

Defining Advanced Therapies (ATMP)

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Washington, October 2017

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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.



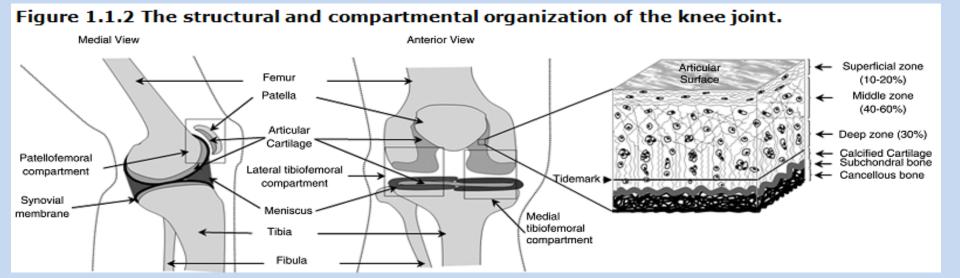
HUMAN CELL-BASED MEDICINAL PRODUCTS Cells are complex biological systems

- 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 <u>extra-corporally</u> <u>multiplied by cultivation</u>.
 - 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)



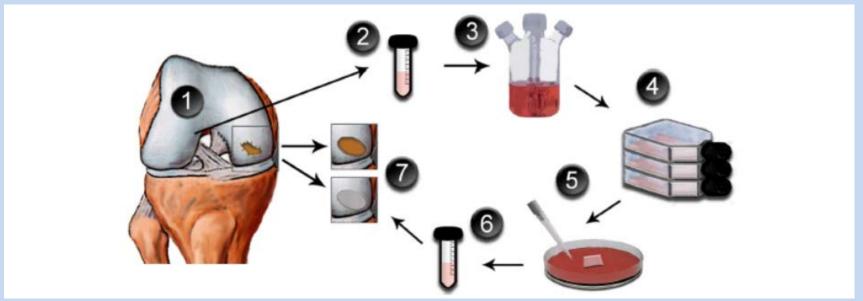


Advanced Therapy Medicinal Product:

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



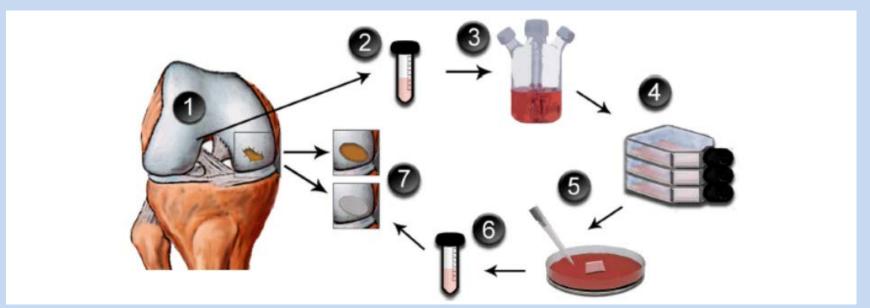
GINAS Advanced Manufa

CAdvanced 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

- <u>ChondroCelect</u>: Cellular expression patterns of genes relevant for cartilage and chondrocyte biology
- MACI: Aggrecan mRNA expression by real-time PCR.
- <u>Hyalograft C</u>: 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





A S 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*.

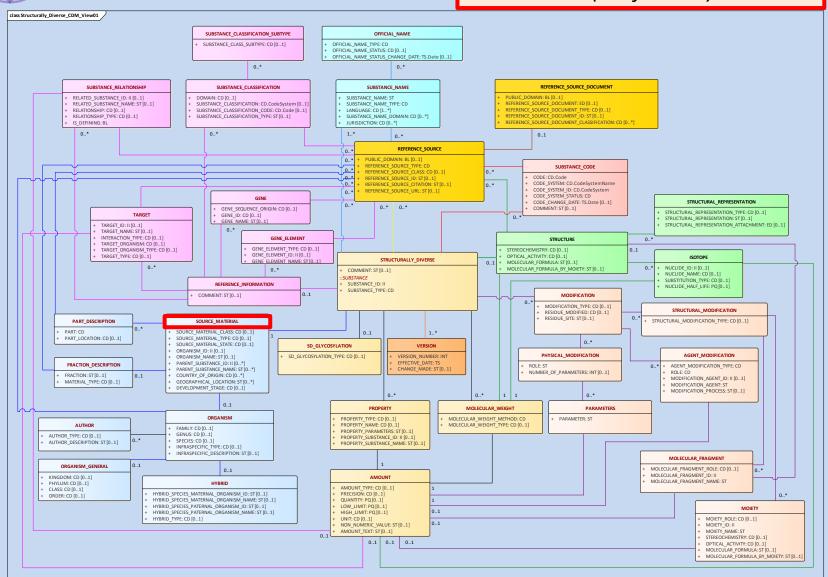
- Autologous chondrocytes (from cartilage biopsy) expanded on monolayer
- <u>Scaffold: non-woven pad composed of hyaluronic acid benzyl ester polymer</u>; class III
 Medical Device (CE marked)

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)

