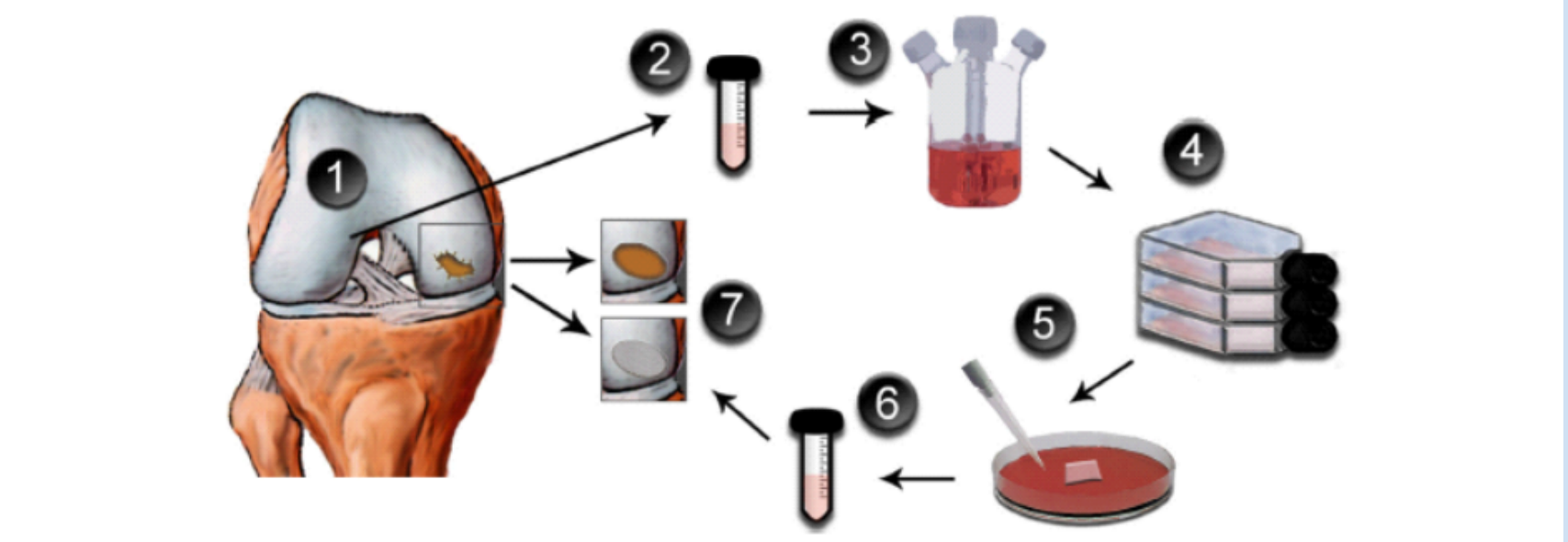
(N-G1-G2-CS-G3-C).

- **Mol. Mass > 2.500 kDa.**
- **Core protein (210 -250 kDa)**
- **100 –150 Glyco-aminonoglycan (GAG) chains**

Advanced Therapy Medicinal Product:
Manufacturing Process, Identification, Characterization

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

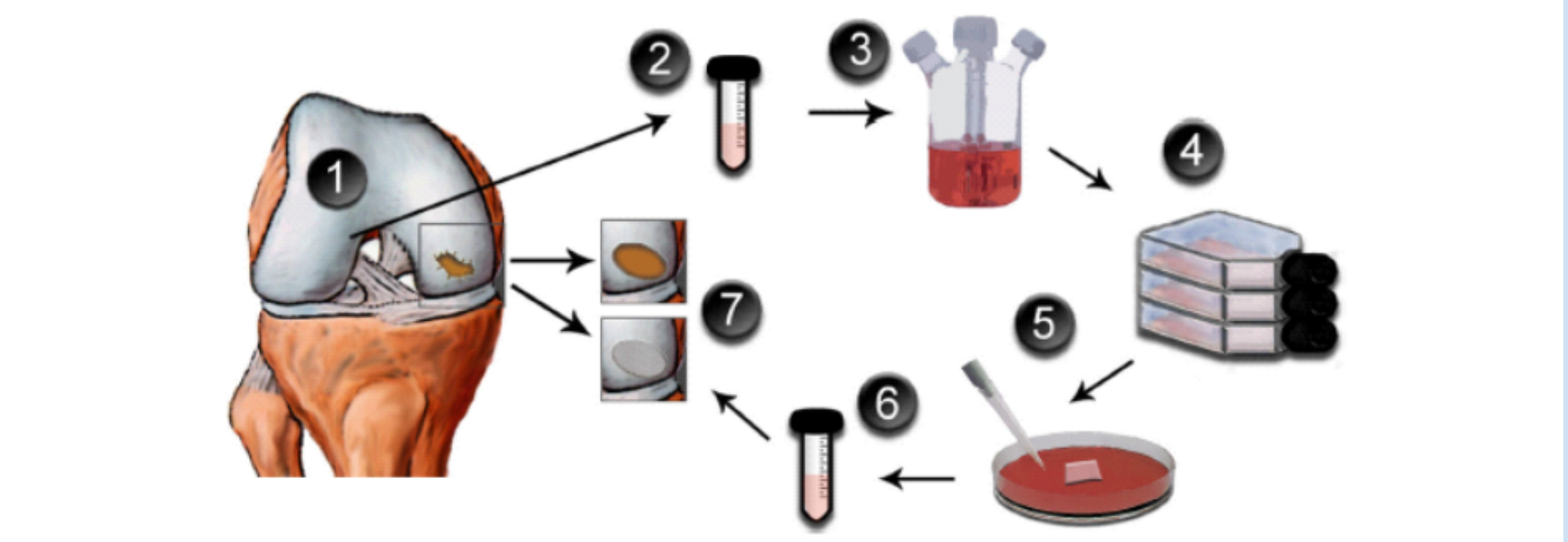
- **Biopsy digestion (mechanical/collagenase)**
- **Expansion culture (growth factors, cell doubling level)**
- **Cell culture harvest (trypsine) and wash**
- **Pooled cell suspension is seeded onto a membrane / scaffold**
- **Incubation period on membrane**



Advanced Therapy Medicinal Product:
Manufacturing Process, Identification, Characterization

Critical Steps:

- Total Cell count and viability after biopsy processing/ collagenase treatment;
- Cell yield, viability, days in culture and viability for the total expansion step;
- Adhesion of cells to the membrane
- Critical quality specifications measured during expansion and growth on the scaffold and specifications for morphology assessment



MACI (Autologous Cultured Chondrocyte Cells)
Identification, Charaterization, Potency

- Identification of essential features needed to form hyaline cartilage
- Molecular markers (at both the phenotypic and epigenetic levels), which provide measures of degree of differentiation towards chondrocytic or fibroblastic lineage
- No truly chondrocyte-specific genes have been found: expression of gene markers normally abundant in chondrocytes decreases greatly in culture

IDENTITY TEST

•An assay to distinguish chondrocytes from synovial fibroblasts (synoviocytes).

- •HAPLN1 over-expressed in chondrocytes,
- •MFAP5 over-expressed in synoviocytes.

•A qPCR assay for HAPLN1 and MFAP5 mRNA expression in a MACI implant drug product sample.

Advanced Therapy Medicinal Product:
MACI (Autologous Cultured Chondrocyte Cells)

Identification, Charaterization, Potency and Results

POTENCY TEST

- The MACI potency assay for gene expression of aggrecan (ACAN)
- qPCR technology on RNA isolated from 0.5 cm2 Identity sample .
- **Aggrecan expression** is normalized to housekeeping gene GAPDH.

