IDMP ISO-11238 Substance Standard

Chemical Substances, Polymer substance

Classification
EU-Regulatory aspects

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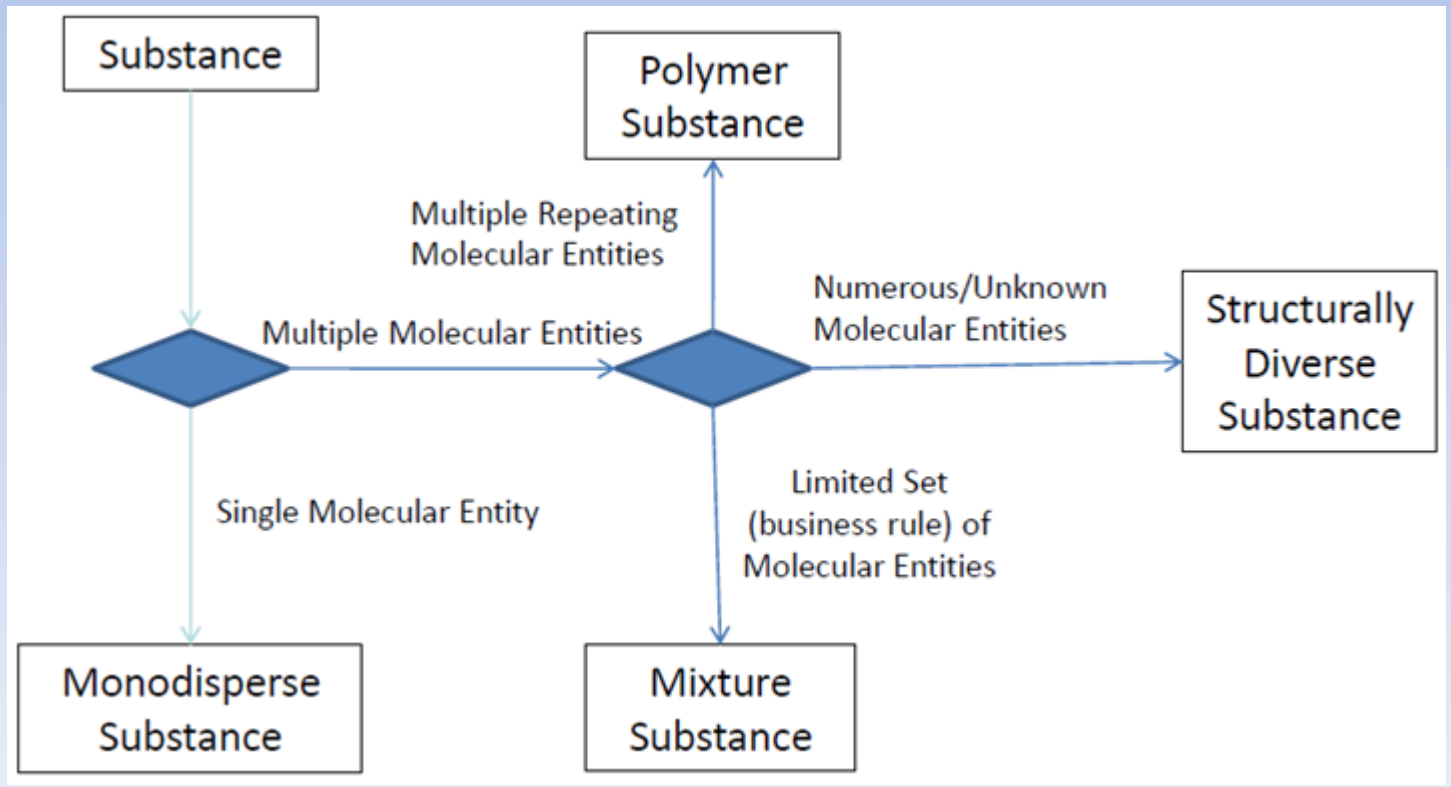
Outline of the Presentation

- **Definition Polymer substance;**
  Description according to the IDMP ISO-11238 Standard;
- Defining elements for a Polymer Substance;
- Primary and secundary captured data;
- **Approach of a Polymer in the GInAS Database;**
- **Structural Information Types;**
- **Example: Biodegradeable Polymers and Specifications for some PLGA-type Copolymers;**
- **Polymethacrylates described in the European Pharmacopoeia;**
- **Specifications of a Acrylate Copolymer pressure sensitive adhesive;**
- **Hypromellose types and specifications;**
- **Biopolymers, Structural Representation, Glycosidic Bond**
  Types of representation of Glucose structure, Disaccharide, Glycosidic bond and oligosaccharides in a conjugate vaccine;
- **Charaterization, Classification Glycoaminoglycans (GAGs)/ Structures and Biosynthesis.**

Definition Polymer substance
Description according to the IDMP ISO-11238 Standard

- **A polymer substance shall refer to material that is inherently heterogeneous and contain structural repeating unit.**
- Polymers shall be defined using a combination of the molecular structure of the structural repeating units, substituents that are attached to the structural repeating unit, molecular weight, and polydispersity of the polymer substance.



- Note: Monodisperse polymers will be classified as chemicals, proteins or nucleic acids.

Description according to the IDMP ISO-11238 Standard for Polymers, Natural and Synthetic

Many natural and synthetic polymers are mixtures of varying molecular mass or degree of polymerisation and will be defined using a combination of the molecular structure of:

- The structural repeating units (SRU);
- Substituents that are attached to the structural repeating unit, molecular weight, and polydispersity of the polymer substance;
- Monomers used to synthesize synthetic polymers or copolymers;
- The source material for naturally derived polymers, polymeric end groups, and physical or biological properties shall also be captured when known and needed to distinguish material.
- Polymers shall be defined to the level of specificity needed to distinguish materials and broad polymeric definitions shall be disfavored.

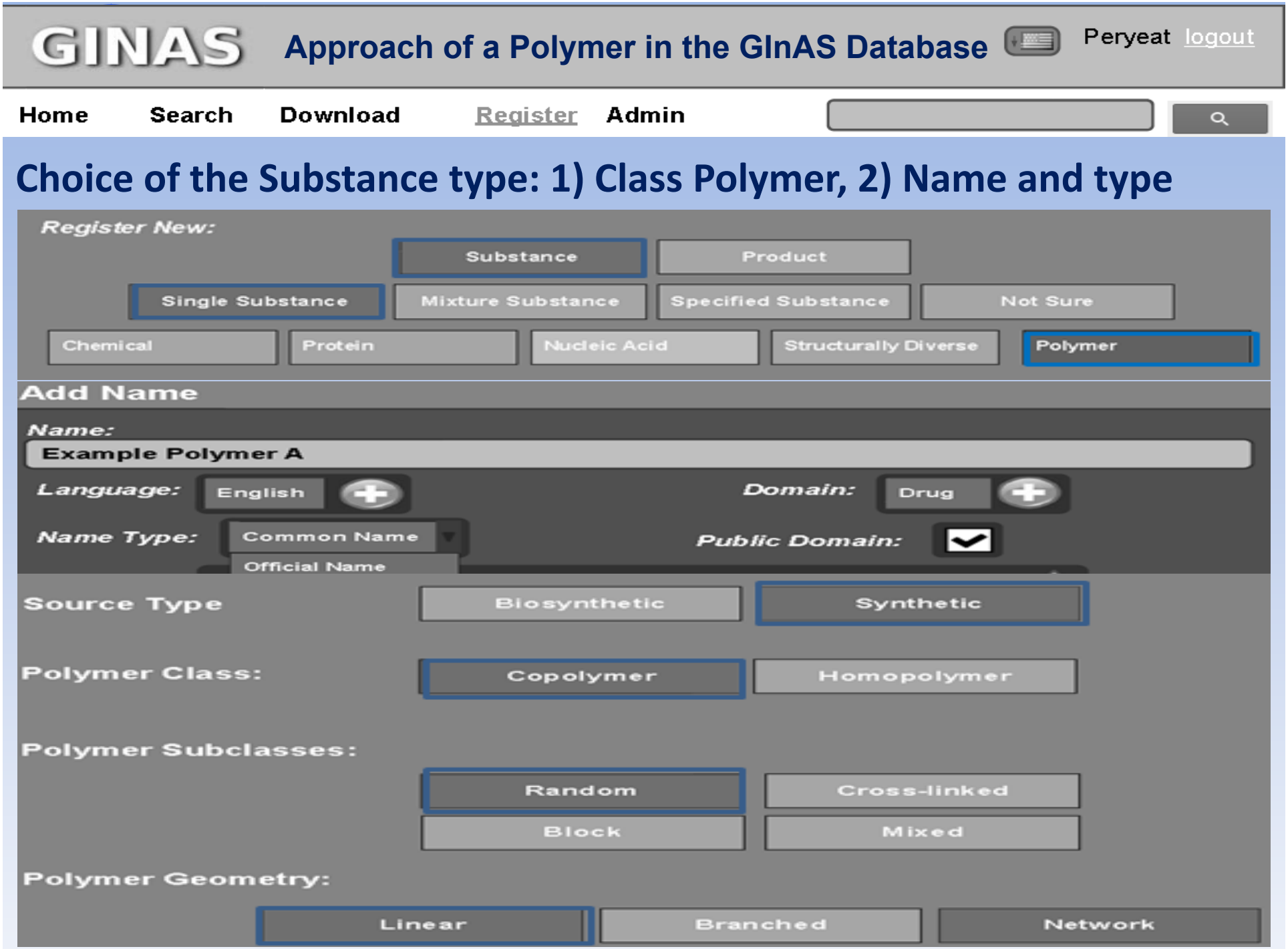
Primary and Secondary Captured Data

Primary Captured Data

- Reference Information:
  - Names
  - Documents
- Monomers
- Fragments
  (Main defining elements):
  - ***Structural Repeat Units (SRU)***
  - ***End groups and moieties with attachment locations and amounts***
  becomes the most informative data on the actual polymer
- Moleculair Weight (Mw):
  Weight Average (Mw); Number Average (Mn); ***Polydispersity P = Mw/ Mn***
  in which Number average Mol. Mass: $\mathbf{M_n} = \sum_i N_i M_i / \sum_l N_i$;
  and *Weight average Mol. Mass:*
  $$\mathbf{M_w} = \sum_i N_i M^2_i / \sum_i N_i M_i$$
  measured by GPC, *size exclusion*
- Viscosity
- Source material

Secondary Captured Data

- Initiators
- Residual monomer amounts limits
- Solvents
- Other relevant properties
  - Appearance; Solubility
  - Hydroxyl value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Choice of the Substance type: 1) Class Polymer, 2) Name and type
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Mixture Substance
Specified Substance
Not Sure
Chemical
Protein
Nucleic Acid
Structurally Diverse
Polymer
Add Name
Name:
Example Polymer A
Language:
English
Domain:
Drug
Name Type:
Common Name
Official Name
Public Domain:
Source Type
Biosynthetic
Synthetic
Polymer Class:
Copolymer
Homopolymer
Polymer Subclasses:
Random
Cross-linked
Block
Mixed
Polymer Geometry:
Linear
Branched
Network