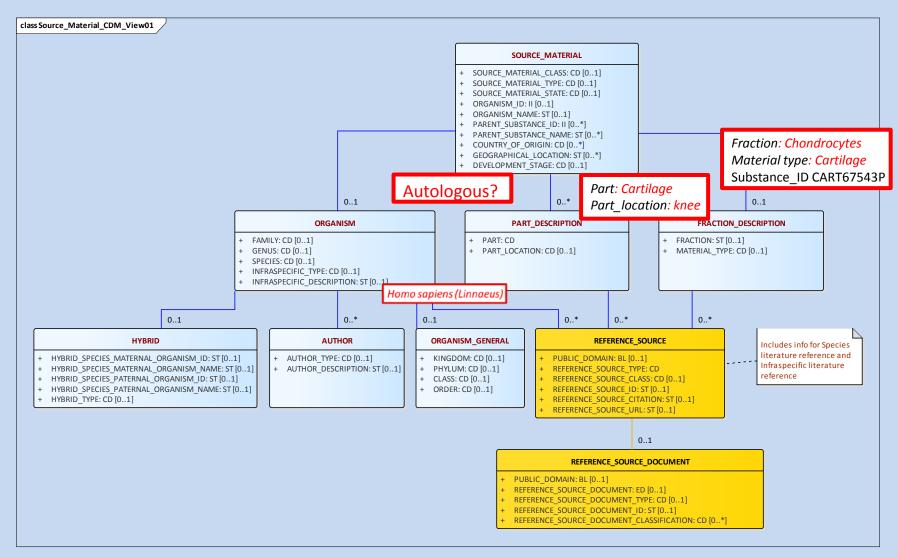


Autologous_Cultured chondrocytes CHON12345 (Artificial ID)