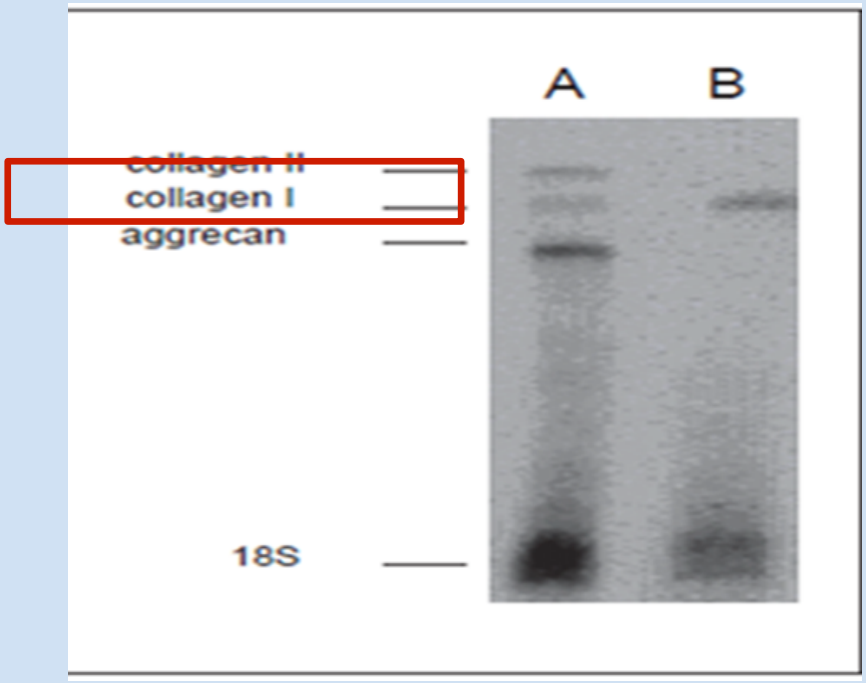


Fig.: Expression of Collagen II, Collagen I and Aggrecan in Chondrocytes (lane A) or Dermatan Fibroblasts (lan B) recovered from MACI Assemblies and Cultured in Alginate.

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 based on expression analysis of ratio of two markers, the chondrocytic marker HAPLN1 and the synovial/fibroblastic marker MFAP5. (synoviocytes/fibroblasts are impurities)

•Hyalograft C: RT-PCR assay of Aggrecan mRNA against a house-keeping gene 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.

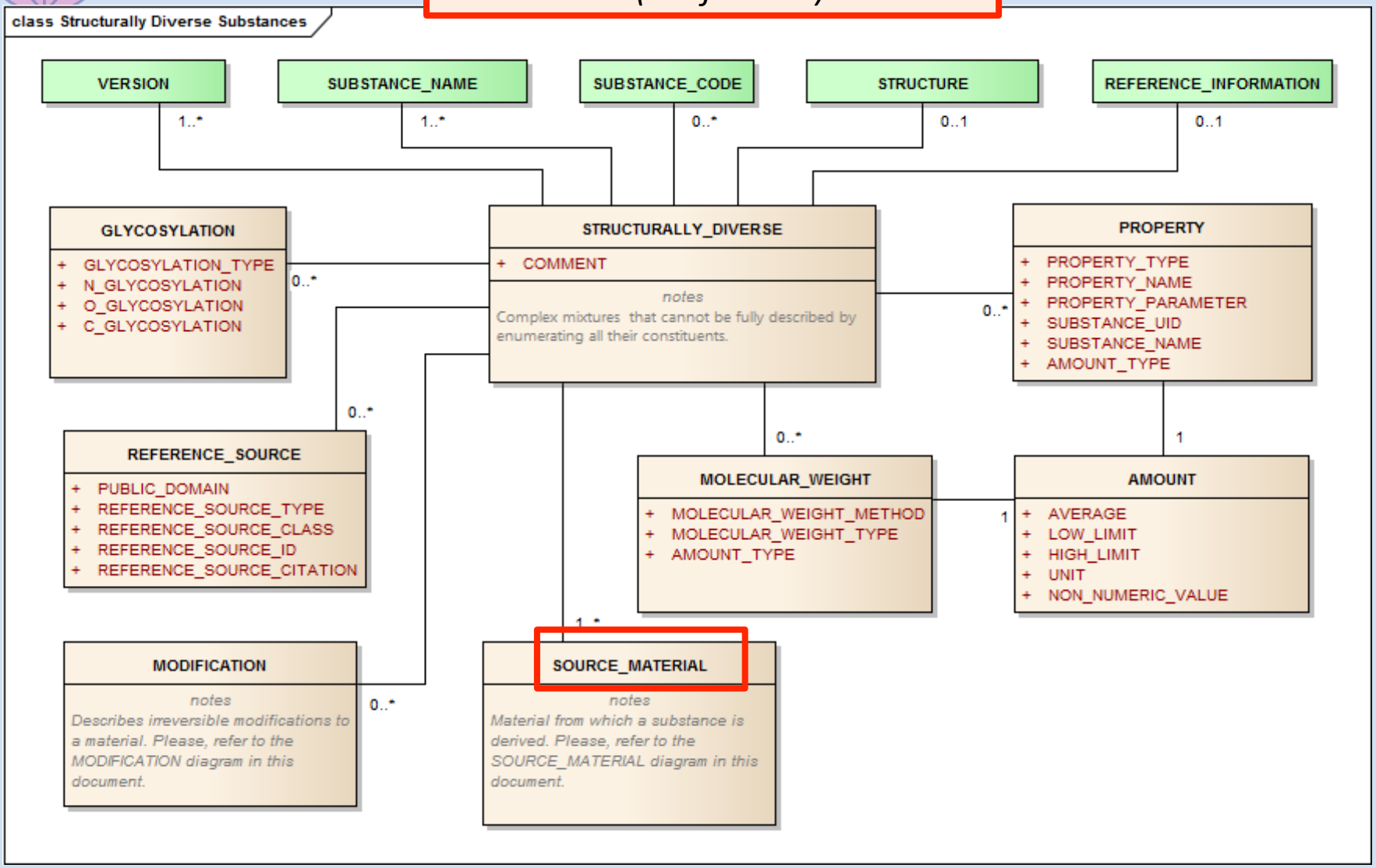
Hyalograft C: characterized viable autologous chondrocytes expanded *in vitro* seeded and cultured on a *hyaluronan based scaffold.*

- **Autologous chondrocytes (from cartilage biopsy) are expanded on monolayer, seeded and cultured on 3D-hyaluronan based scaffold (Hyalograft C).**
- **The scaffold is a non-woven pad composed of a hyaluronic acid benzyl ester polymer and is a class III Medical Device CE marked by a Notified Body.**

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

- **Membrane is a purified resorbable porcine peritonium collagen scaffold and is trimmed to the correct size and shape of the cartilage defect and held in place onto the lesion with a fibrin sealant. The matrix is a CE marked Class III device in Europe.**

Autologous_Cultured chondrocytes
CHON12345 (Artificial ID)



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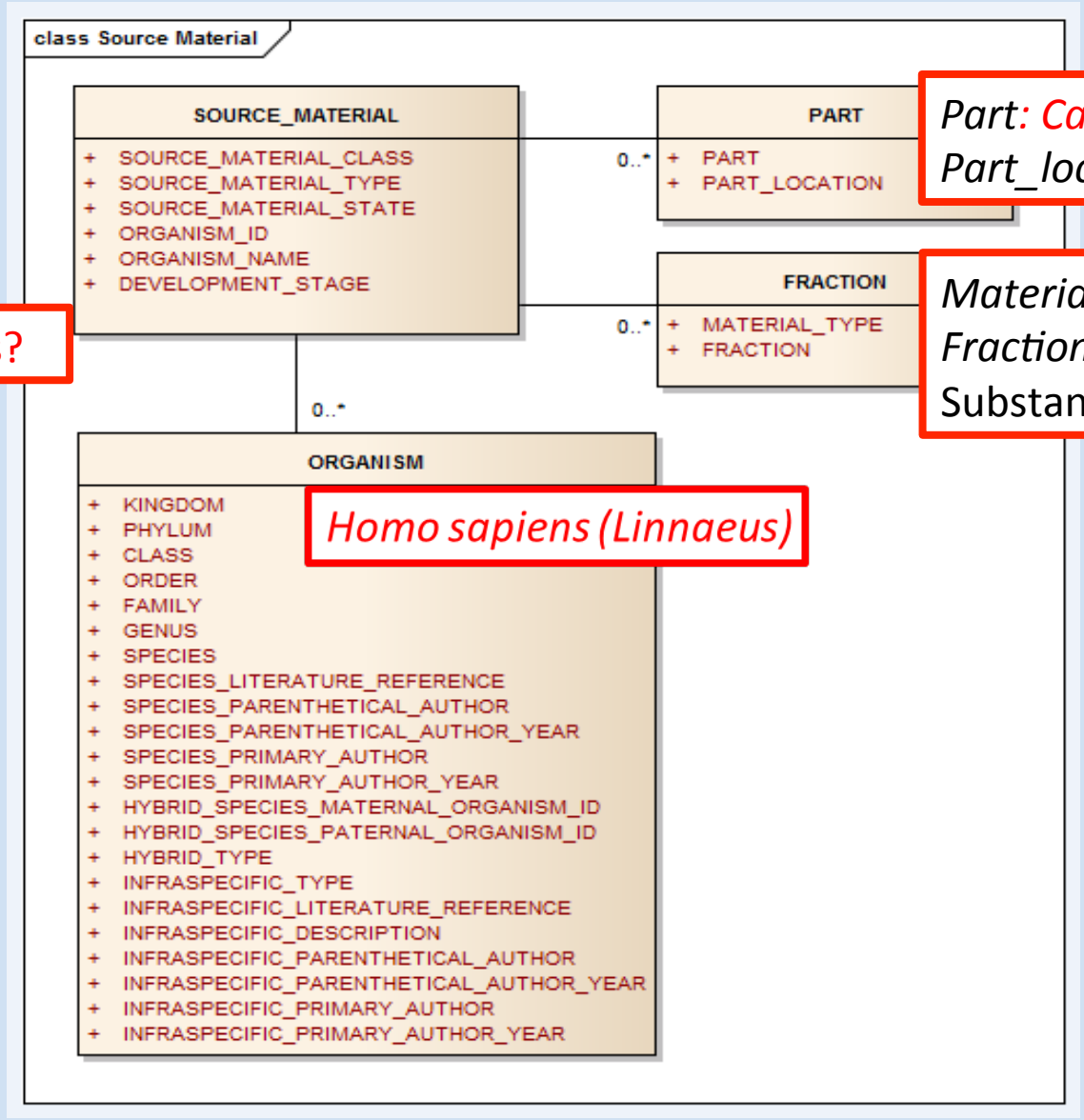