GINAS **Approach of a Polymer in the GInAS Database** Peryeat logout

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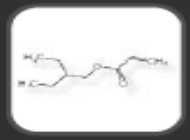
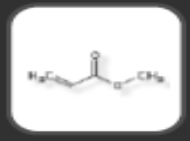
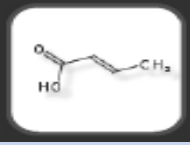
Description of Monomers and Structural Representation, Mol. Weight

Monomer Table **Amount Type:** Weight Percent

	2-ETHYLBUTYL ACRYLATE	Choose	62	0	0	%
	METHYL ACRYLATE	Choose	32	0	0	%
	CROTONIC ACID	Choose	6	0	0	%

Structural Units: **Degree of Polymerization**

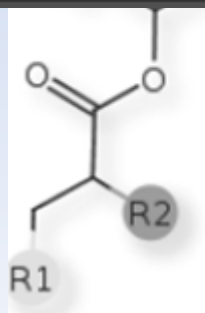
A SRU Connectivity 4 3 5

Also for Unit B/C

Allowed Connections

R1 R2

R2 R1

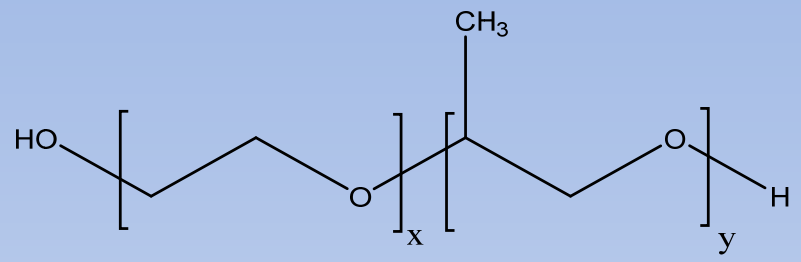


Add Property

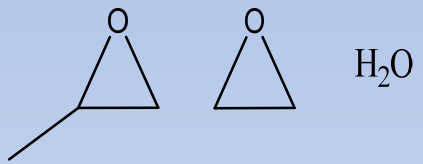
Property: Molecular Weight (NA)

Value: *Avg:* 480 *Low:* 380 *High:* 600 kDa

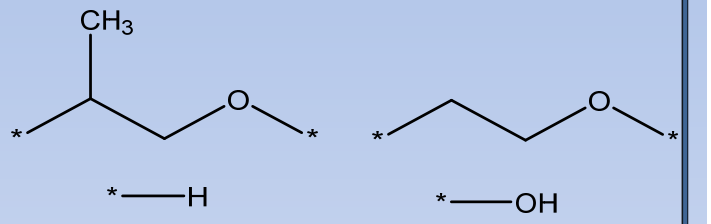
Structural Information Types



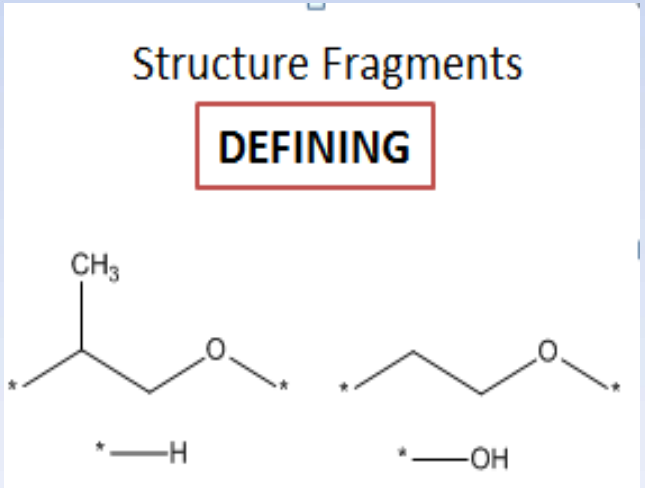
Conceptual Depiction Polymer



Polymer Starting Materials



Structure Polymer Fragments

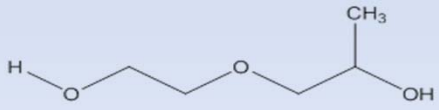


Additional Indexing Type:

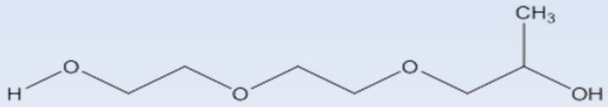
Structure Enumeration:

Enumeration List used for INDEXING

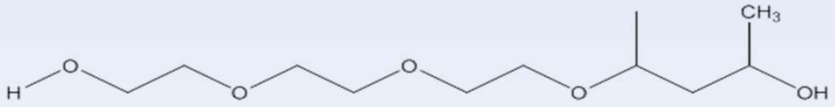
(1)



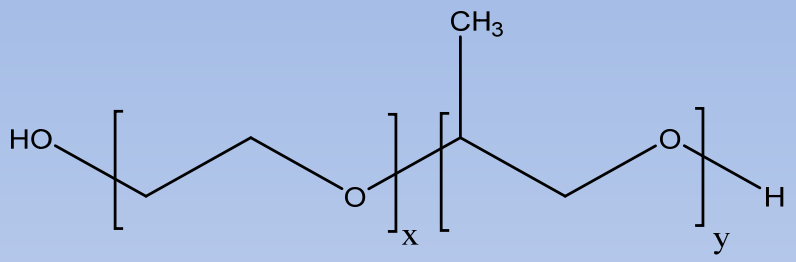
(2)



(3)

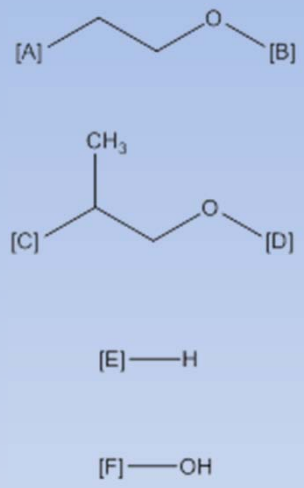


Structural Information Types, variable connectivity of structural units



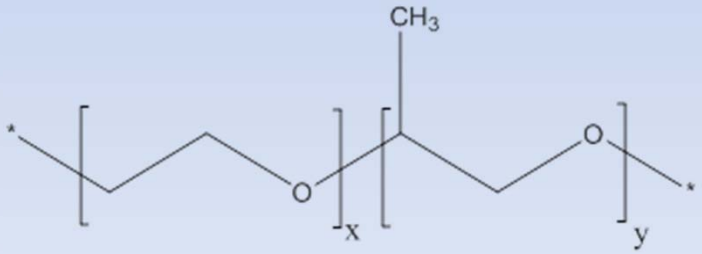
This Block Co-polymer Configuration

Is systematically captured as systematic fragments with:

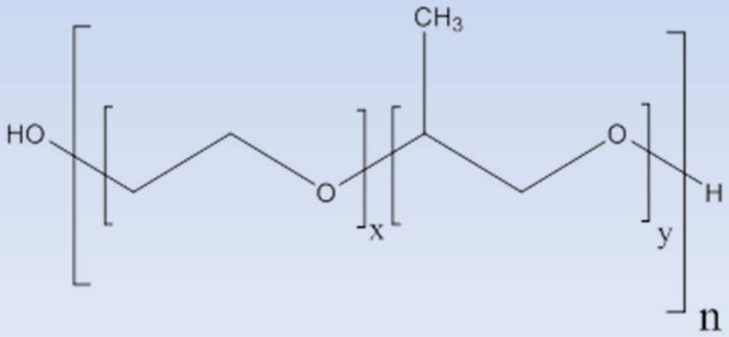


Allowed Connections:

[A] – [B]; (R1 – R2)
[A] – [F]; (R1 – R6)
[B] – [C]; (R2 – R3)
[C] – [D]; (R3 – R4)
[D] – [E]; (R4 – R5)



Fragment	Count Per Block	Block Count
x	3 to 5	4 to 5
Y	4 to 8	4 to 5



Advantages: 1) Straight forward presentation
2) Captures summary statistics that may be necessary to distinguish certain polymers ***e.g.***

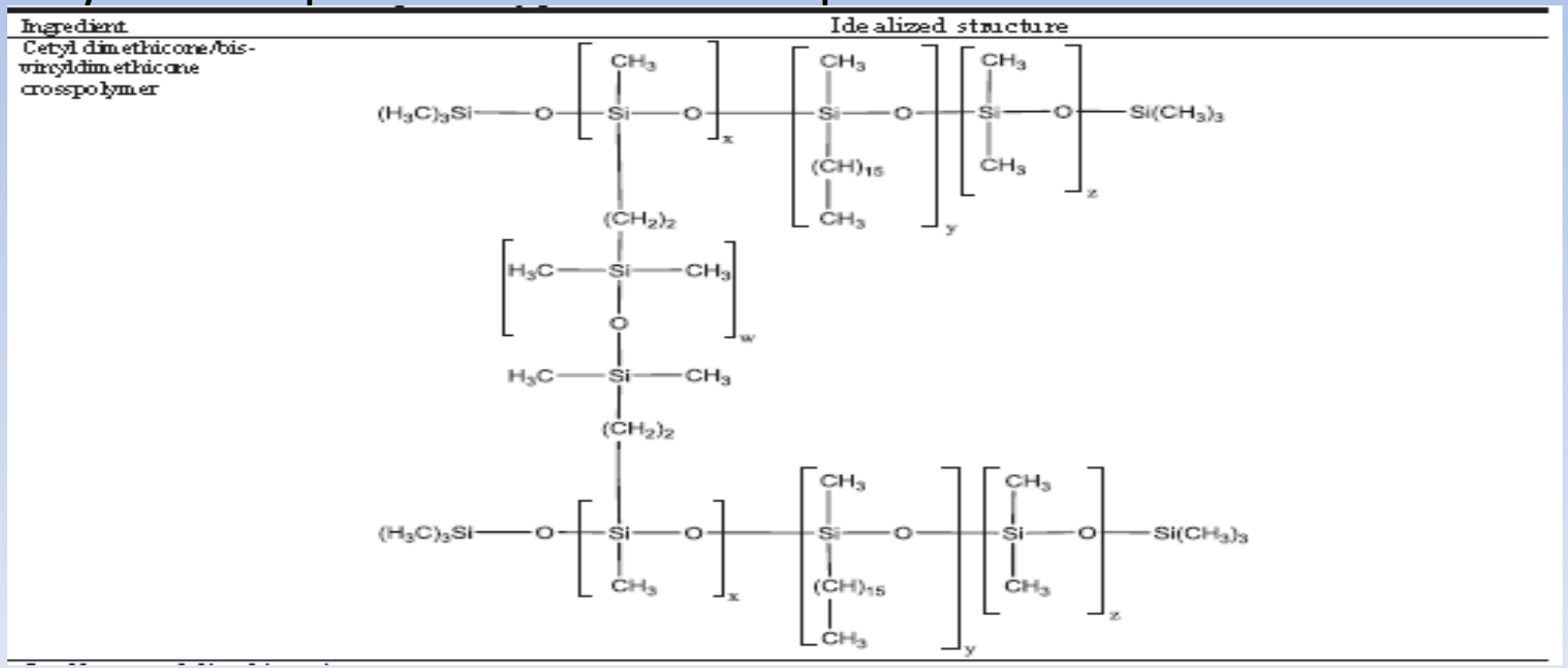
Structural Information Types, variable connectivity of structural units, *e.g.:*

Name: Cetyl Dimethicone/ Bis-Vinyl Dimethicone Crosspolymer

Reference: http://www.cir-safety.org/sites/default/files/Dimeth092012rep.pdf

Note: As noted in the source, the variability is not easy to completely characterize.