Description Source_Material



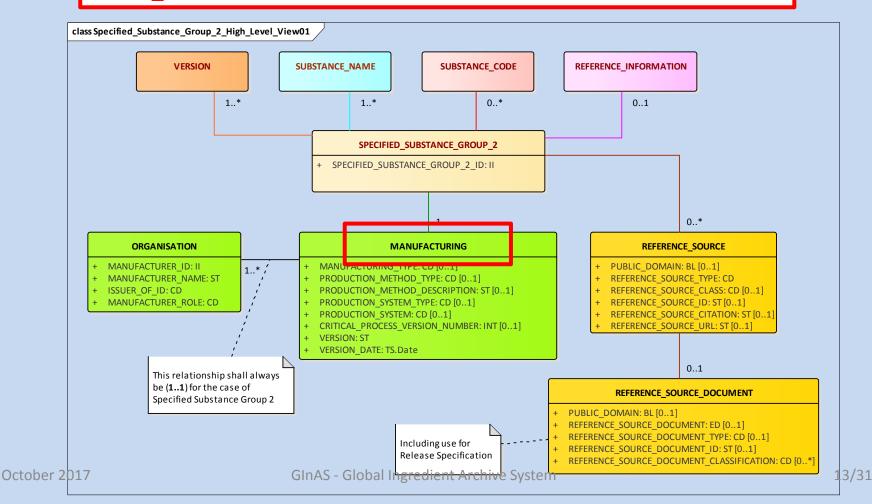


SSG2 Name: Autologous_Cultured_chondrocytes_Manuf_AA

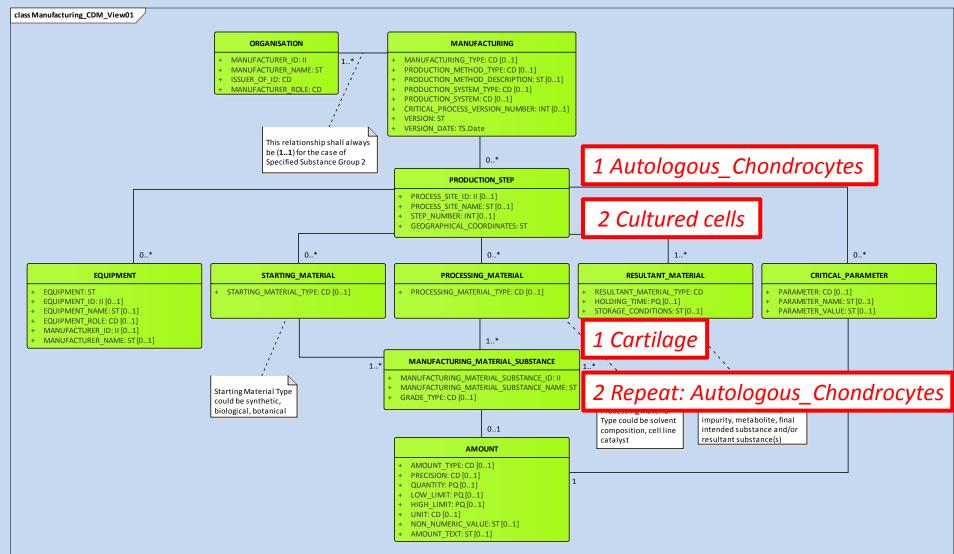
Parent_substance ID: < CARTILAGE_ID>

SSG2 ID: CCHONFG7865

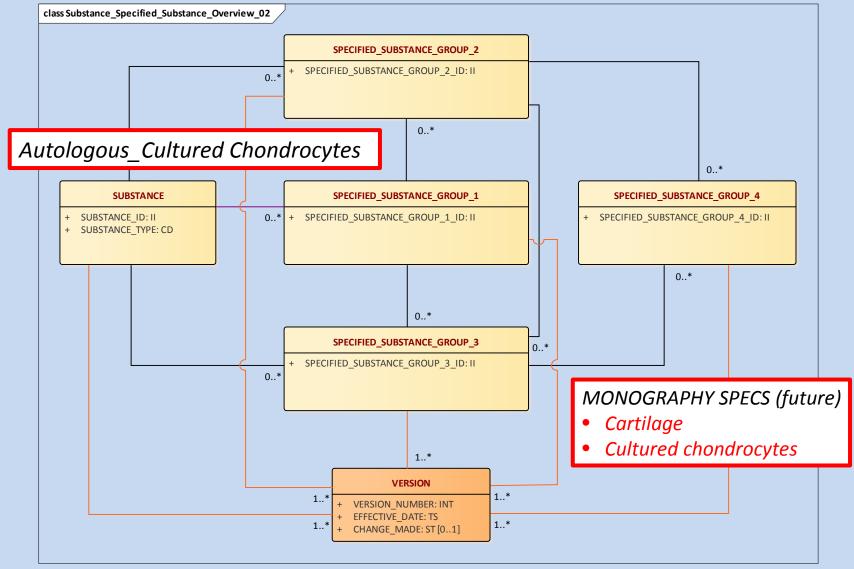
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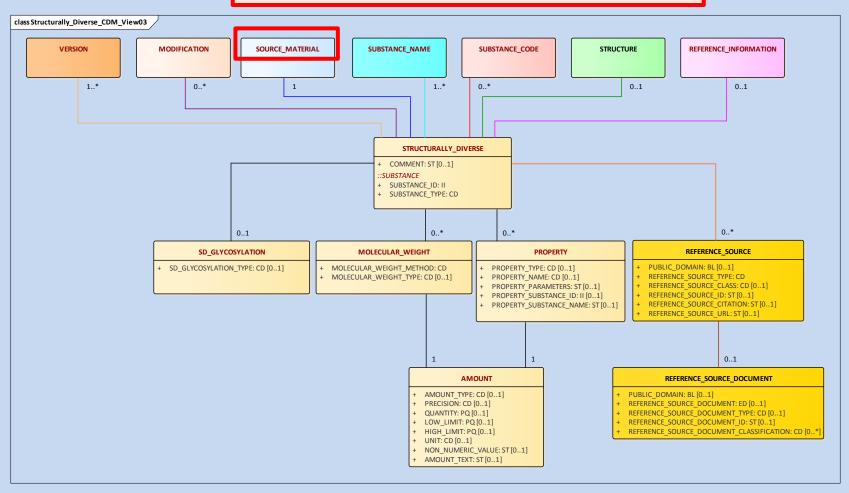






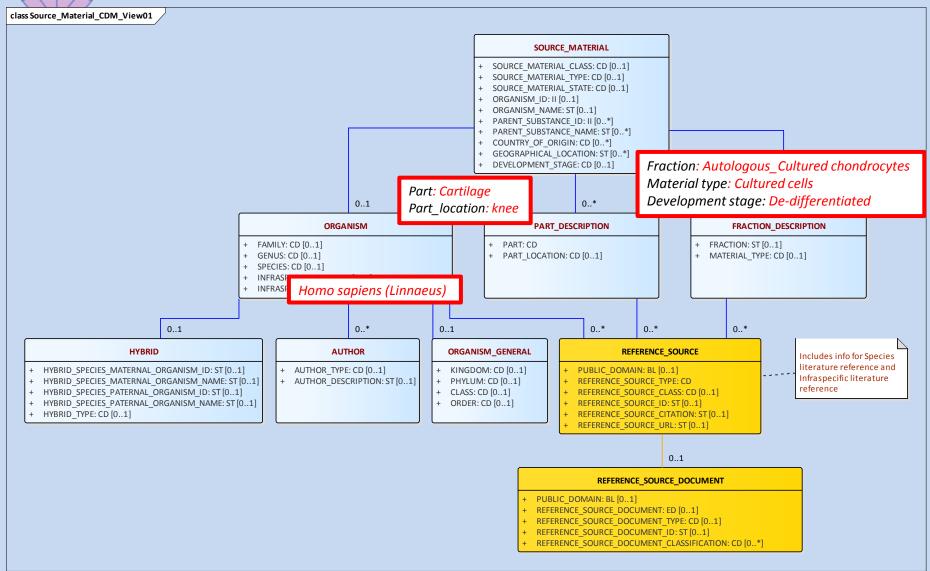


Autologous_Cultured chondrocytes on Matrix CHONM12345 (Artificial ID)