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Part_location: knee

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Fraction: Chondrocytes
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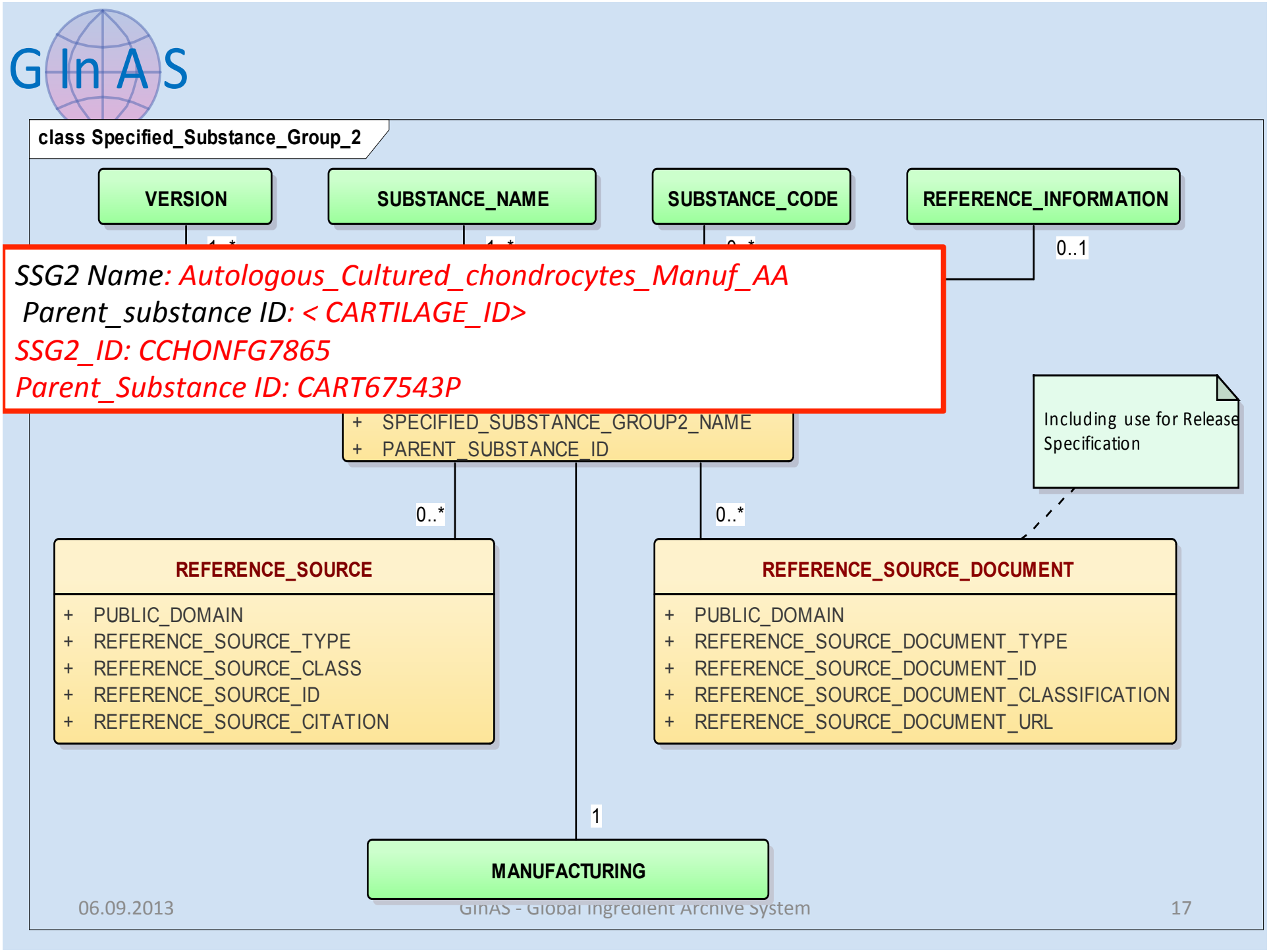
Autologous?