Any structural representation is an "idealized" representation.

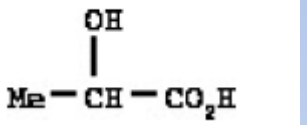


Dimethicone crosspolymers function in cosmetics as absorbents, bulking agents, film formers, hair conditioning agents, skin-conditioning agents-emollient, slip modifiers, surface modifiers, and viscosity increasing agents-nonaqueous. The **62** dimethicone crosspolymer ingredients in this report are silicone elastomers comprised of dimethicone copolymers that are crosslinked with a bi-functional agent.

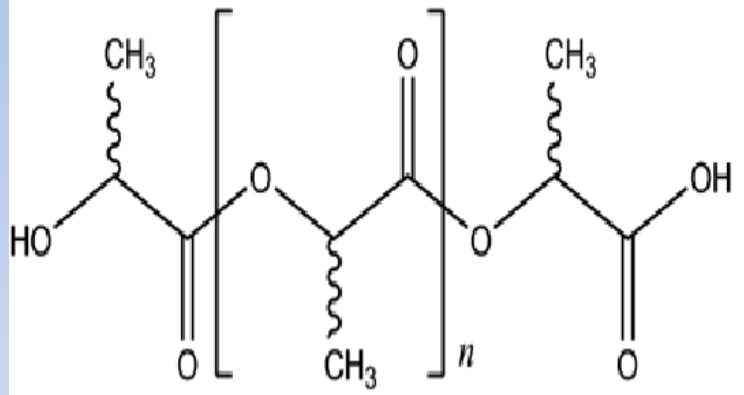
Example: Biodegradeable Polymers for Sutures, Medical Devices, Drug Delivery Systems and Tissue Engineering; Poly(DL-Lactic acid); Poly(DL-Lactide)[PLA], Poly(Glycolide)[PGA], Poly(DL-Lactide-co-Glycolide) [PLGA]

1) **Poly(DL-Lactic acid)**; **Propanoic acid, 2-hydroxy-, homopolymer; DL-lactic acid homopolymer; Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] Cas no. 26100-51-6; Mol. Form.: $[C_3 H_6 O_3]_n$ Starting material:**

Structure Diagram

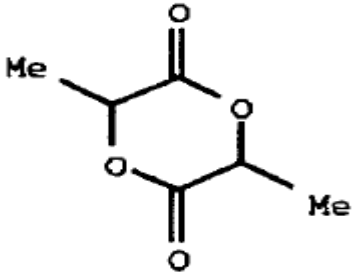


Structure



2) Poly(DL-Lactide); 3,6-dimethyl-1,4-dioxane-2,5 dione homopolymer ; DL-Dilactide homopolymer; Cas no. 26680-10-4; Mol. Form.: $[C_6 H_8 O_4]_n$; Starting material:

Structure Diagram



End group: Ester, hydroxyl or carboxylic acid.
Properties: Density 1.21 – 1.28 g/ $cm^{3.}$
Melting point: Amorphous 165° – 180° C.
Solubility: Soluble in Dichloromethane, THF, EtAc, Chloroform, Acetone, **Insoluble in water.**
Stability: Stable under dry conditions.
Biodegrades over a period of 10-15 month according to the molecular weight.

Example: Biodegradeable Polymers for Sutures, Poly(DL-Lactic acid); Poly(DL-Lactide)[PLA], Poly(Glycolide)[PGA], Poly(DL-Lactide-co-Glycolide)[PLGA]

Inherent viscosity: see fig 1, [PLA]

Degradation of PLGA (fig 2) involves hydrolysis of the ester bonds independently of microbial activity to produce low-molecular weight polymer. Below Mw of 10 kDa microorganisms digest the polymer into **CO_2 and H_2O.**

PEGylation: The introduction of **chemical modification by incorporating polyethylene glycol** to the polyesters opens new possibilities for applications.

PEGylation has a measurable impact on degradation and erosion, as shown in Figure 2**.** **For PLGA,** degradation takes place for about three weeks before erosion occurs.

Erosion starts once the molecular weight drops to ~7,000–8,000 Da, and occurs at a relatively rapid rate.

PEGylated PLGA copolymers (PEG-PLGA) show both degradation and erosion **without any lag time**

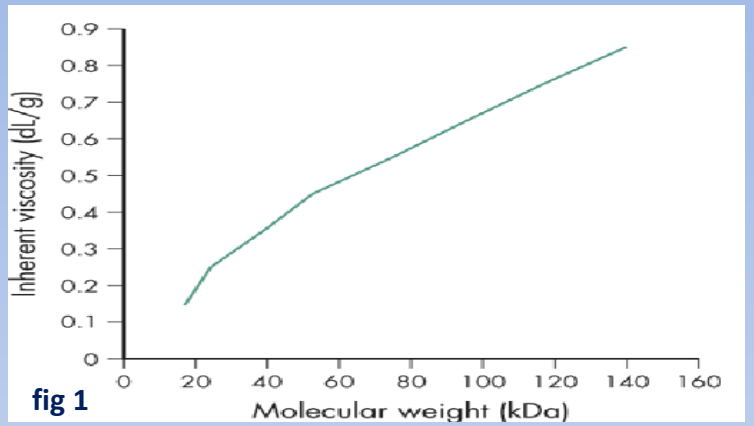


fig 1

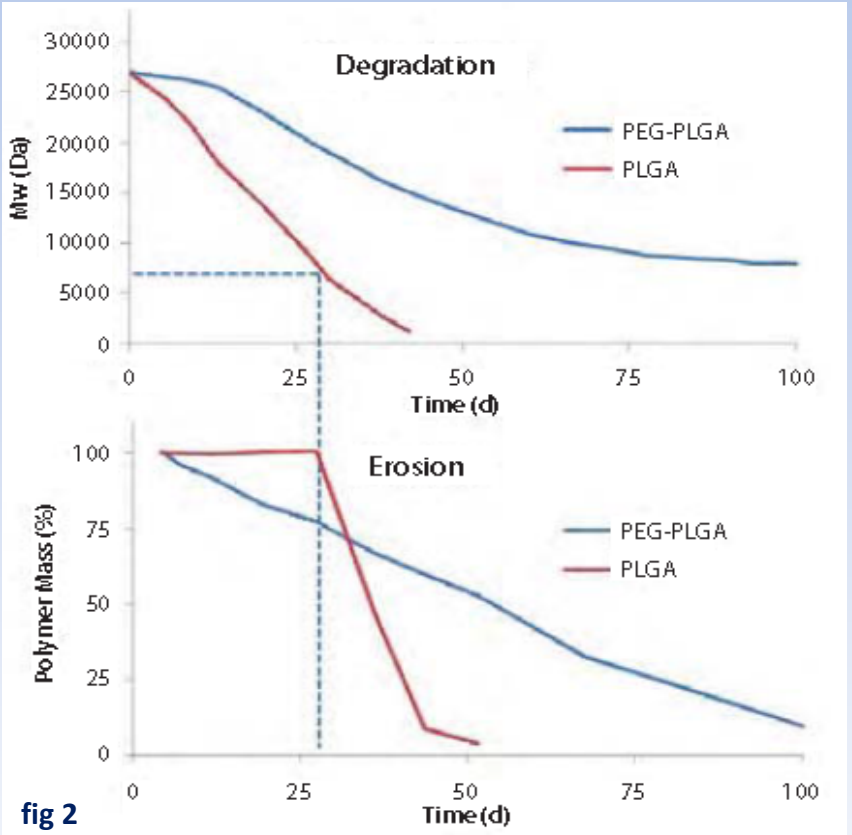
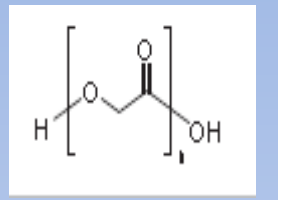


fig 2

Example: Biodegradeable Polymers for Sutures, Poly(DL-Lactic acid); Poly(DL-Lactide)[PLA], Poly(Glycolide)[PGA], Poly(DL-Lactide-co-Glycolide)



3) Poly(Glycolide)[PGA], polyglycolic acid, (type A6);
Mol. Weight: 1932 Da; Structural formula: HO[CH2-COO-]*32* CH2COOH

4) Poly(DL-Lactide-Co-Glycolide)[PLGA]; Cas name:
1,4-Dioxane-2,5-dione, 3,6-dimethyl-, polymer with 1,4-dioxane-2,5-dione.

Brand name: "Resormer RG type ……."

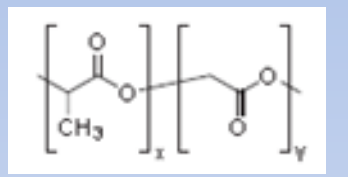
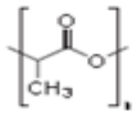
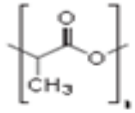
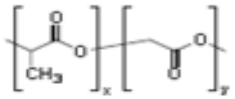
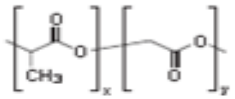
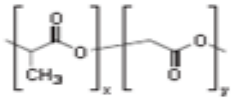
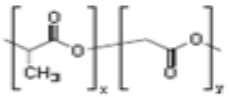
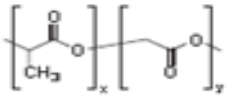
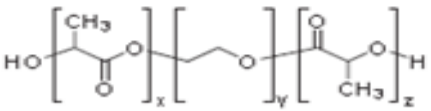
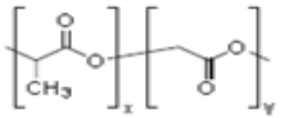


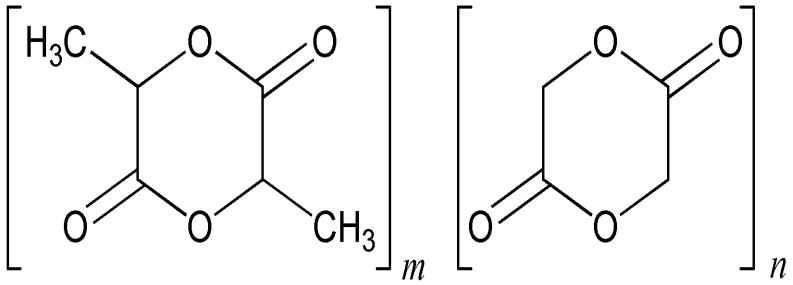
Table 1. Key parameters and corresponding effects on RESOMER® properties.