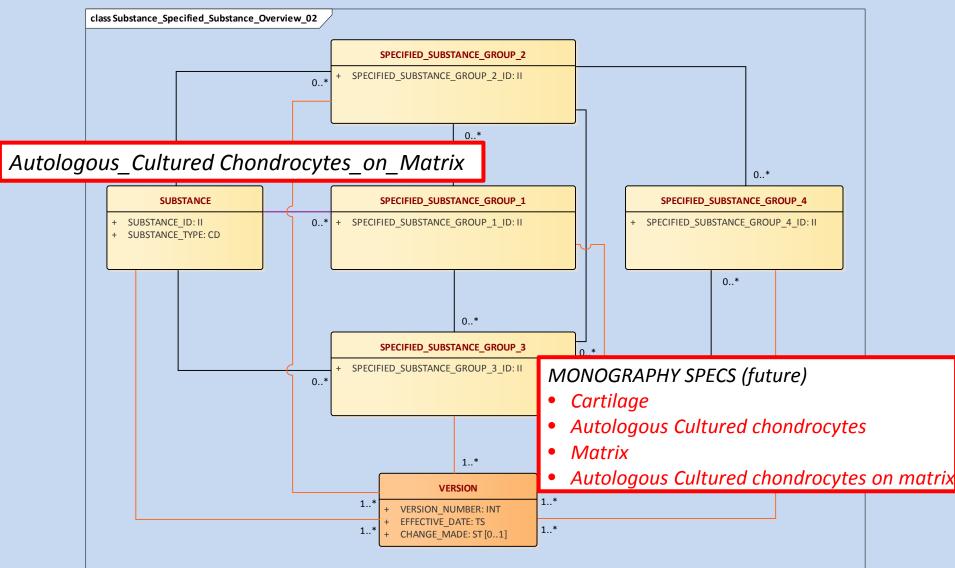




Description Source material







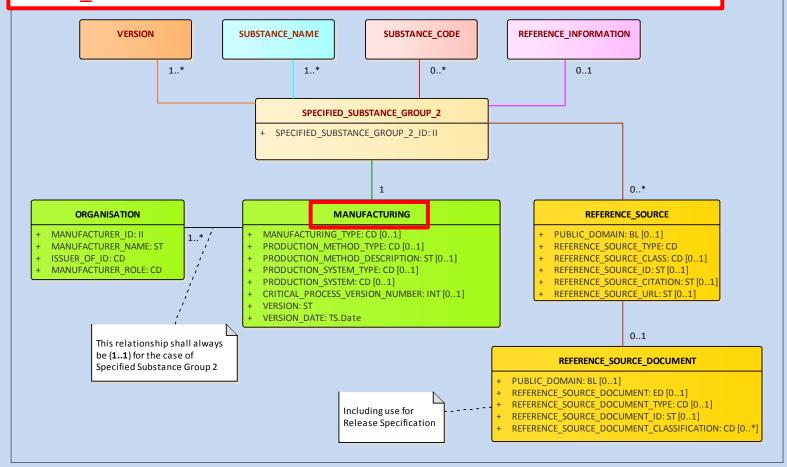


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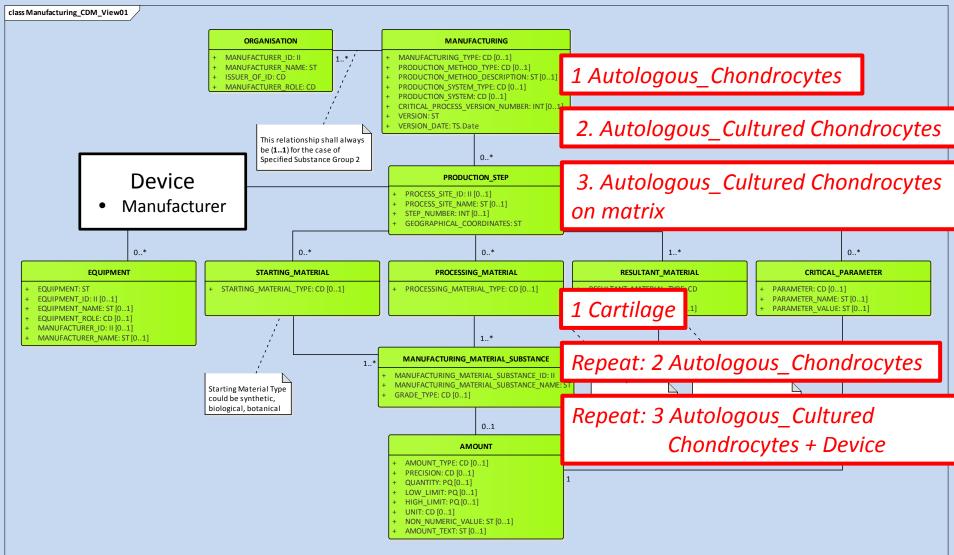
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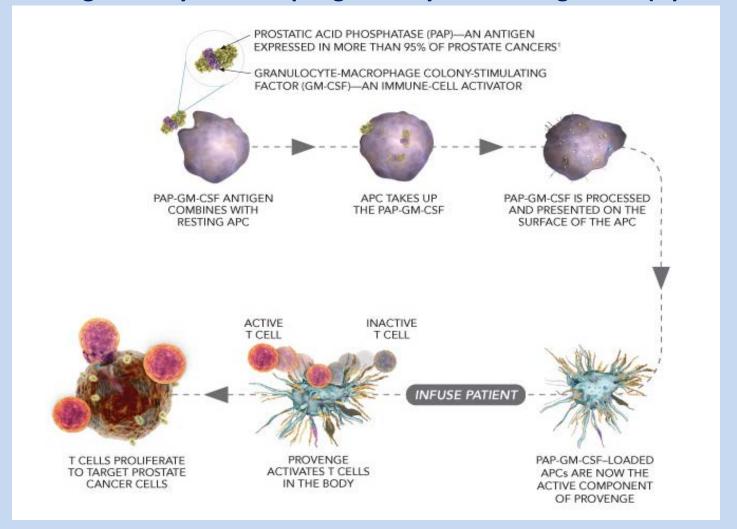






Advanced Therapy Medicinal Products Cellular immunotherapy product: Provenge

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).

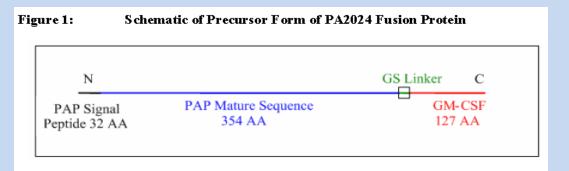
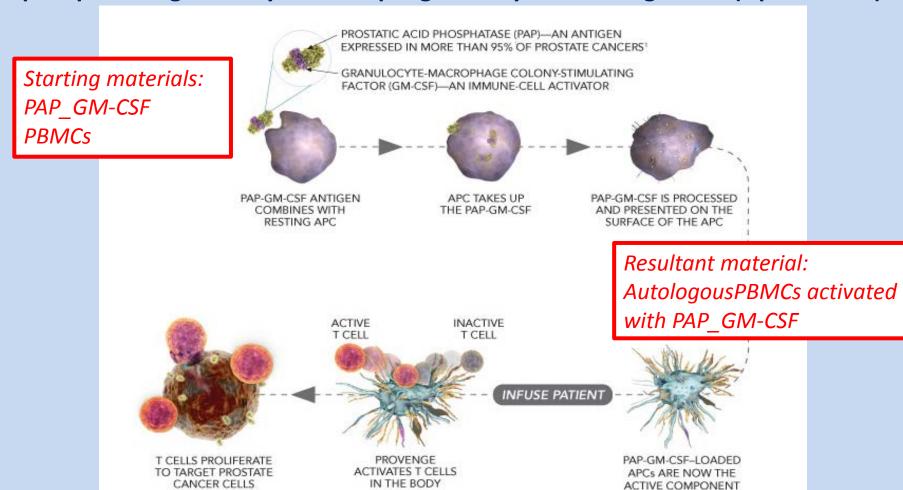