Homo sapiens (Linnaeus)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Including use for Release Specification
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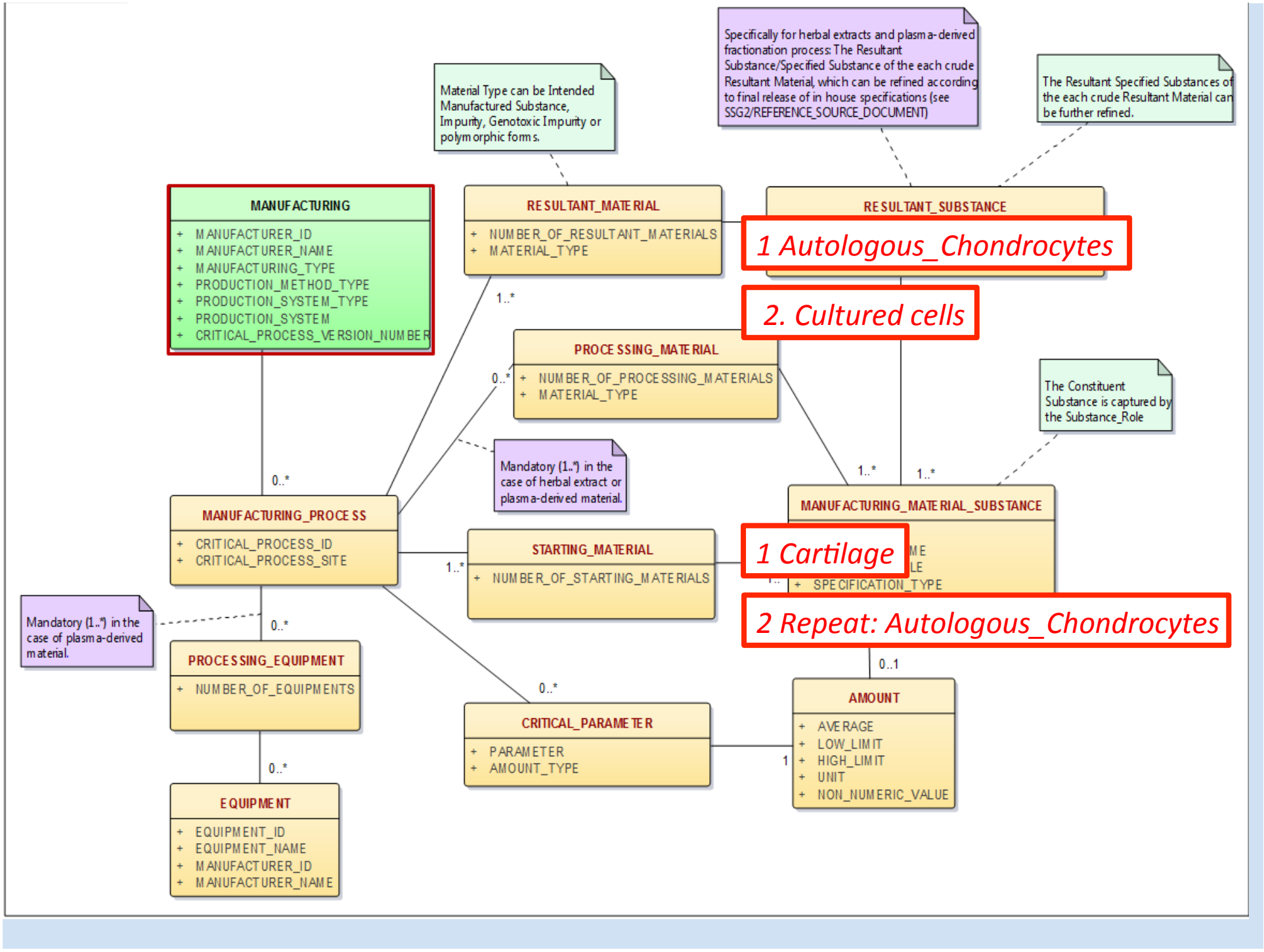
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Specifically for herbal extracts and plasma-derived fractionation process: The Resultant Substance/Specified Substance of the each crude Resultant Material, which can be refined according to final release of in house specifications (see SSG2/REFERENCE_SOURCE_DOCUMENT)
The Resultant Specified Substances of the each crude Resultant Material can be further refined.
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2. Cultured cells
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+ MATERIAL_TYPE
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1..*
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+ SPECIFICATION_TYPE
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2 Repeat: Autologous_Chondrocytes
Mandatory (1..*) in the case of plasma-derived material.
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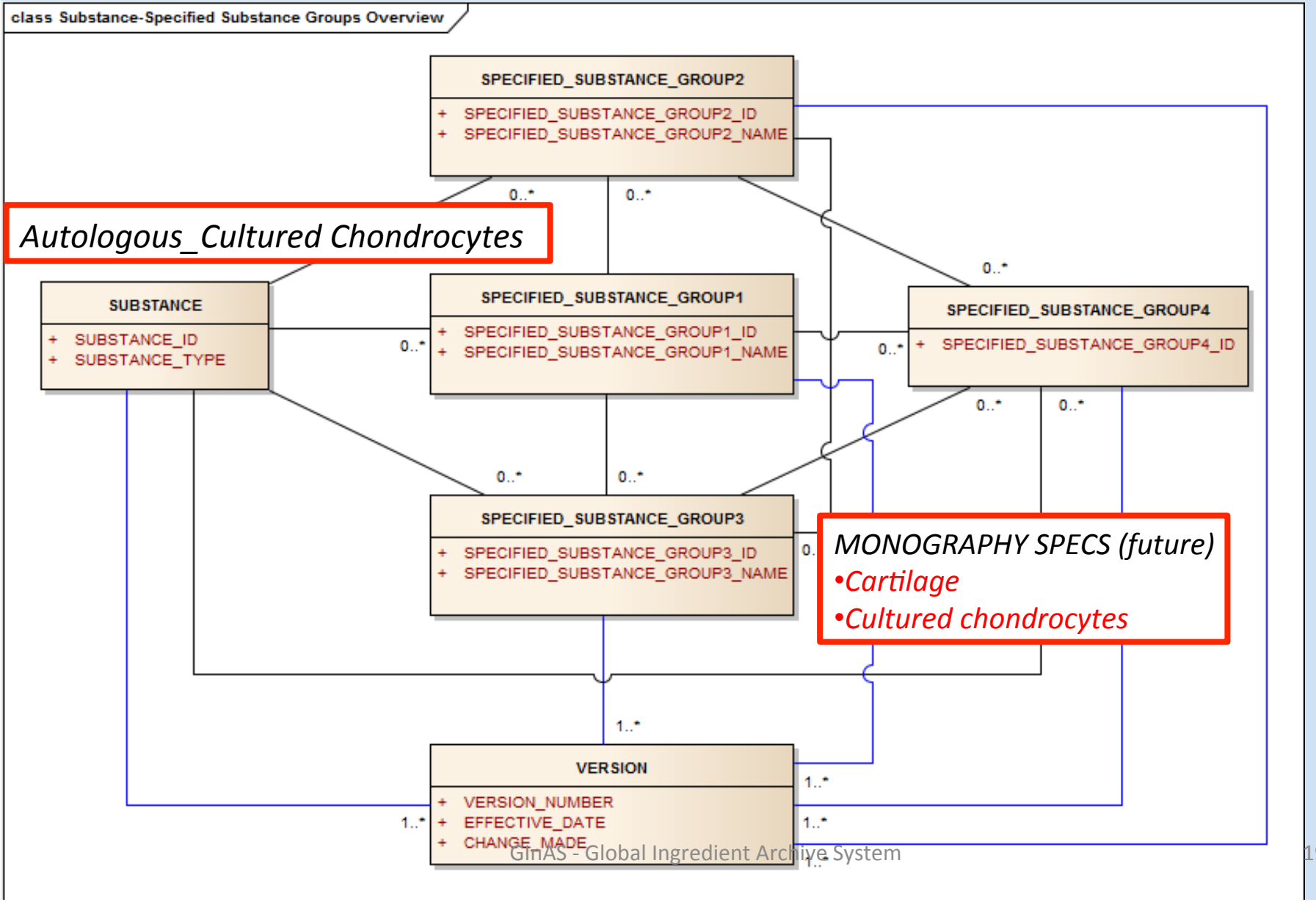
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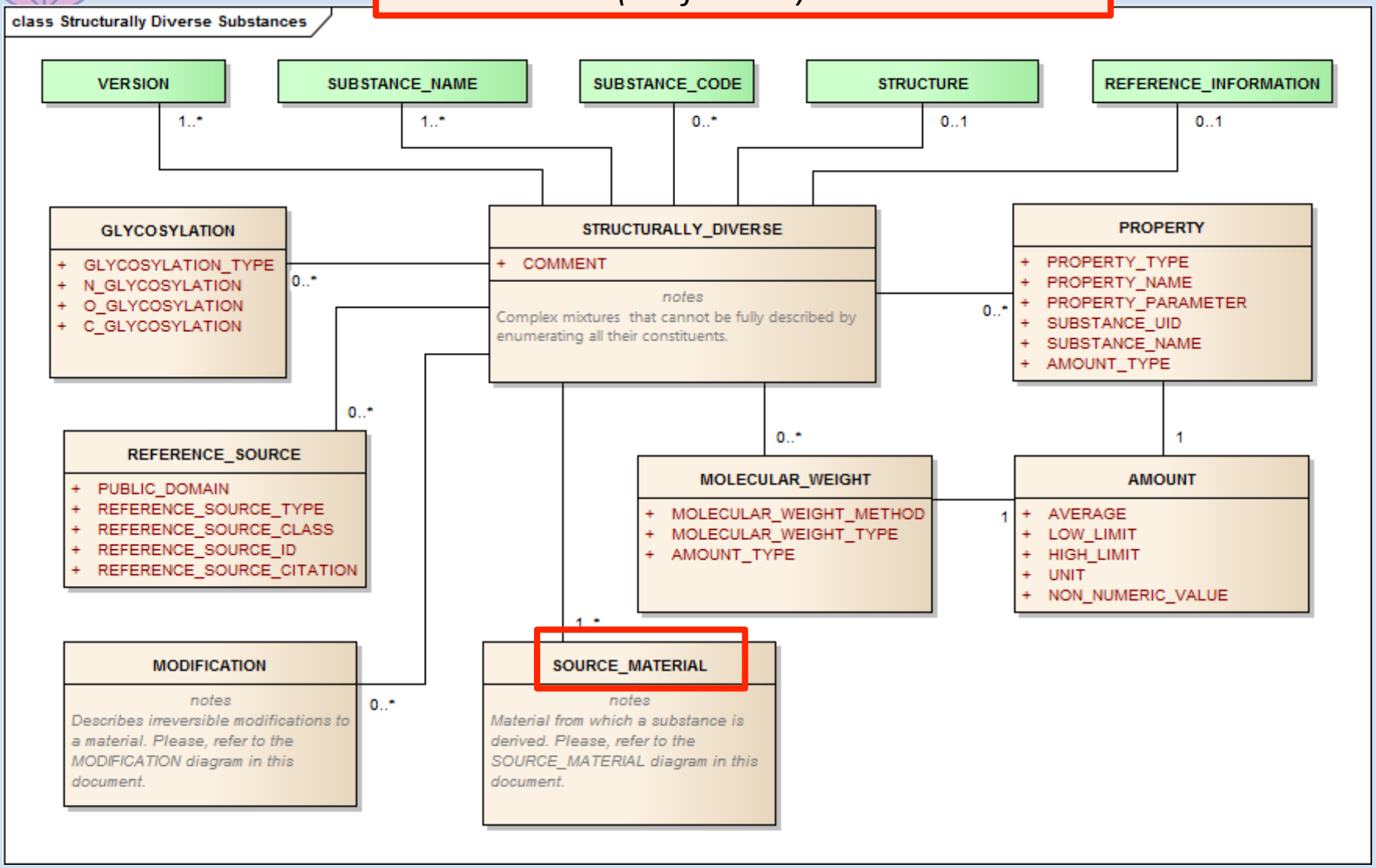
Autologous_Cultured chondrocytes on Matrix
CHONM12345 (Artificial ID)