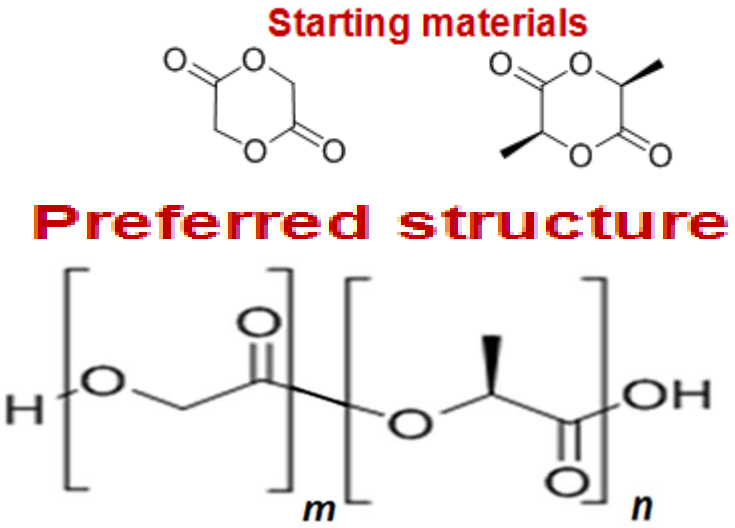
Parameter	Influence
Molecular Weight	High M_w increases the degradation time
Ratio Lactide/Glycolide	Polymers with one monomer degrade more slowly. Degradation times: PLA > PGA > PLGA 50:50
Stereochemistry	L PLA: semicrystalline D,L PLA: amorphous
Blockage of Acidic Endgroups	Polymers with free COOH groups are more hydrophilic (e.g., R503H compared to R503)
PEGylation	Increase in hydrophilicity, change of degradation and release behavior

Biodegradable Copolymers, some examples

Poly(D,L-lactide), acid terminated	RESOMER® R 202 H		M_w 10,000-18,000
Poly(D,L-lactide), alkyl ester terminated	RESOMER® R 203 S		M_w 18,000-28,000
Poly(D,L-lactide-*co*-glycolide), ester terminated, (50:50)	RESOMER® RG 502		M_w 7,000-17,000
Poly(D,L-lactide-*co*-glycolide), acid terminated, (50:50)	RESOMER® RG 502 H		M_w 7,000-17,000
Poly(D,L-lactide-*co*-glycolide), ester terminated, (50:50)	RESOMER® RG 503		M_w 24,000-38,000
Poly(D,L-lactide-*co*-glycolide), alkyl ester terminated, (75:25)	RESOMER® RG 756 S		M_w 76,000-115,000
Poly(D,L-lactide-*co*-glycolide), alkyl ether terminated, (85:15)	RESOMER® RG 858 S		M_w 190,000-240,000
Polylactide-*block*-poly(ethylene glycol)-*block*-polylactide			PEG average M_n10,000 PLA average M_n2,000
Poly(D,L-lactide-*co*-glycolide), 85:15 lactide glycolide			M_w 50,000-75,000

USAN entry for polyglactin 910





Mol. Formula: (C6H8O4)m (C4H4O4)n

(1) Names:

(2) 1,4-Dioxane-2,5-dione, 3,6-dimethyl-, polymer with 1,4-dioxane-2,5-dione;

(3) 3,6-Dimethyl-p-dioxane-2,5-dione polymer with p-dioxane-2,5-dione;

(4) Poly[(oxycarbonylmethylene)m-co-(oxycarbonylethylidene)n].

(5) Preferred name: Poly[(Glycolide)90-Co-(**L**-lactide)10]

Molecular weight is approximately 80,000. CAS-26780-50-7;

Surgical aid (surgical suture material, absorbable) VicrylEthicon

Vicryl, Defining vs Nondefining

- Defining
  - » Random co-polymer, SRU structure, and ratio (90%/10%)
  - » Molecular weight (~80,000):
    - o Not given in product literature, but is in USAN definition
    - o Might use viscosity, but not relevant / unavailable here
    - o Won't capture another proxy for molecular weight since it is defined
- Non-defining
  - » Maximum suture oversize (product property)
  - » Tensile strength
  - » Monomer starting materials

Problems with current definition

- ❑ Structure wrong (stereochemistry not given in USAN)
- ❑ Structure is for starting material, not substance

Specifications for some PLGA-type Copolymers provided at the application

Poly(DL-Lactide-co-Glycolide)(55:45) used as polymer matrix for prolonged release of a small peptide in powder for suspension formulation.

Poly(DL-lactide-co-glycolide):

Title of test, Principle	Requirements
Appearance by visual examination	Off-white, glassy granules
Viscosity (inherent)	0.29 – 0.35 dl/g
Molecular mass (GPC)	47000 – 63000 g/mole
Clarity of the solution	Clear
Colour of the solution	Colourless to faintly brown or fa
Identity by IR (ATR)	Corresponds to the reference
Identification and determination of the components	50 – 60 mole-% of lactide and 40 – 50 mole-% of glycolide
Impurities by GC	
• Sum of lactide and glycolide	Not more than 0.5%
Residual solvent by GC	
• Acetone	Not more than 1.0%.
Water (Karl Fischer)	Not more than 1.0%
Sulfated ash	Not more than 0.1%
Heavy metals by ICP-OES	
• Sn	Not more than 3 ppm

SPECIFICATIONS - PEG-co-polyester B19

Name: Block co-polymer of PEG and poly (dl-lactide-co-glycolide); **Chemical name:**
20/80 [PEG b (60-40 poly dl-lactide-co-glycolide)]

Physical form: viscous colorless liquid at 25 ºC

Molecular form.: C80 H114 O58; Mw = 3500 Da

Structural formula: HO-(-CHCH3COO-)z-(-CH2COO-)y-[(CH2CH2O)8.7]x-(-OOCCH2-)y -(OOCCHCH3-)Z-OH; x : y : z = 1 : 4.82 : 7.25

Parameter	Specification	Method
Appearance	high viscous, light yellow	Visual examination
FT-IR spectra	Complies to reference spectra	EP 2.2.24
^{1}H-NMR spectra	Complies to reference spectra	EP 2.2.33
Molecular weight by SEC (Mw)	3000 – 4000 Da	EP 2.2.30, DIN 55672-1
Polydispersity by SEC (Mw/Mn)	≤ 2.0	EP 2.2.30, DIN 55672-1
Complex viscosity	2200 – 2800 Pa s	Oscillation viscosimetry
Free acid	> 12'000 g/Eq	Titration EN ISO 11 909, DIN EN ISO 16 945
Glycolide	≤ 0.1 %	^{1}H-NMR, EP 2.2.33
dl-Lactide	≤ 1.0 %	^{1}H-NMR, EP 2.2.33
Tin	≤ 200 ppm	AAS, EP 2.2.23
Toluene	≤ 890 ppm	HPLC, EP 2.2.29

Nonproprietary names of Polymethacrylates described in the European Pharmacopoeia:

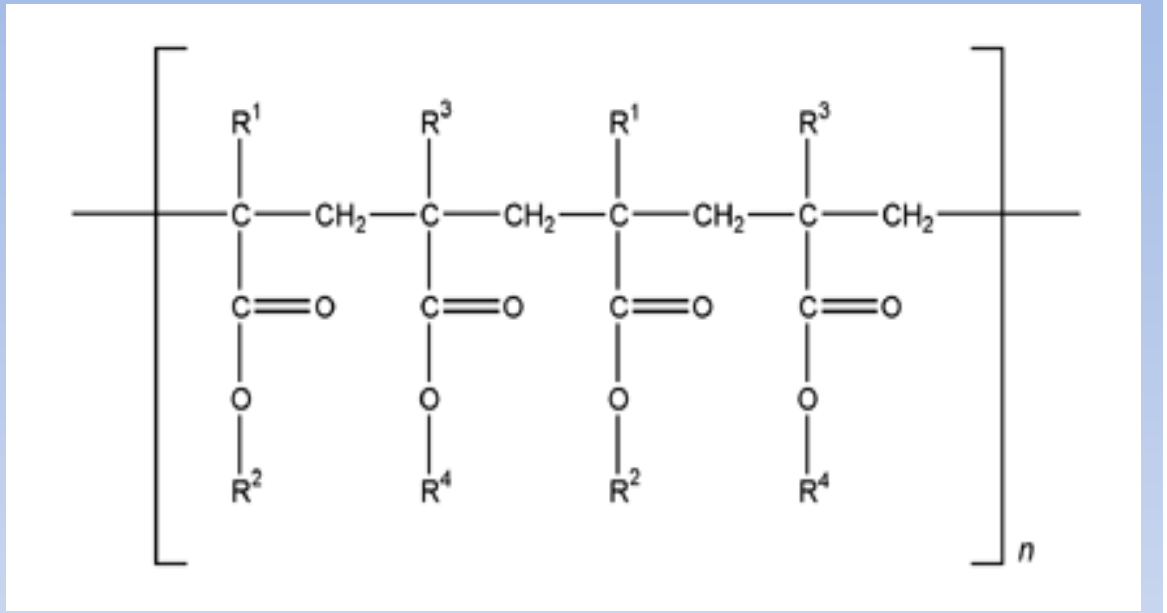
- **Ammonio Methacrylate Copolymer (Type A)**; Mw = 150.000,
  Ratio Co-polymers: 1:2: 0,2;
- **Ammonio Methacrylate Copolymer (Type B)**; Mw = 150.000,
  Ratio Co-polymers: 1:2: 0,1.
  [Poly(ethyl propenoate-*co*-methyl 2-methylpropenoate-*co*-2-(trimethylammonio)ethyl 2-methylpropenoate) chloride]
- **Basic Butylated Methacrylate Copolymer**; Mw = 150.000
  [Copolymer of (2-dimethylaminoethyl) methacrylate, butyl methyacrylate, and methyl methacrylate]
  Ratio (2-dimethylaminoethyl) methacrylate groups to butyl methyacrylate and methyl methacrylate groups is about 2 : 1 : 1.)
- **Methacrylic Acid–Ethyl Acrylate Copolymer (1 : 1);** Mw = 250.000;
  Ratio COOH- /Ester groups = 1:1
- **Methacrylic Acid–Methyl Methacrylate Copolymer (1 : 1);** Mw =135.000;
  Ratio COOH- /Ester groups = 1:1
- **Methacrylic Acid–Methyl Methacrylate Copolymer (1 : 2);** Mw = 135.00;
  Ratio COOH- /Ester groups = 1:2

Nonproprietary names of Polymethacrylates described in the European Pharmacopoeia: Structure

For ***Eudragit E***: R^1, $R^3 = CH_3$; $R^2 = CH_2CH_2N(CH_3)_2$; $R^4 = CH_3, C_4H_9$;

For ***Eudragit L*** **and** ***Eudragit S*****:**
R^1, $R^3 = CH_3$; $R^2 = H$; $R^4 = CH_3$

For ***Eudragit RL*** **and** ***Eudragit RS*****:**
$R^1 = H, CH_3$; $R^2 = CH_3, C_2H_5$; $R^3 = CH_3$;
$R^4 = CH_2CH_2N(CH_3)_3\ ^+Cl^-$



For ***Eudragit NE 30 D*** **and** ***Eudragit NE 40 D*****:**
R^1, $R^3 = H, CH_3$; R^2, $R^4 = CH_3, C_2H_5$

For ***Acryl-EZE 93A*** and ***Acryl-EZE MP***;
Eudragit L 30 D-55 and ***Eudragit L 100-55****;*
and ***Kollicoat MAE 30 DP***:
R^1, $R^3 = H, CH_3$; $R^2 = H$;$R^4 = CH_3, C_2H_5$