Figure 2: PA2024 Amino Acid Sequence (Precursor Protein) 1 MRAAPLLLAR AASLSLGFLF LLFFWLDRSV LAKELKFVTL VFRHGDRSPI 50 101 OVYIRSTDVD RTLMSAMTNL AALFPPEGVS IWNPILLWOP IPVHTVPLSE 150 151 DQLLYLPFRN CPRFQELESE TLKSEEFQKR LHPYKDFIAT LGKLSGLHGQ 200 201 DLFGIWSKVY DPLYCESVHN FTLPSWATED TMTKLRELSE LSLLSLYGIH 250 251 KQKEKSRLQG GVLINEILNH MKRATQIPSY KKLIMYSAHD TTVSGLQMAL 300 301 DVYNGLLPPY ASCHLTELYF EKGEYFVEMY YRNETQHEPY PLMLPGCSPS 350 351 CPLERFAELV GPVIPQDWST ECMTTNSHQG TEDRTDGSAP ARSPSPS WEHVNAIOEA RRLLNLSRDT AAEMNETVEV ISEMFDLOEP TCLOTRLELY 450 451 KQGLRGSLTK LKGPLTMMAS HYKQHCPPTP ETSCATQIIT FESFKENLKD 500 501 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 protein 127 amino acids



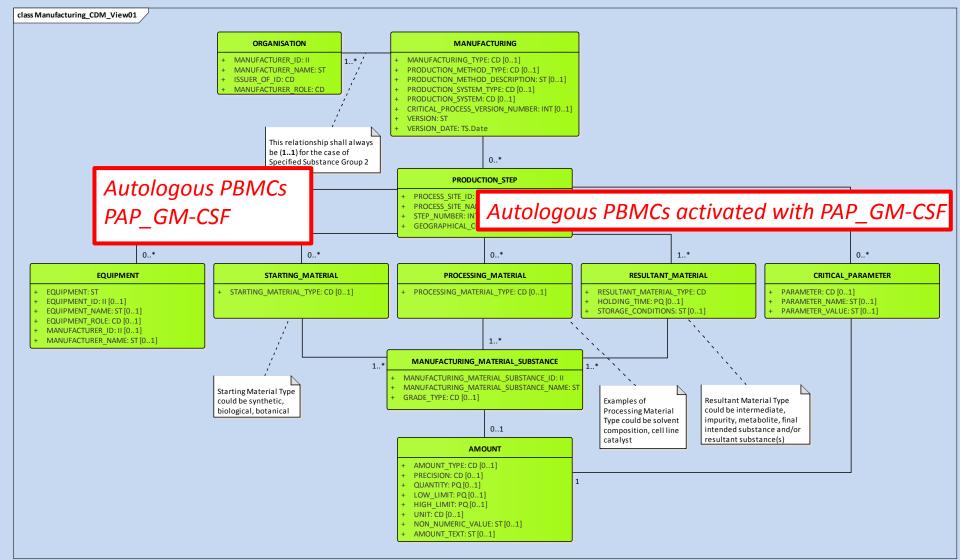
Advanced Therapy Medicinal Products Cellular immunotherapy product: Provenge

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



OF PROVENGE







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, included 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 throi
 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 lymphobla leukemia (ALL).

"The panel's unanimous recommendation in favor of CTL019 moves us closer to potentially

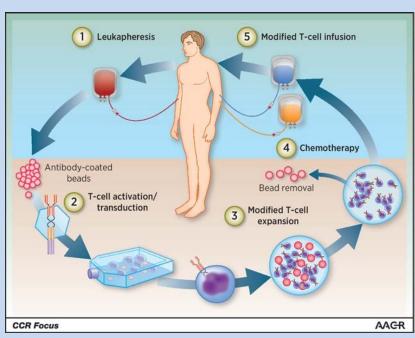
the first-ever commercially approved CAR-T cell therapy to patients in need," said Bruno Strigini, CEO, Novartis Oncology. "We're very proud to be expanding new frontiers in cancer treatment by advancing immunocellular therapy for children and young adults with r/r B-cell ALL and other critically ill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



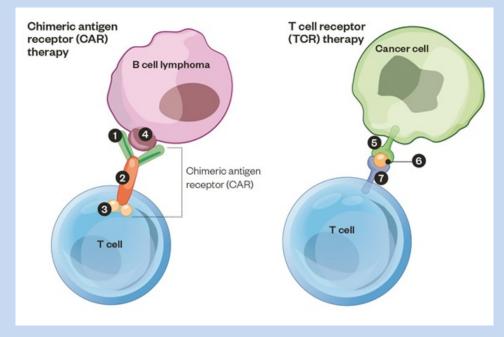
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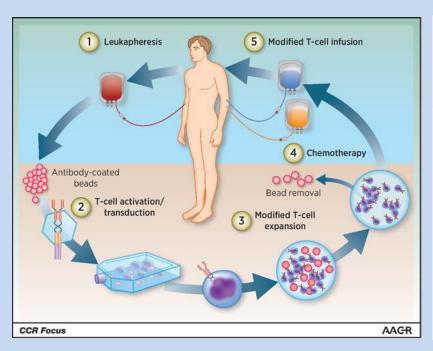
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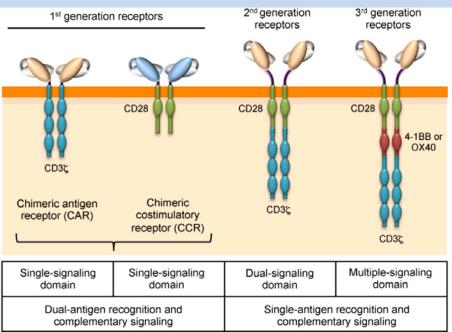