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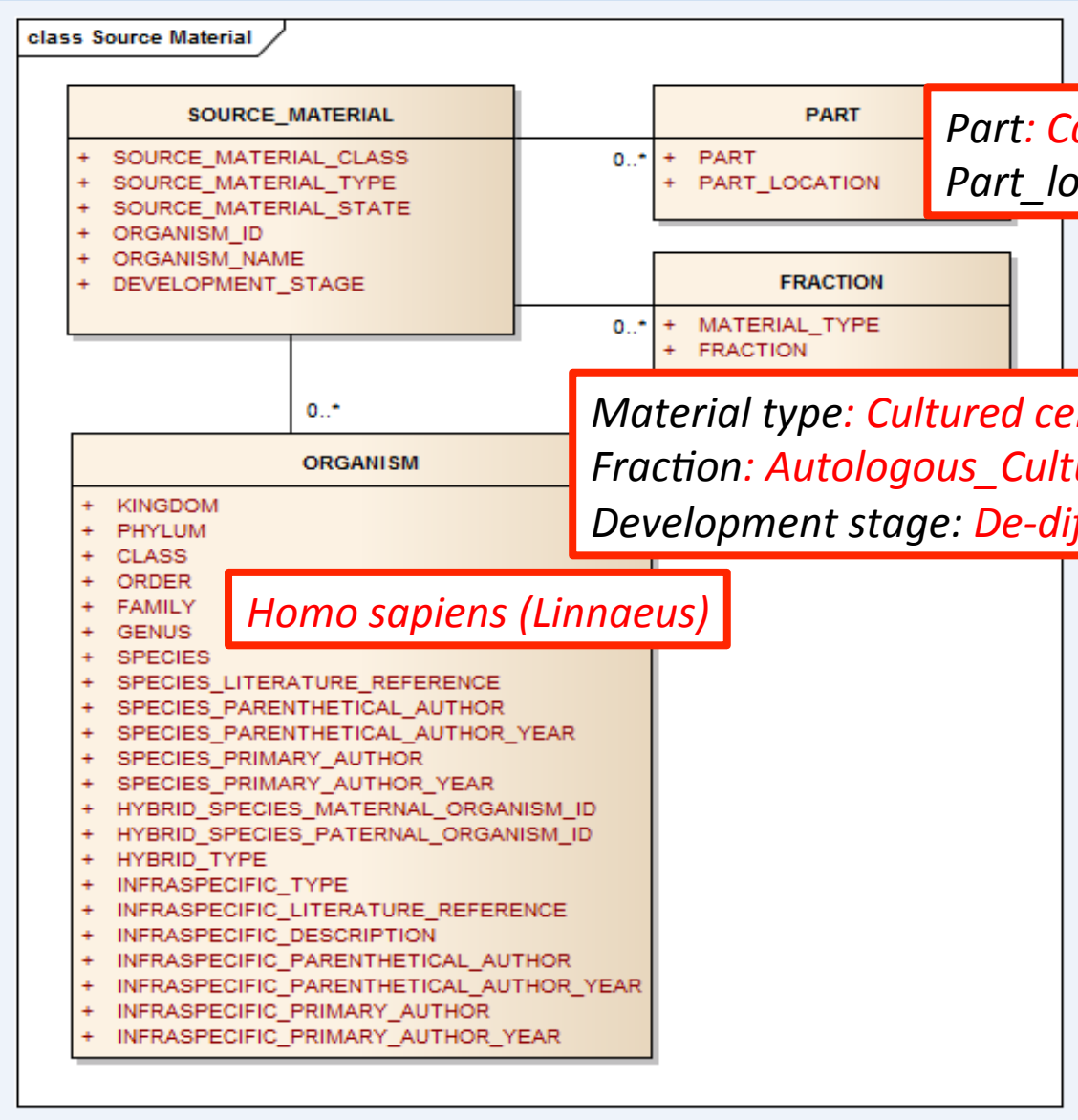
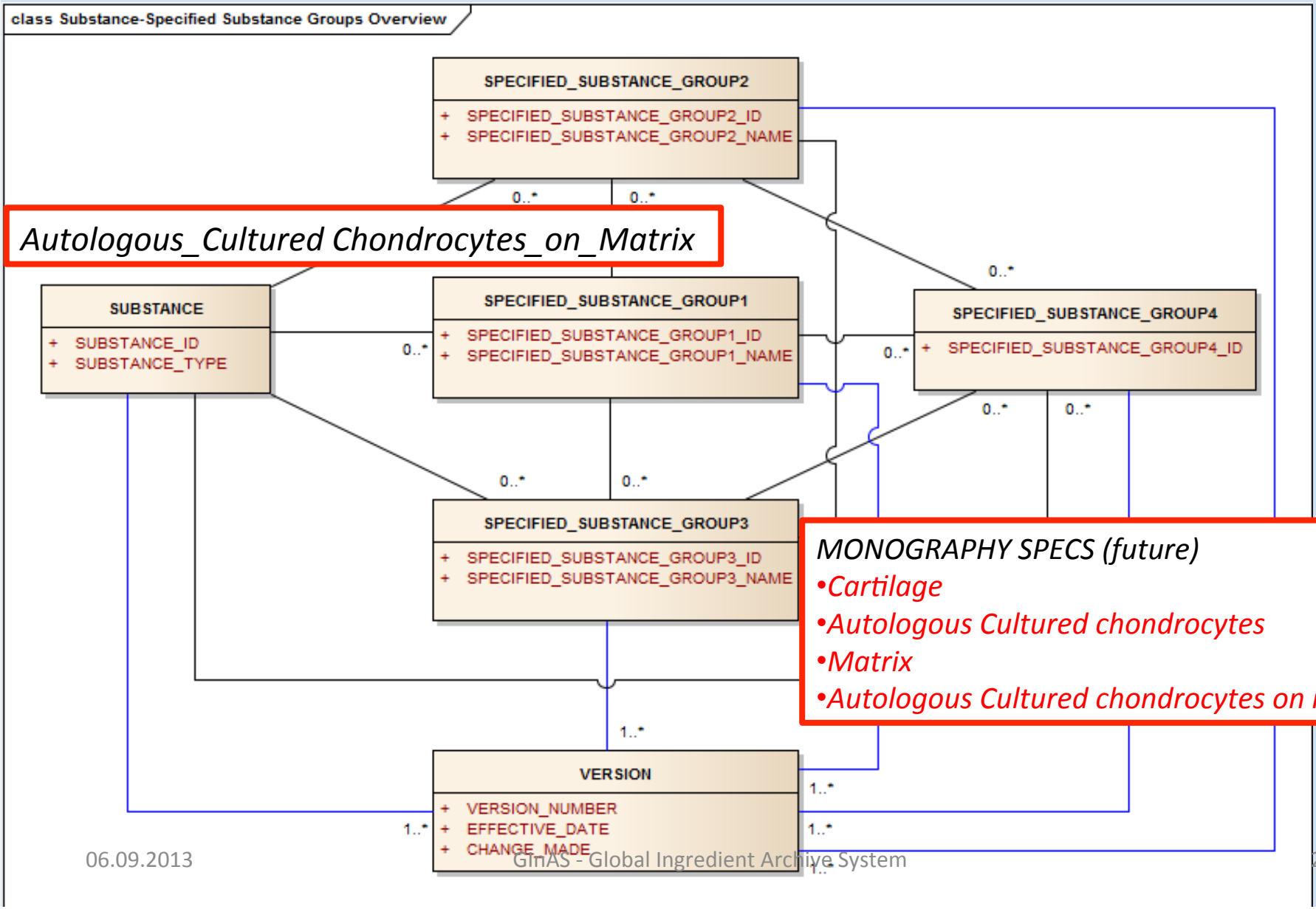


Part: Cartilage
Part_location: knee

Material type: Cultured cells
Fraction: Autologous_Cultured chondrocytes
Development stage: De-differentiated