Eudragit E: is **soluble in gastric fluid below pH 5**

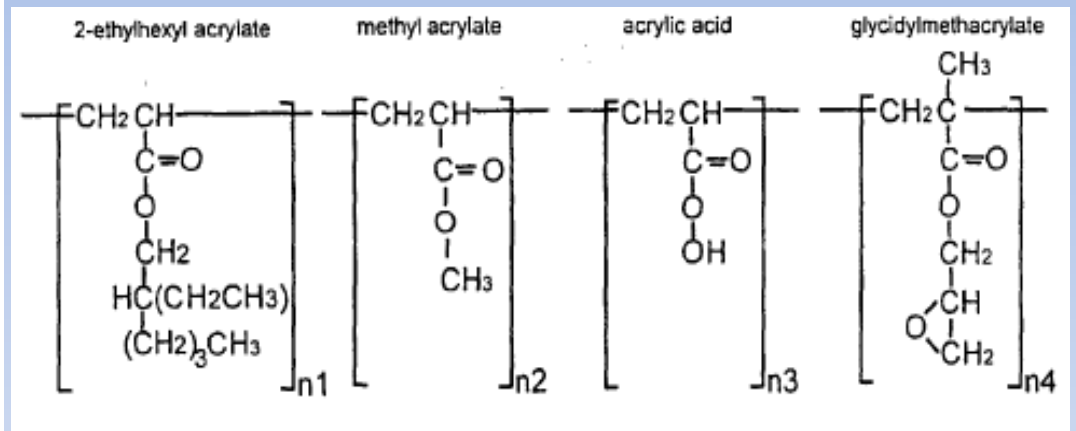
Eudragit L is soluble at pH > 6;
Eudragit S and FS are soluble at pH > 7

Eudragit RL, *RS*, *NE 30 D*, *NE 40 D*, and *NM 30 D* are used to form **water-insoluble film coats for sustained-release products.**

Specifications of Acrylate Copolymer pressure sensitive adhesive used in a transdermal drug delivery system (Duro-Tak, type)

Name Dutch record: Copolymer of 2-Ethylhexylacrylate (62.2), Methylacrylate (32.0), Acrylic acid (5.7), Glycidylmethacrylate (0.03)

Structural formula of the random Polymer: (schema)



	Molecular formula	CAS Number
Starting Monomers:		
2-ethylhexylacrylate	$C_{11}H_{20}O_2$	103-11-7
methylacrylate	$C_4H_6O_2$	96-33-3
glacial acrylic acid	$C_3H_4O_2$	79-10-7
glycidylmethacrylate	$C_7H_{10}O_3$	106-91-2
Solvents:		
ethylacetate	$C_4H_8O_2$	141-78-6
hexanes	C_6H_{14}	64742-49-0
Initiator:		
2,2'-azobis(2-methyl-propanenitrile)	$C_8H_{12}N_4$	78-67-1

Specification of the Acrylic Copolymer

Parameter	Specification	Testmethod
Appearance:	clear, yellowish viscous solution	organoleptic
Identity:	The IR-spectrum corresponds to the reference spectrum shown in figure 1	Ph. Eur.
Viscosity	4.0 – 12.0 [Pa • s]	Ph. Eur.
Solids content:	34.5 % - 38.5 % (w/w)	Determination of the Residue on Evaporation
Sulphated ash:	max. 0,2 %	Ph. Eur.
Heavy metals:	max. 20 ppm	Ph. Eur.
Residual monomers:	2-Ethylhexylacrylat max. 1.2 % (w/w) Glycidylmethacrylat max. 0.01 % (w/w) Methylacrylat max. 0.6 % (w/w) Acrylic acid max. 0.2 % (w/w)	Data from batch related certificate of analysis of the manufacturer will be accepted

Hypromellose

Portions of this monograph that are national *USP* text, and are not part of the harmonized text, are marked with symbols (◆◆) to specify this fact.

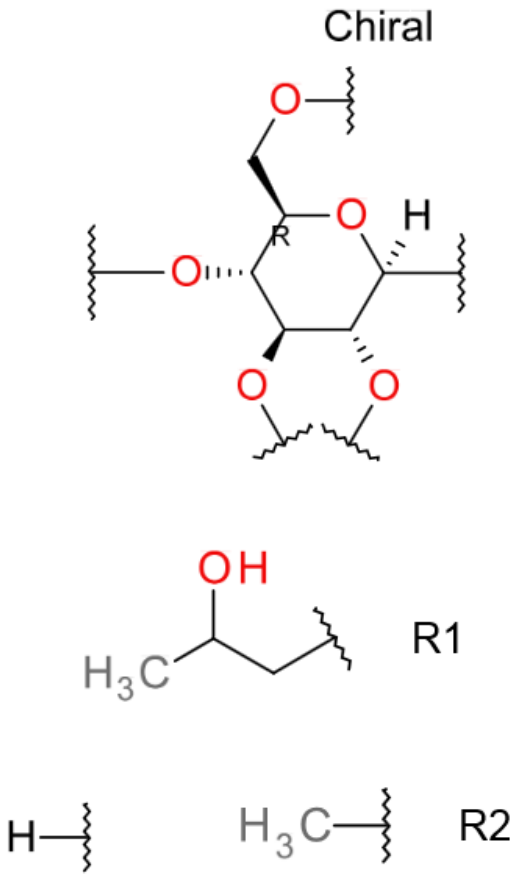
Cellulose, 2-hydroxypropyl methyl ether;
Cellulose hydroxypropyl methyl ether [9004-65-3].

DEFINITION

Hypromellose is a methyl and hydroxypropyl mixed ether of cellulose. It contains, calculated on the dried basis, methoxy ($-OCH_3$: 31.03) and hydroxypropoxy ($-OC_3H_6OH$: 75.09) groups conforming to the limits for the types of Hypromellose (hydroxypropyl methylcellulose) set forth in the table below.

Substitution Type	Methoxy (%)		Hydroxypropoxy (%)	
	Min.	Max.	Min.	Max.
1828	16.5	20.0	23.0	32.0
2208	19.0	24.0	4.0	12.0
2906	27.0	30.0	4.0	7.5
2910	28.0	30.0	7.0	12.0

HYPROMELLOSE 2910 (4000 Mpa.s)



<POLYMER_TYPE>HOMOPOLYMER
<NUMBER_OF_SRU>1
<ORIENTATION_OF_POLYMERIZATION>HEAD-TAIL
<R_ID>R1
<LIMIT_TYPE>WEIGHT
<AVERAGE>10
<LOW_LIMIT>7
<HIGH_LIMIT>12
<R_ID>R2
<LIMIT_TYPE>WEIGHT
<AVERAGE>29
<LOW_LIMIT>28
<HIGH_LIMIT>30
<TYPE_MW>NUMBER
<MW_AVERAGE>8000
<LOW_LIMIT_MW/>
<HIGH_LIMIT_MW/>
<PHYSICAL_PROPERTY_TYPE>VISCOSITY
<AVERAGE>3
<LOW_LIMIT>2.4
<HIGH_LIMIT>3.6
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Nomenclature

METHOCEL™ is a trademark of The Dow Chemical Company for a line of cellulose ether products. An initial letter identifies the type of cellulose ether, its "chemistry." "A" identifies methylcellulose (MC) products. "E," "F," and "K" identify different hypromellose products (Figure 1). METHOCEL™ E and METHOCEL™ K are the most widely used for controlled-release drug formulations.

The number that follows the chemistry designation identifies the viscosity of that product in millipascal-seconds (mPa·s), measured at 2% concentration in water at 20°C.† In designating viscosity, the letter "C" is frequently used to represent a multiplier of 100, and the letter "M" is used to represent a multiplier of 1000.

Several different suffixes are also used to identify special products. "LV" refers to special low-viscosity products, "CR" denotes a controlled-release grade, and "LH" refers to a product with low hydroxypropyl content. "EP" denotes a product that also meets European Pharmacopeia requirements; "JP" grade products also meet Japanese Pharmacopeia requirements.

Figure 1: Example of nomenclature for a METHOCEL™ E Cellulose Ether

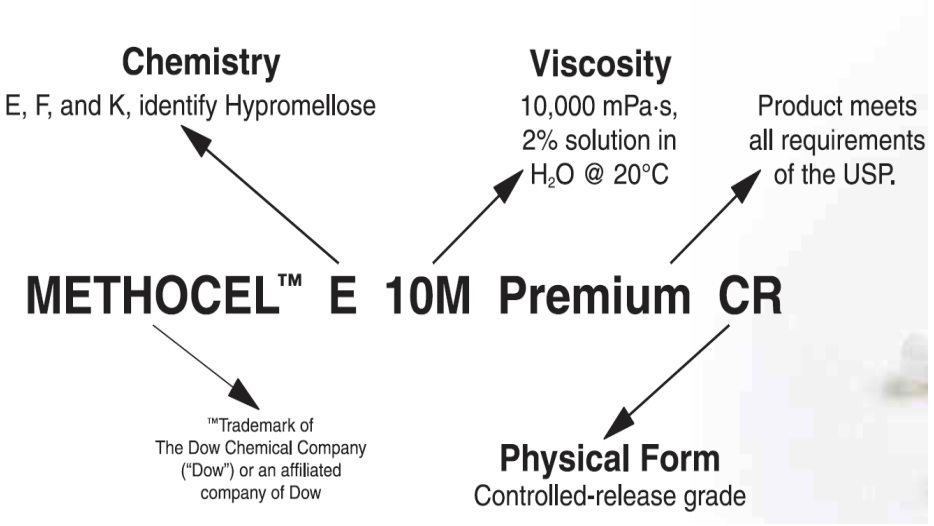
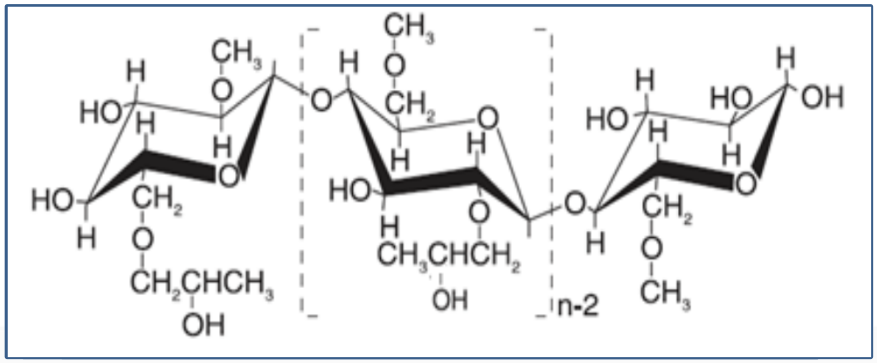


Figure 2: Chemical structures of METHOCEL™ Hydroxypropyl Methylcellulose products



Properties of selected Methocel Products of water-soluble cellulose ethers to be used in controlled release formulations

METHOCEL™ Premium Products for Pharmaceutical Applications

METHOCEL™ Product	Chemical Type[1]	Methoxyl Content, %	Hydroxypropyl Content, %	Viscosity of 2% solution in water, cps
METHOCEL™ E50 Premium LV	Hypromellose 2910	28 - 30	7 - 12	40 - 60
METHOCEL™ E4M Premium[2]	Hypromellose 2910	28 - 30	7 - 12	3000 - 5600
METHOCEL™ E10M Premium CR	Hypromellose 2910	28 - 30	7 - 12	7500 – 14,000
METHOCEL™ K100 Premium LV[2]	Hypromellose 2208	19 - 24	7 - 12	80 – 120
METHOCEL™ K4M Premium[2]	Hypromellose 2208	19 - 24	7 - 12	3,000 – 5,600
METHOCEL™ K15M Premium[2]	Hypromellose 2208	19 - 24	7 - 12	11,250 – 21,000
METHOCEL™ K100M Premium[2]	Hypromellose 2208	19 - 24	7 - 12	80,000 – 120,000