From: Maus & June (2016) Clin Cancer Res 22







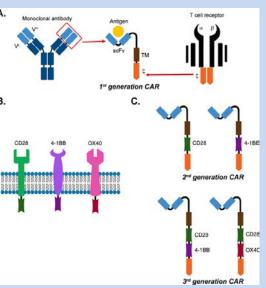


From Alonso-Camino et al. (2016), Biochem.Soc.Trans. 44



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

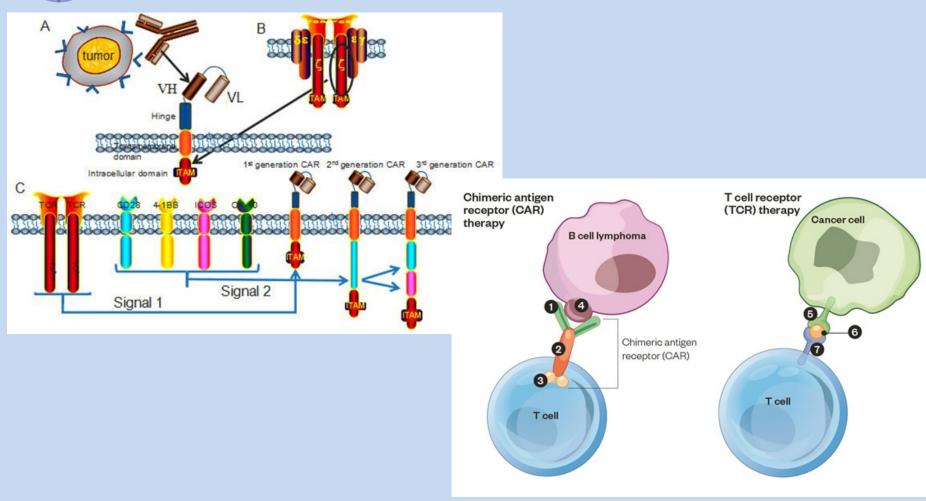


Thanks to: Panagiotis Telonis (EMA) Herman Diederik (EMA)



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ISO 11238 TOC

ISO 11238:2017(2)

ISO 11238:2017(2)

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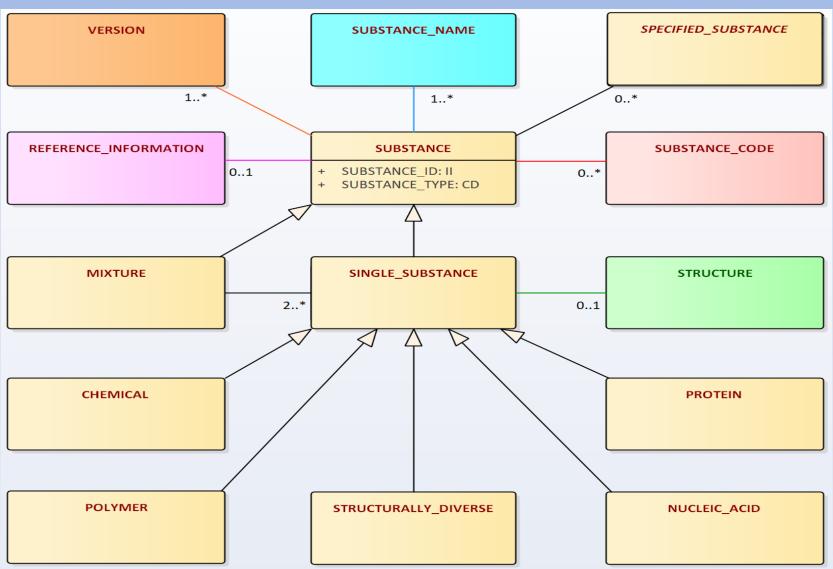
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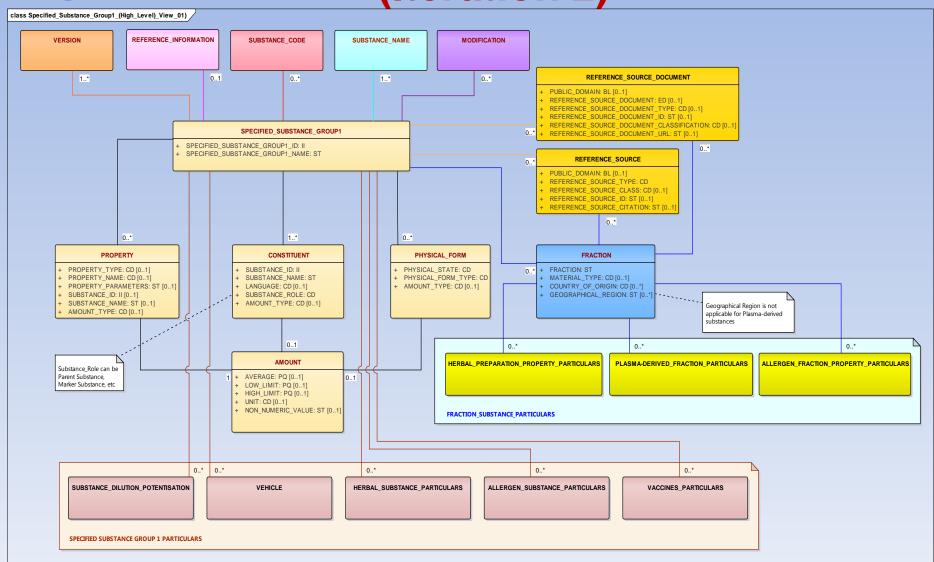


n A SISO 11238/19844 Substance (high-level)