Homo sapiens (Linnaeus)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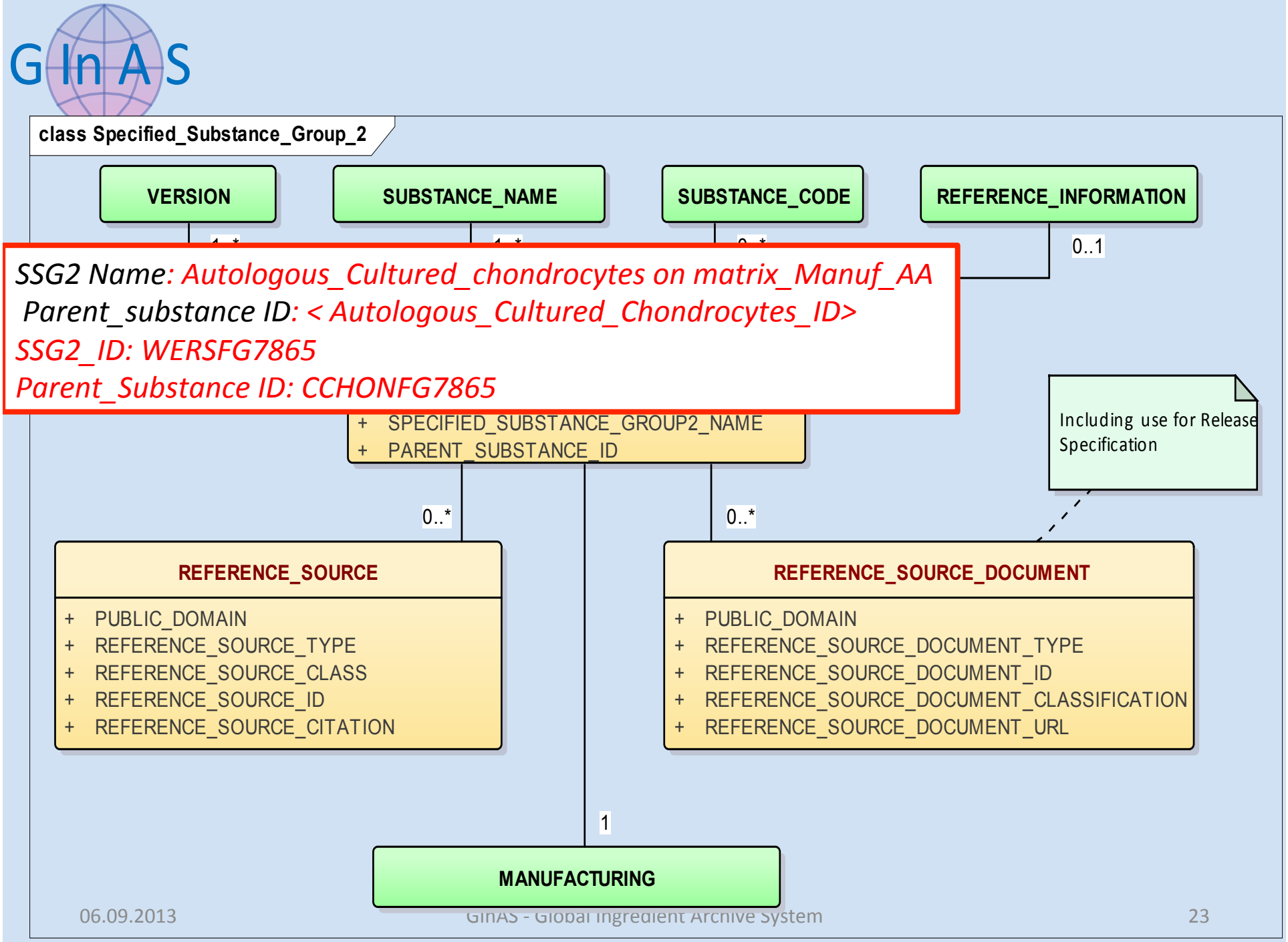
•Autologous Cultured chondrocytes
•Matrix
•Autologous Cultured chondrocytes on matrix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Including use for Release Specification
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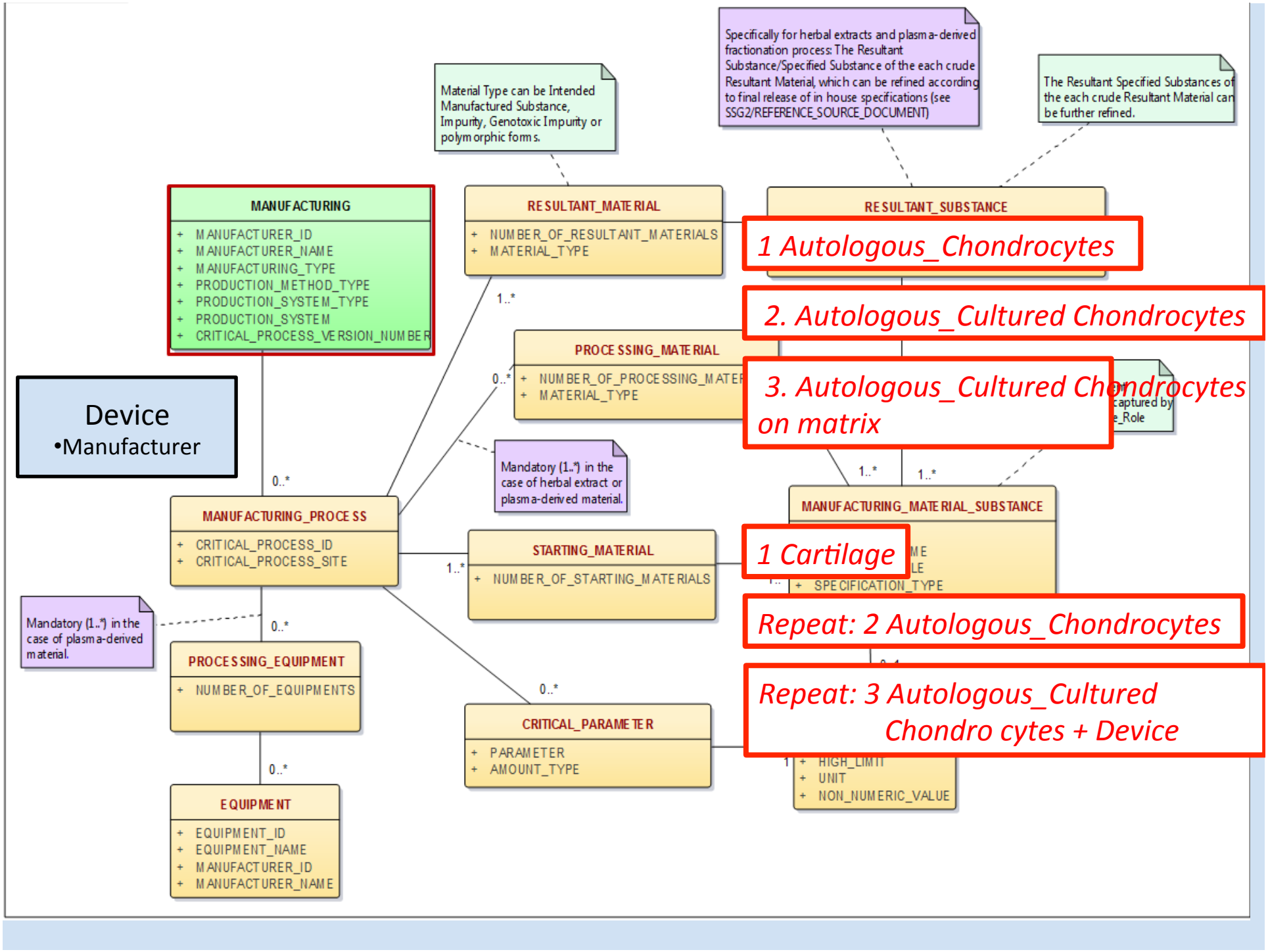
MANUFACTURING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MANUFACTURING_MATERIAL_SUBSTANCE
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+ HIGH_LIMIT
+ UNIT
+ NON_NUMERIC_VALUE
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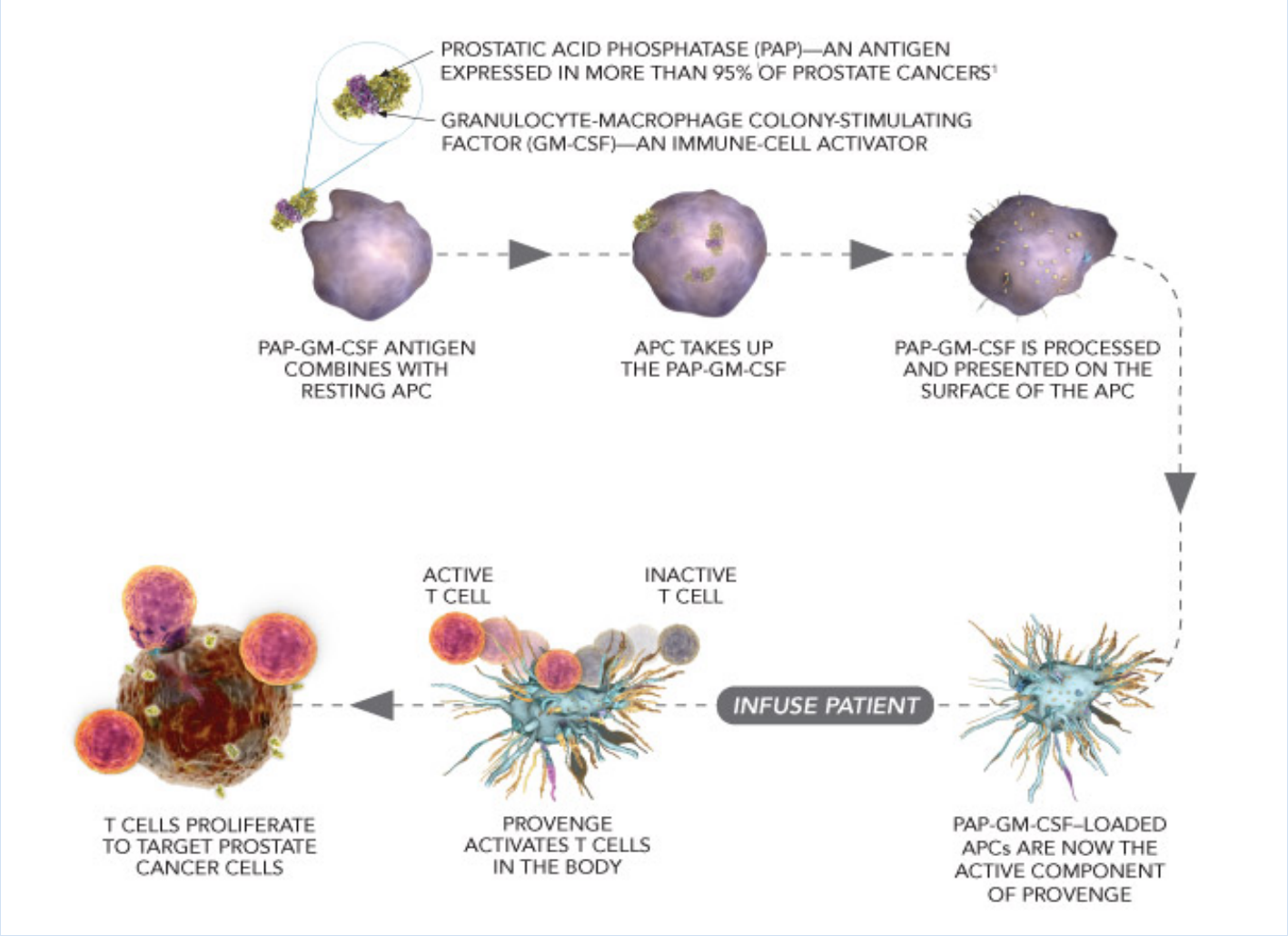
captured by
e_Role
1 Autologous_Chondrocytes
2. Autologous_Cultured Chondrocytes
3. Autologous_Cultured Chondrocytes on matrix
1 Cartilage
Repeat: 2 Autologous_Chondrocytes
Repeat: 3 Autologous_Cultured Chondro cytes + Device
0..*
1..*