- Properties can be defining (viscosity)
- Hypromellose 2910 or Hypromellose 2208 is more specific than “Hypromellose”

Hypromellose

HYPROMELLOSE 2910 (3 MPA.S)	0VUT3PMY82
HYPROMELLOSE 2910 (5 MPA.S)	R75537T0T4
HYPROMELLOSE 2910 (6 MPA.S)	0WZ8WG20P6
HYPROMELLOSE 2910 (15 MPA.S)	36SFW2JZ0W
HYPROMELLOSE 2910 (50 MPA.S)	1IVH67816N
HYPROMELLOSE 2910 (4000 MPA.S)	RN3152OP35
HYPROMELLOSE 2910 (15000 MPA.S)	288VBX44JC
HYPROMELLOSE 2906 (50 MPA.S)	612E703ZUQ
HYPROMELLOSE 2906 (4000 MPA.S)	5EYA69XGAT
HYPROMELLOSE 2208 (3 MPA.S)	9H4L916OBU
HYPROMELLOSE 2208 (100 MPA.S)	B1QE5P712K
HYPROMELLOSE 2208 (4000 MPA.S)	39J80LT57T
HYPROMELLOSE 2208 (15000 MPA.S)	Z78RG6M2N2
HYPROMELLOSE 2208 (100000 MPA.S)	VM7F0B23ZI

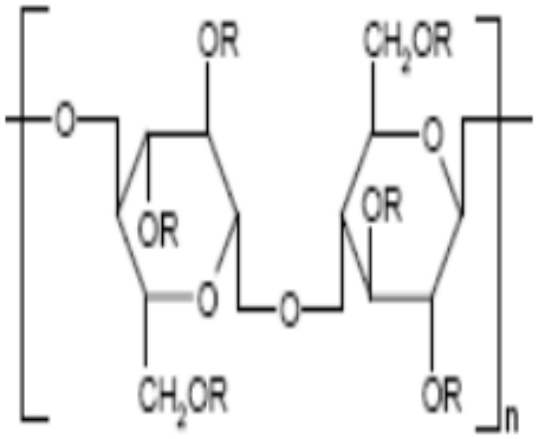
Table 1. Typical Properties of selected METHOCEL™ CR Grade Products*

METHOCEL™ Premium Product Grade	—	E4M Premium CR	E10M Premium CR
Methoxyl, %	USP	28–30	28–30
Hydroxypropoxyl,%	USP	7–12	7–12
Substitution type	USP/EP	2910	2910
Chlorides, max., %	EP	0.5	0.5
Apparent viscosity, 2% in water at 20°C, cP	USP	3000–5600	7500–14000
Apparent viscosity, 2% in water at 20°C, mPa·s	EP	2308–3755 [2903 Nom]	4646–7070 [5673 Nom]
ID Test A, B, C	USP	Pass	Pass
ID Test A, B, C, D, E, F	EP	Pass	Pass
Opalescence of solution	EP	Pass	Pass
Solution color, yellowness, 1% in water	EP	Pass	Pass
pH, 1% in water	EP	5.5–8.0	5.5–8.0
Loss on drying, max., %	USP/EP	5.0	5.0
Organic impurities, volatile	USP	Pass	Pass
Residue in ignition, max., %	USP	1.5	1.5
Ash, sulfated, max., %	EP	1.0	1.0
Heavy metals, as Pb, max., ppm	USP/EP	10	10
% through 40 mesh sieve	None	>99%	>99%
% through 100 mesh sieve	None	>95%	>95%

*Not to be construed as Sales Specifications.

Vemurafenib- Hydroxypropyl Methylcellulose Acetate Succinate co-precipitate (30:70);
Specification of the HPMC-AS

Hydroxypropyl methylcellulose acetate succinate



R= -H
-CH_3
-$CH_2CH(CH_3)OH$
-$COCH_3$
-$COCH_2CH_2COOH$
-$CH_2CH(CH_3)OCOCH_3$
-$CH_2CH(CH_3)OCOCH_2CH_2COOH$

Appearance: granulated powder
Color: white to yellowish white
Identity (ATR-IR or IR): corresponds
Viscosity (2% sol in 0.43% NaOH at 20 °C): 2.4 – 3.6 mm^2/s
Loss on drying: max. 1.5%
Sulphated ash: max. 0.20%
Heavy metals (Ph.Eur. Method A or XRF): max. 10 ppm.

Free acids (as acetic and succinic acids, HPLC): max. 1.0%

Content of acetyl groups (dried, HPLC): 5.0 – 9.0%

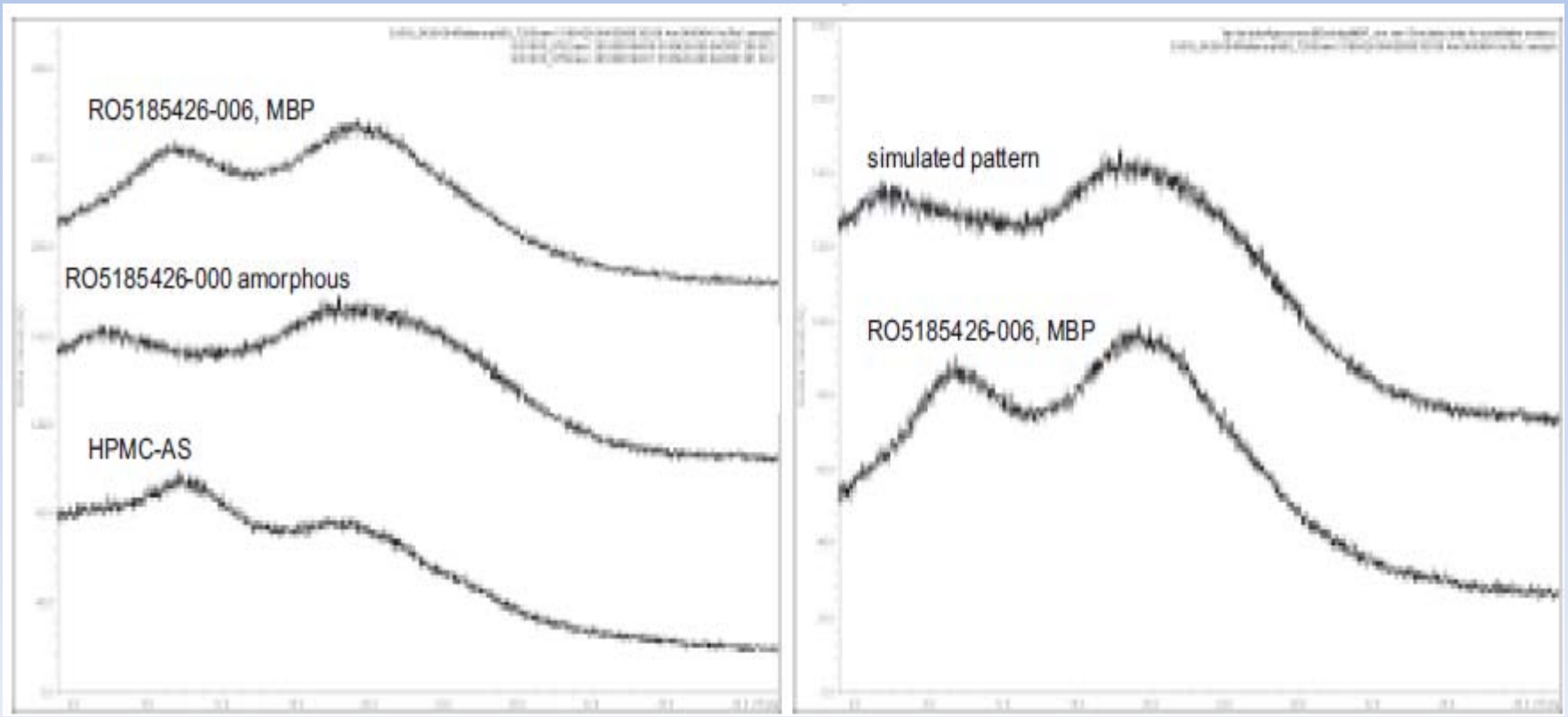
Content of succinoyl groups (dried, HPLC): 14.0 – 18.0%

Content of methoxy groups (dried, GC): 20.0 – 24.0%

Content of hydroxypropoxy groups (dried, GC): 5.0 – 9.0%
Residual solvents (GC): passes test, complies with USP and Ph.Eur.

Left: Overlay of XRPD patterns of HPMC-AS, amorphous Vemurafenib (RO5185426-000) and Vemurafenib-Hypromellose Acetate Succinate (RO5185426006, MBP)

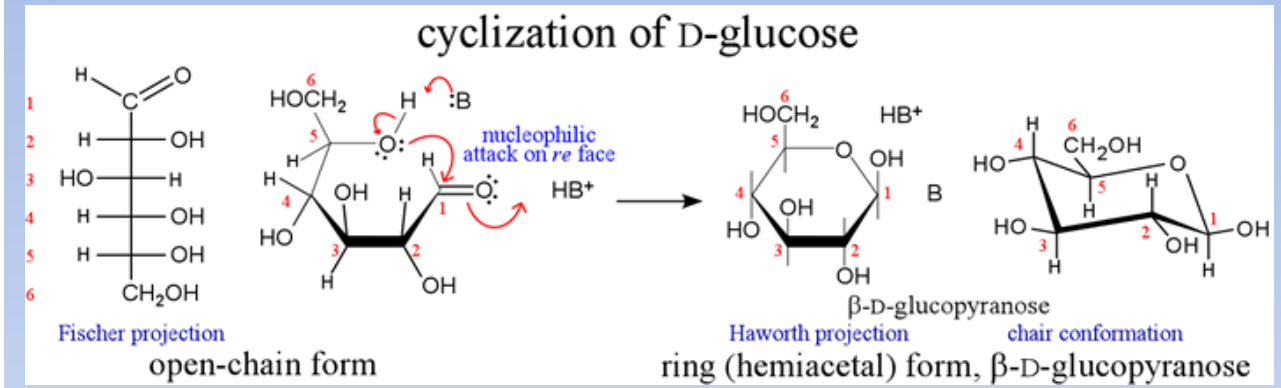
Right: Simulated pattern (Least squares fit) and experimental pattern physical mixture



Biopolymers, Structural representation, Glycosidic Bond

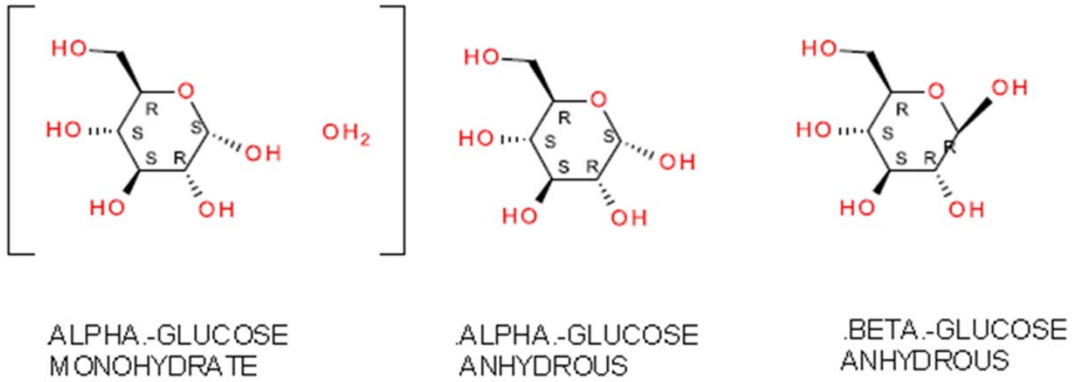
1) Types of representation of Glucose structure, Disaccharide, Glycosidic bond

Cyclization of the open-chain form of D-glucose by intramolecular hemiacetal formation results in a D-glucopyranose molecule. The cyclization creates an extra chiral center at C1 giving two forms of D-glucopyranose designated α and β. The representation of the forms are known as the Haworth projections. A *O*-Glycosidic bond is a type of covalent bond that joins a carbohydrate (sugar) molecule to another group, which may be another carbohydrate.