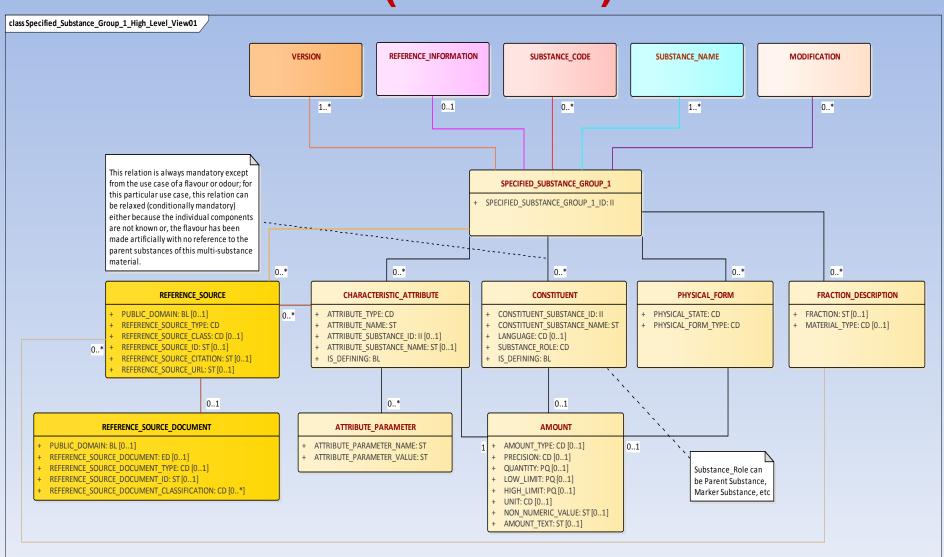


ISO 11238/19844 Specified Substance Group 1 (Iteration 2)



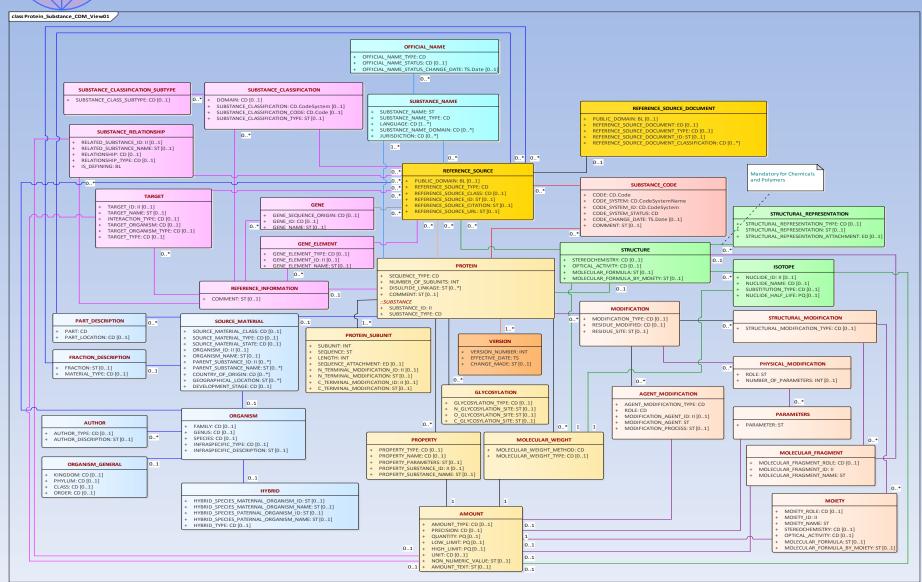


S ISO 11238/19844 Specified Substance Group 1 (Iteration 3)





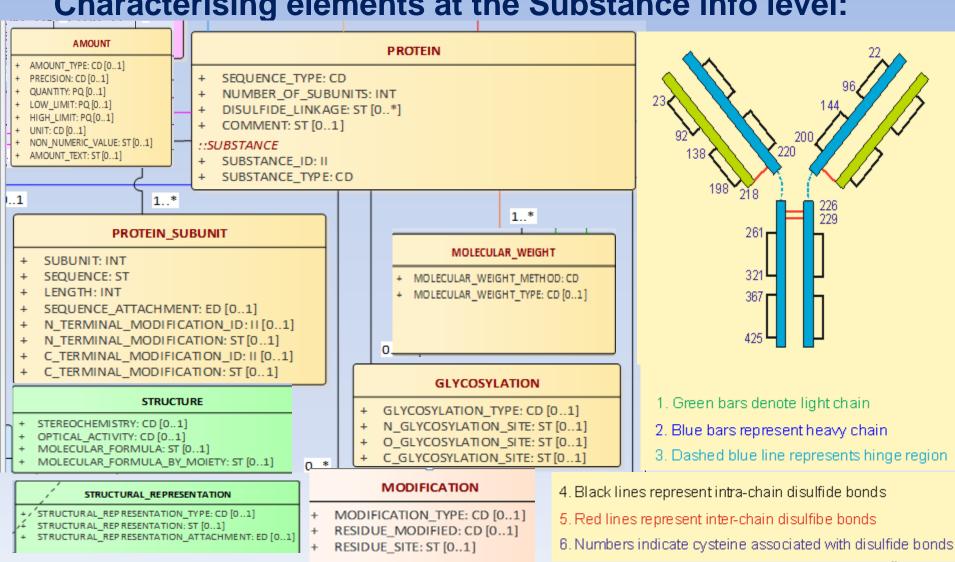
> Protein CMD, Substance Information level