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

- The active substance (Sipuleucel-T) consists of autologous PBMCs activated ex vivo with recombinant fusion protein PA2024.
- Fusion protein composed of prostatic acid phosphatase (PAP) fused to GM-CSF (granulocyte-macrophage colony-stimulating factor).
- PAP uptake into APCs is followed by intracellular processing and presentation of PAP-derived peptides on Major Histocompatibility Complex (MHC) molecules to T cells.

- **PBMCs include: T cells, B cells, Natural Killer (NK) cells, and APCs (including monocytes and dendritic cells (DCs)).**
- **Activated APCs are contained within the CD54+ cell population, which includes monocyte-derived APCs and DCs.**
- **DCs (the most effective APCs) represent a small percentage of all cells.**
- **CD54 expression is used to assess product potency of Provenge by measuring the number of CD54+ cells, and CD54 upregulation during ex vivo culture.**

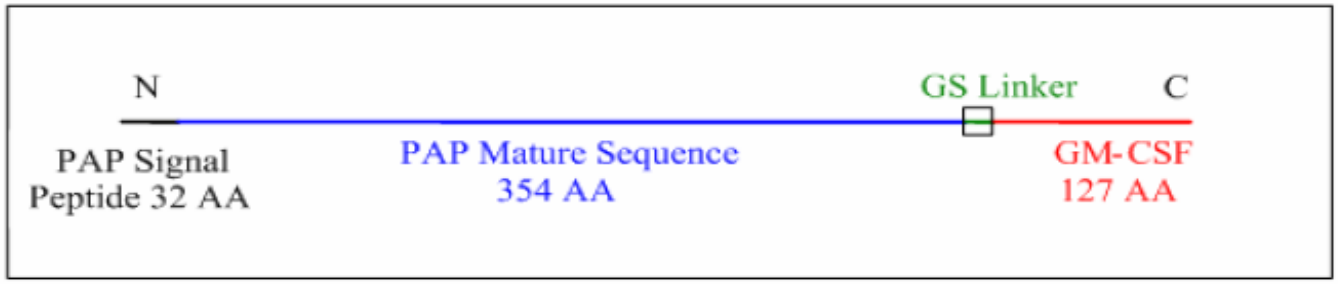
Cellular immunotherapy product: Provenge
Fusion Protein

- The recombinant fusion glycoprotein is a starting material used in the manufacture of sipuleucel-T consisting of a prostatic acid phosphatase (354 AA) linked to granulocyte-macrophage colony-stimulating factor (127 AA) by a glycine-serine dipeptide.
- It has 5 potential N-glycosylation sites and 1 potential O-glycosylation site.
- The molecular mass of the PA2024 is appr. 132 kDa because it exists in solution as a dimer.

PA2024 consists of the following:

- **PAP signal peptide** - 32 amino acids, proteolytically removed during post-translational processing
- **PAP mature protein** - 354 amino acids with three potential N-glycosylation sites (two amino acid substitutions: valine to isoleucine at residue 264 and serine to arginine at residue 384)
- **Glycine/serine dipeptide synthetic linker**

Figure 1: Schematic of Precursor Form of PA2024 Fusion Protein



Cellular immunotherapy product: Provenge
Fusion Protein (*continued*)

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

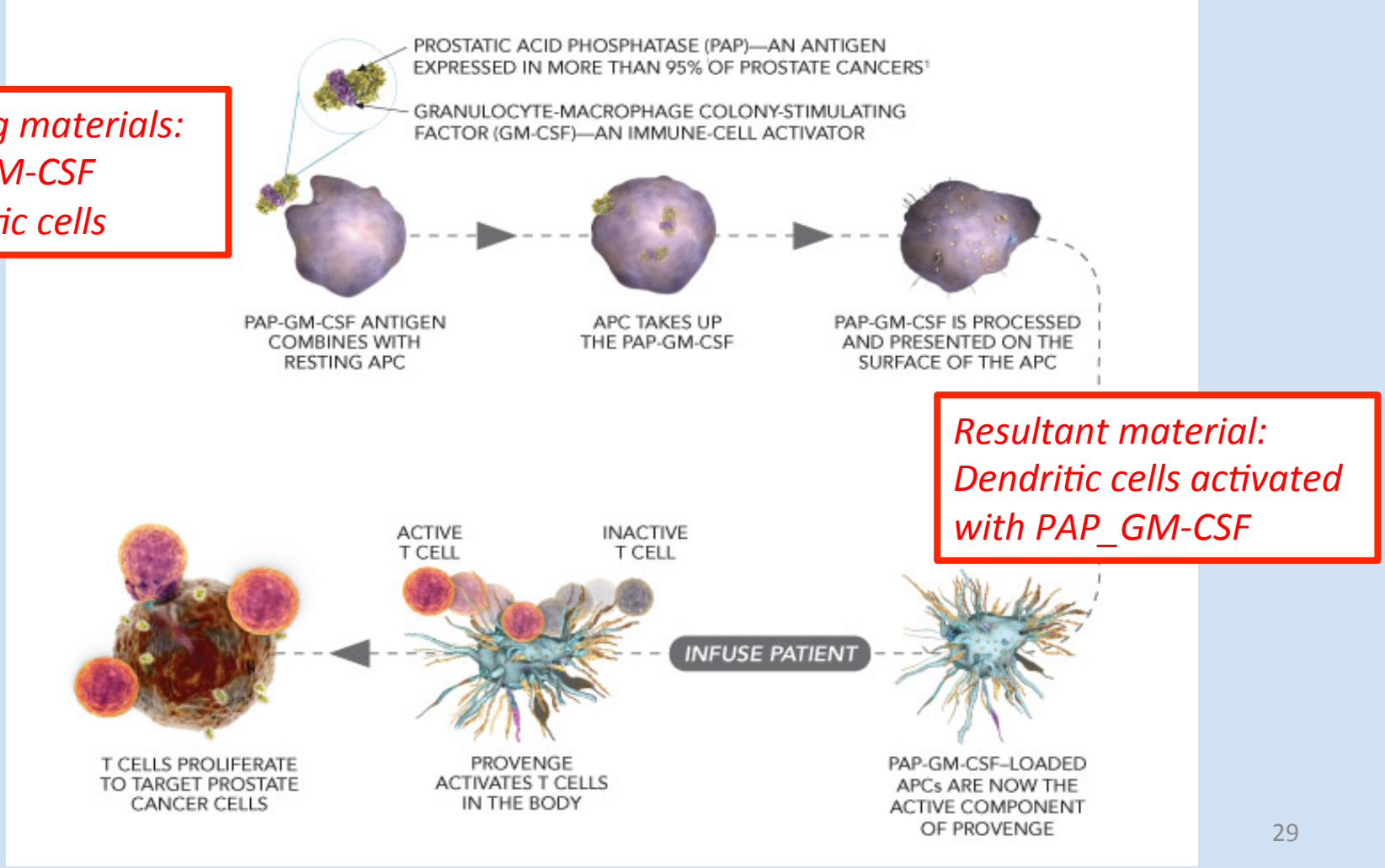
The mature PAP amino acid composition is presented