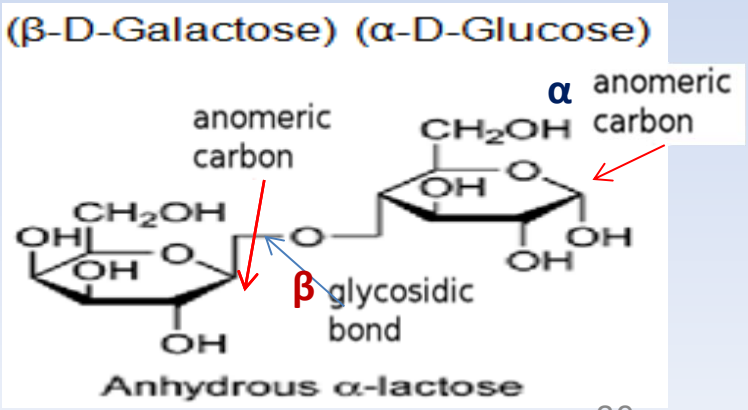
Representation of Glucose according to the ISO-Implementation Guide

Example DEXTROSE (GLUCOSE): Exists as three separate substances in the crystalline state. For a crystalline substance one of the following representations should be chosen.



In the liquid state dextrose and most other monosaccharides exist as a mixtures of interconverting substances as illustrated in the five structures below.

In the Haworth-projection the C^*_1-OH group is *cis* to the C_5-CH2OH group resulting in the β-anomeric form:

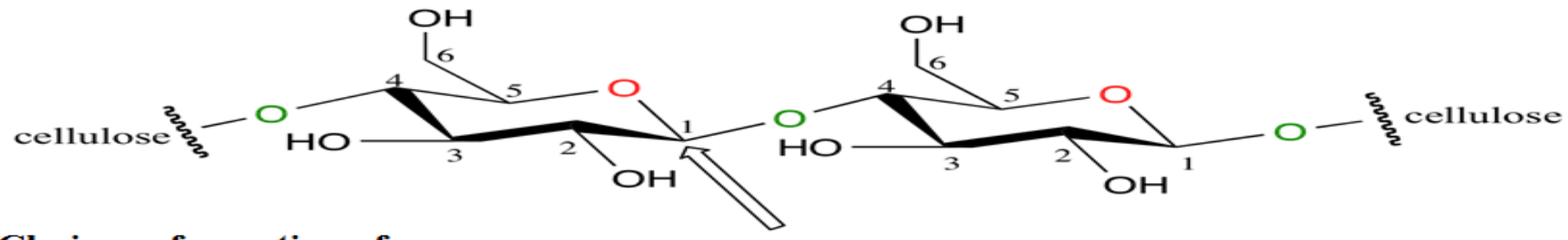


***O*-β-D-galactopyranosyl-(1 to 4)-α-D-glucopyranose**

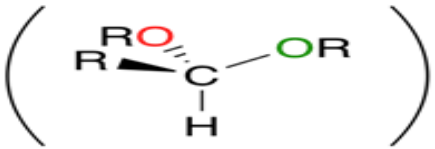
Biopolymers, Structural representation, Glycosidic Bond

2) Types of representation of Cellulose, Chair conformation of Glycosidic bond

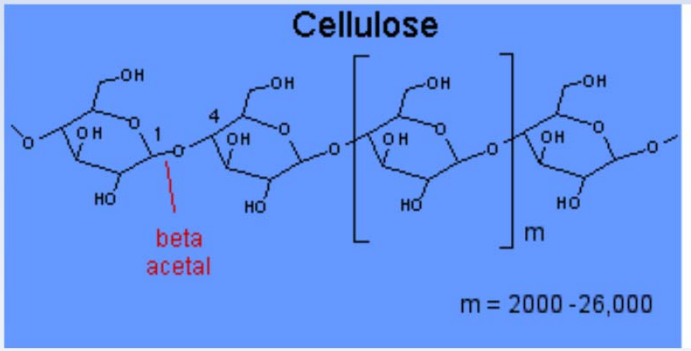
Example: β-1,4 linkage e.g. Cellulose, microcrystalline

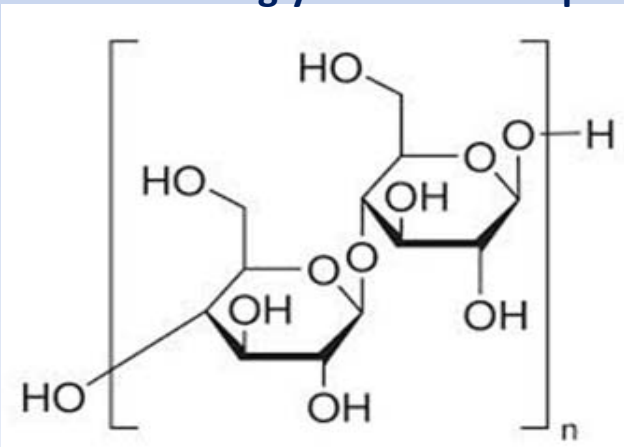


Chair conformation of Cellulose β-(1-4) glycosidic bond



Microcrystalline cellulose is prepared from alpha-Cellulose which contains between 2000 . 26000 residues. Acid-catalysed hydrolyses of cellulose long chain polymer cleaves the ß-1-4-glycosidic bond up to a certain degree of depolymerisation up to 3000 D-glucose units. The particle size is 20 -200 µm. Powdered cellulose is microcrystalline cellulose up to a degree of polymerisation of < 350 D-glucose units. **Monomer:** **ß-D-Glucose is the monomer unit in cellulose as a result of the bond angles in the beta acetal linkage. Cellulose is mostly a lineair chain**



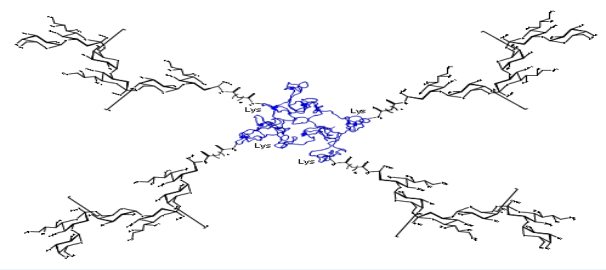


Haworth projection of Cellulose β-(1-4) glycosidic bond

Biopolymers, Structural representation, Glycosidic Bond
Example Oligosaccharides of Meningococcal ACWY conjugate vaccine (MenACWY)

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 (β197) 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

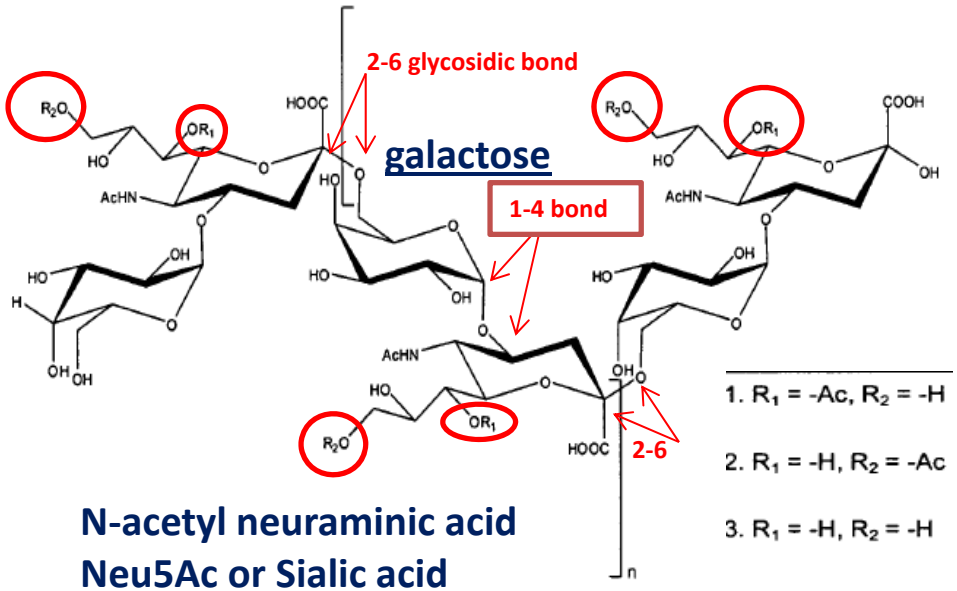
Structures of MenW and MenY Polysaccharide of Meningococcal ACWY conjugate vaccine (MenACWY)

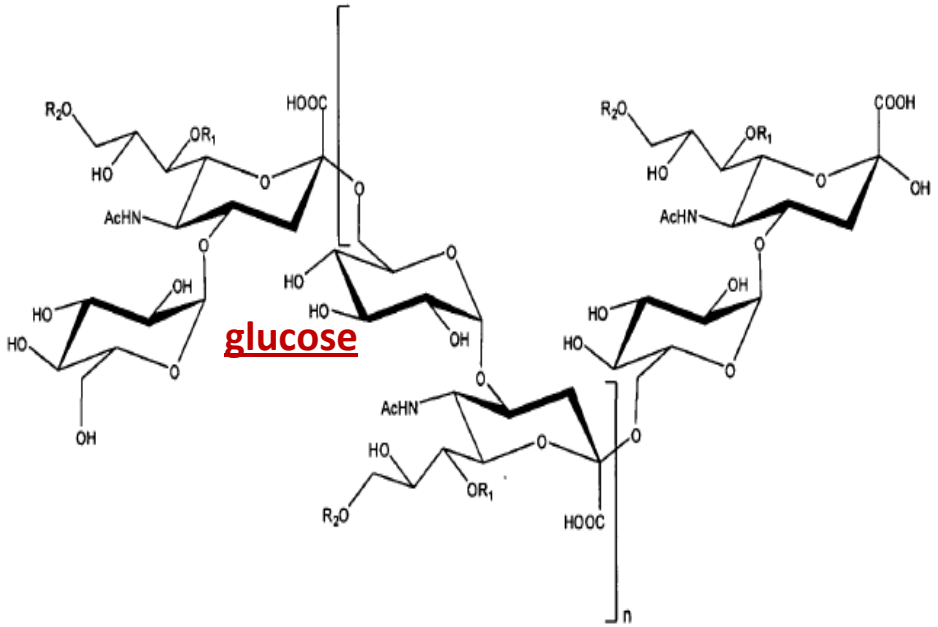
The structure of MenW and MenY polysaccharide is a heteropolymer whose repeating unit is composed of N-acetylneuraminic acid and galactose and of N-acetyl neuraminic acid and glucose respectively.