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Characterising elements at the Substance info level:





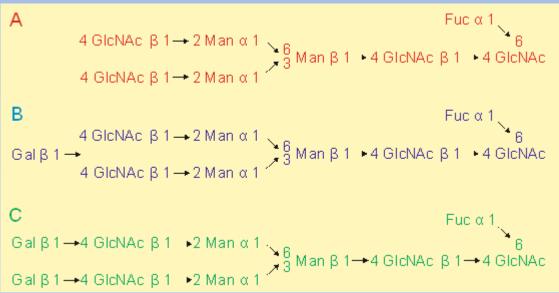
Sequence and Sequence Attachment of Protein Subunit

- 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

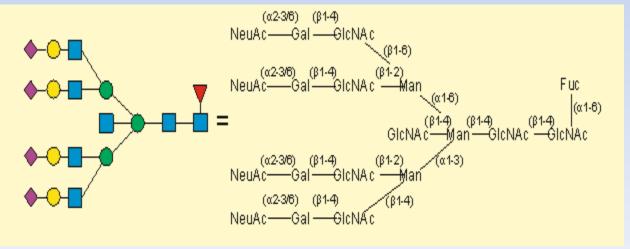
		1			1
		t Group	N-Glycosylation	1_297; 2_297	ST
Sequence Type	Complete		E	lement Group: Modification (N-Terminal modification	n)
Sequence attachment	Q IQLQQSGPEVVKPG	Subunit	Modification Type	Structural Modification	CD
	KPGQGLEWIGWIYPG	Sequen	Residue Modified	Glutamine (Q)	CD
	TAFMQLSSLTSEDTA\ VSAASTKGPSVFPLAP	•	Residue Site	1_1; 2-1	ST
	TVSWNSGALTSGVHT			Element Group: Structural Modification	
	TQTYICNVNHKPSNTI ELLGGPSVFLFPPKPK		Structural Modification Type	Amino Acid Substitution	CD
	EVKFNWYVDGVEVH	*		Element Group: Molecular Fragment	·
	HQDWLNGKEYKCKV: VYTLPPSRDELTKNO		Molecular Fragment Role	N-Terminal Pyroglu Formation	CD
	PENNYKTTPPVLDSD		Molecular Fragment ID	PYROG45321 (Artificial ID); [SZB8301W42 (UNII)]	II
	CSVMHEALHNHYTQK	SLSLSPG	Molecular Fragment	Pyroglutamic acid (pE)	ST
Element Group: Protein			Name		
TVSWNSGALTSGVHTFPAVLQS		Eleme	ent Group: Modification (Repeat) (C-Terminal Modific	cation)	
	TQTYICNVNHKPSNTK	•	Modification Type	Structural Modification	CD
	ELLGGPSVFLFPPKPKI		Residue Modified	Lysine (K)	CD
	EVKFNWYVDGVEVHN		Residue Site	1-447; 2-447	ST
	HQDWLNGKEYKCKVS VYTLPPSRDELTKNQV			Element Group: Structural Modification	·
	PENNYKTTPPVLDSDG			Amino Acid Removal	CD
	CSVMHEALHNHYTQKS	SLSLSPG	Туре		
Length 446			Element Group: Molecular Fragment		
			Molecular Fragment Role	C-Terminal Lysine removal	CD

MAB, Brentuximab Vedotin

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



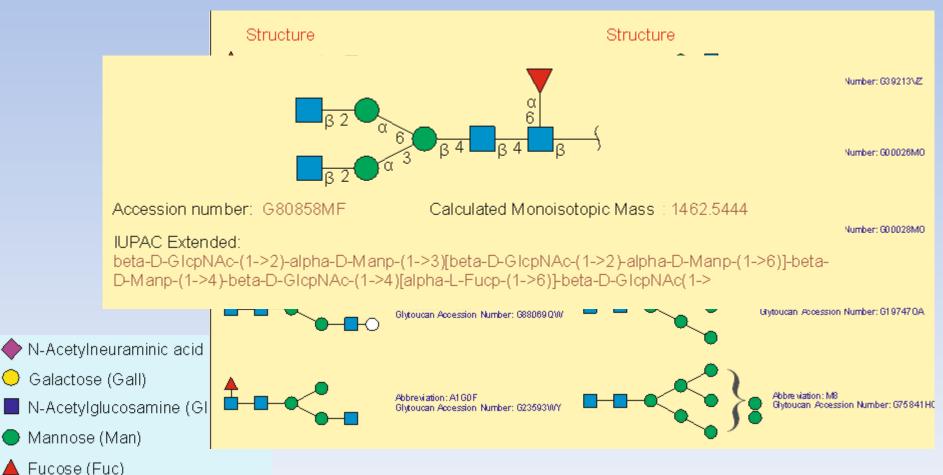
- N-Acetylneuraminic acid (NANA)
- 🔾 Galactose (Gall)
- N-Acetylglucosamine (GlcNAc)
- Mannose (Man)
- 🛕 Fucose (Fuc)



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)



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