Biological activity of fusion protein has determined by measuring the bioactivity of GM-CSF using an in vitro TF-1 cell-proliferation based assay.

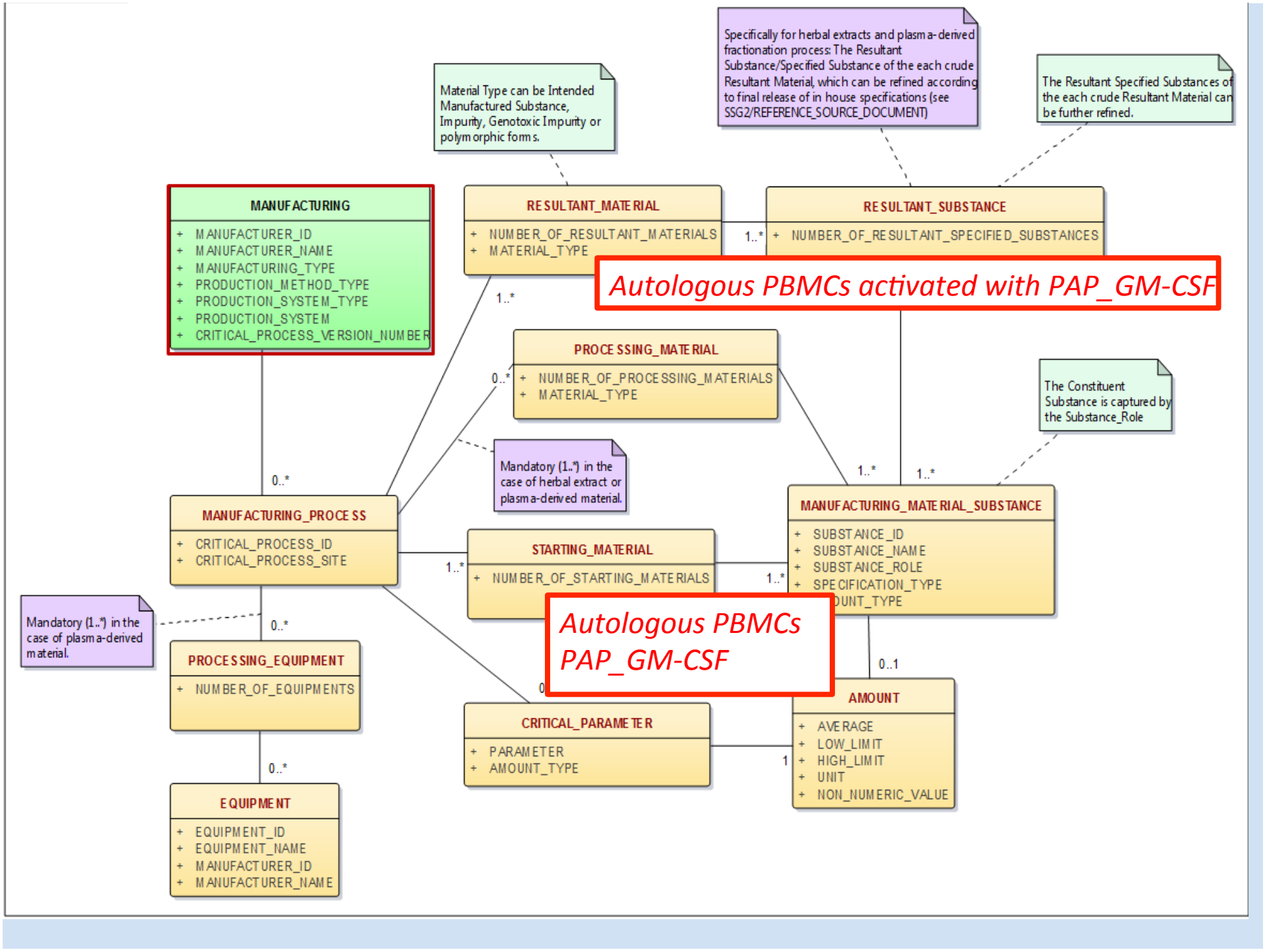
Advanced Therapy Medicinal Products
Cellular immunotherapy product: Provenge

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

Starting materials:
PAP_GM-CSF
Dendritic cells



Resultant material:
Dendritic cells activated with PAP_GM-CSF


Specifically for herbal extracts and plasma-derived fractionation process: The Resultant Substance/Specified Substance of the each crude Resultant Material, which can be refined according to final release of in house specifications (see SSG2/REFERENCE_SOURCE_DOCUMENT)
The Resultant Specified Substances of the each crude Resultant Material can be further refined.
Material Type can be Intended Manufactured Substance, Impurity, Genotoxic Impurity or polymorphic forms.
MANUFACTURING
+ MANUFACTURER_ID
+ MANUFACTURER_NAME
+ MANUFACTURING_TYPE
+ PRODUCTION_METHOD_TYPE
+ PRODUCTION_SYSTEM_TYPE
+ PRODUCTION_SYSTEM
+ CRITICAL_PROCESS_VERSION_NUMBER
RESULTANT_MATERIAL
+ NUMBER_OF_RESULTANT_MATERIALS
+ MATERIAL_TYPE
RESULTANT_SUBSTANCE
+ NUMBER_OF_RESULTANT_SPECIFIED_SUBSTANCES
Autologous PBMCs activated with PAP_GM-CSF
PROCESSING_MATERIAL
+ NUMBER_OF_PROCESSING_MATERIALS
+ MATERIAL_TYPE
The Constituent Substance is captured by the Substance_Role
Mandatory (1..*) in the case of herbal extract or plasma-derived material.
MANUFACTURING_PROCESS
+ CRITICAL_PROCESS_ID
+ CRITICAL_PROCESS_SITE
STARTING_MATERIAL
+ NUMBER_OF_STARTING_MATERIALS
MANUFACTURING_MATERIAL_SUBSTANCE
+ SUBSTANCE_ID
+ SUBSTANCE_NAME
+ SUBSTANCE_ROLE
+ SPECIFICATION_TYPE
Mandatory (1..*) in the case of plasma-derived material.
Autologous PBMCs PAP_GM-CSF
PROCESSING_EQUIPMENT
+ NUMBER_OF_EQUIPMENTS
CRITICAL_PARAMETER
+ PARAMETER
+ AMOUNT_TYPE
AMOUNT
+ AVERAGE
+ LOW_LIMIT
+ HIGH_LIMIT
+ UNIT
+ NON_NUMERIC_VALUE
EQUIPMENT
+ EQUIPMENT_ID
+ EQUIPMENT_NAME
+ MANUFACTURER_ID
+ MANUFACTURER_NAME

Conclusion and Challenges

- Some 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) still to be tackled

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