MenW: The partly O-acetylated structure is - 6)-α-D-Gal(1→4)-α-D-Neu*p*NAc-(2→).

MenY: The partly O-acetylated structure is: -6)-α-D-Glc(1→4)-α-D-Neu*p*5NAc-(2→).

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

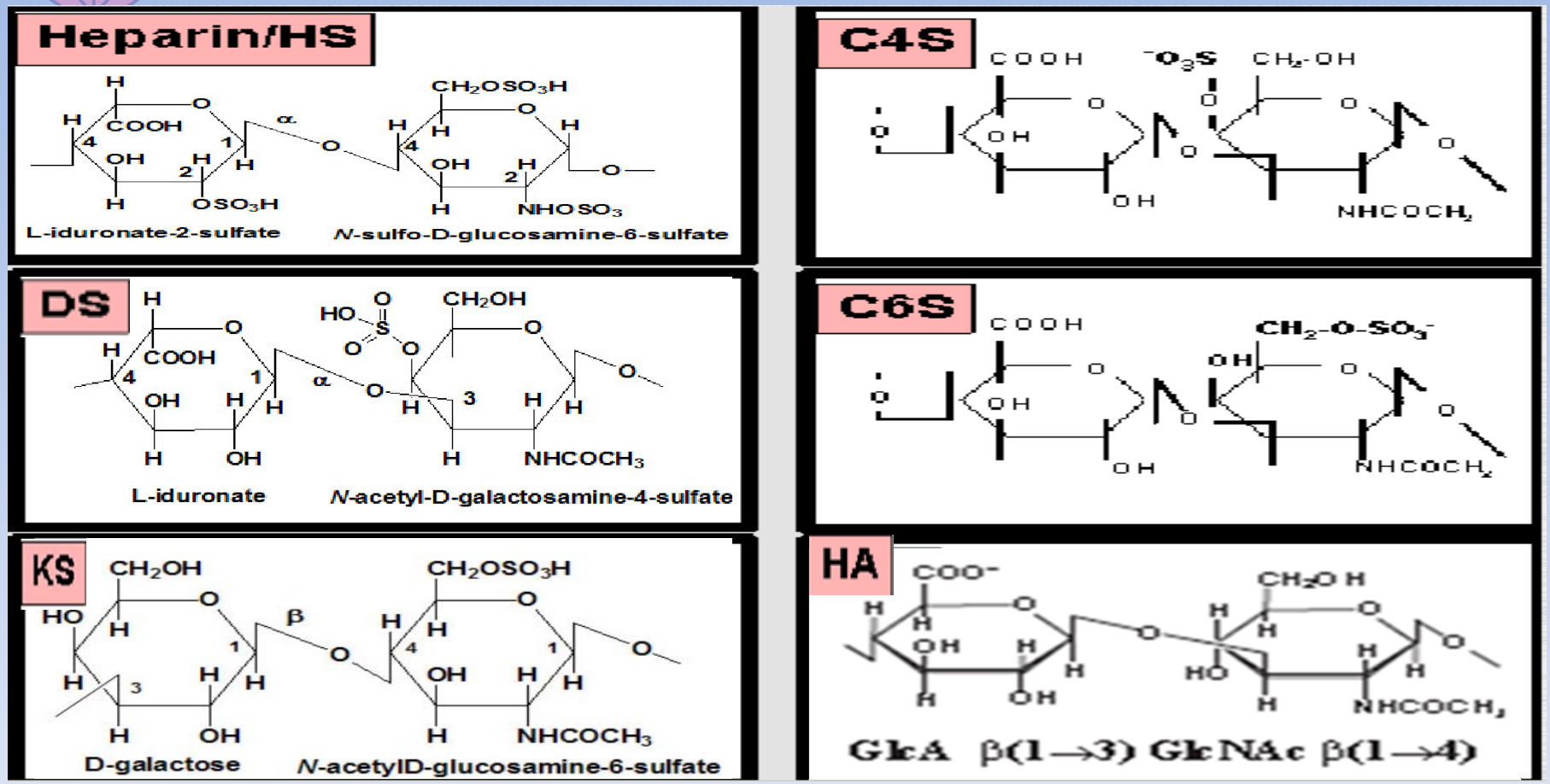




[Men W, SRU: —»4)-D-Neu*p5*NAc(7/9 OAc)-α-(2—>6) -D-Gal-α-(l—>,].

[MenY, SRU: —»4)-D-Neu*p5*NAc(7/9 OAc)-α-(2—>6) -D-Glc-α-(l—>,].

Biopolymers, Structural representation, Glycosidic Bond
Charaterization, Proteoglycans (Aggrecan), **Classification**
Glycoaminoglycans (GAGs)/ Structures in *e.g.* Articular Cartilage



Schematic structures of GAGs. 1) Heparin/HS and Hyaluronic acid (HA) are glycosaminoglycans; 2) Chondroitin-4-sulfate (C4S), Chondroitin-6-sulfate (C6S) and dermatan sulfate (DS) are galactosaminoglycans; 3) Keratan sulfate (KS) is a sulfated polylactosamine. Since heparin/HS structures are highly heterogeneous, only their most abundant disaccharide unit IdoA(2-OSO_3)-GlcNSO_3(6-OSO_3) is shown here.

Classification Glycoaminoglycans (GAGs)

Based on core dissaccharide structures GAGs are classified into 4 groups: 1) Heparin/ Heparan sulfate (HSGAGs) and **2) Chondroitin/ Dermatan sulfate (CSGAGs), 3) Keratan sulfate may modified by N- or O-glycosylation. 4) Hyaluronic acid (not synthetised by the Golgi).**

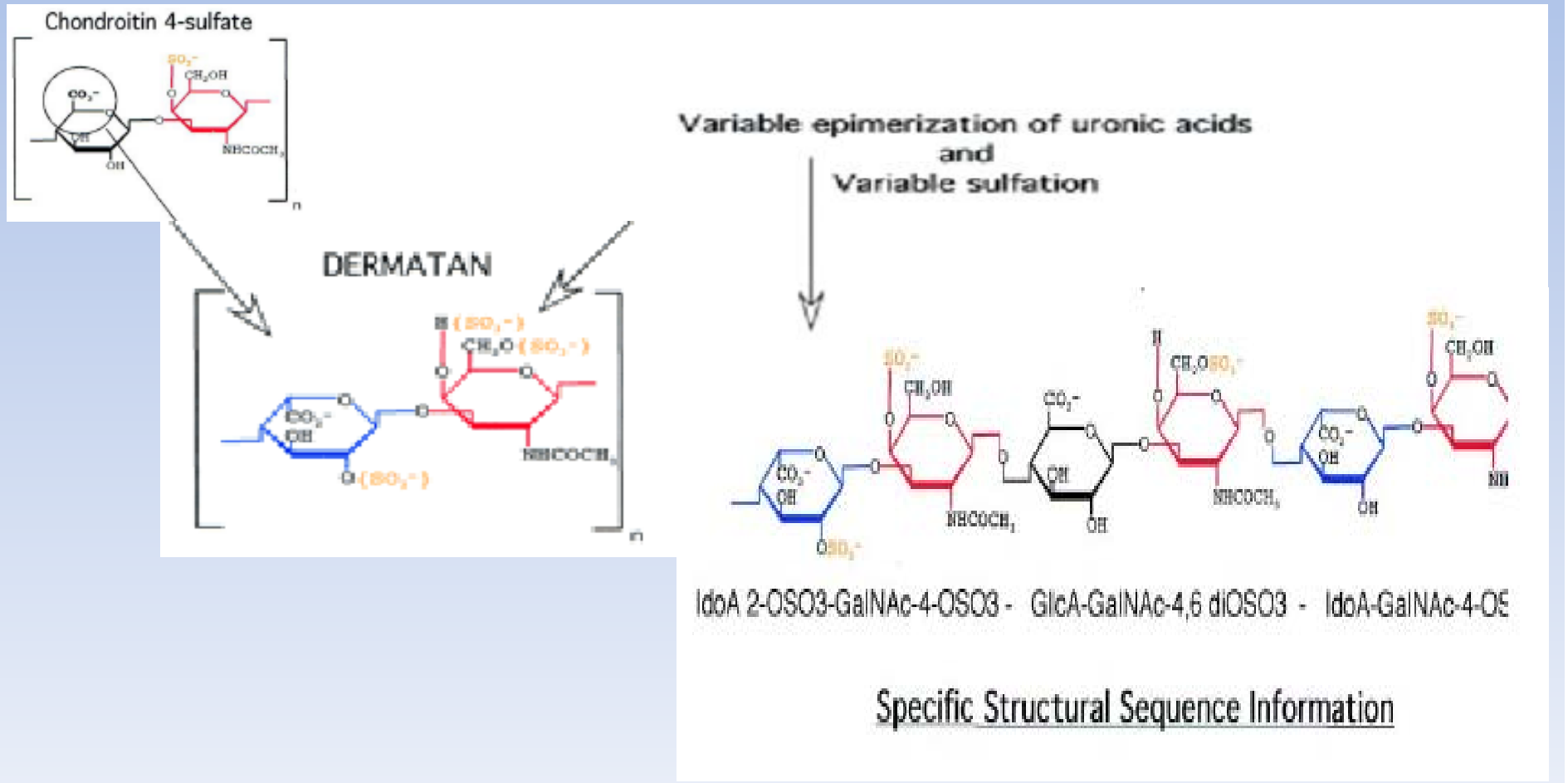
Name	Hexuronic acid / Hexose	Hexosamine	Linkage geometry between predominant monomeric units	Unique features
Chondroitin sulfate	GlcUA or GlcUA (2S)	GalNAc or GalNAc(4S) or GalNAc(6S) or GalNAc(4S,6S)	'***GlcUA***β*1-3*'GalNAc***β1-4***	Most prevalent GAG
Dermatan sulfate	GlcUA or IdoUA or IdoUA(2S)	GalNAc or GalNAc(4S) or GalNAc(6S) or GalNAc(4S,6S)	***IdoUA****α1-3*GalNAc***β1-4***	Distinguished from chondroitin sulfate by the presence of iduronic acid, although some hexuronic acid monosaccharides may be glucuronic acid.[15]
Keratan sulfate	Gal or Gal(6S)	GlcNAc or GlcNAc(6S)	-Gal(6S)***β1-4***GlcNAc(6S)***β1-3***	Keratan sulfate type II may be fucosylated.[19]
Heparin	GlcUA or IdoUA (2S)	GlcNAc or GlcNS or GlcNAc(6S) or GlcNS(6S)	-IdoUA(2S)***α1-4***GlcNS(6S)***α1-4***	Highest negative charge density of any known biological molecule
Heparan sulfate	GlcUA or IdoUA or IdoUA(2S)	GlcNAc or GlcNS or GlcNAc(6S) or GlcNS(6S)	-GlcUA***β1-4***GlcNAc***α1-4***	Highly similar in structure to heparin, however heparan sulfate's disaccharide units are organised into distinct sulfated and non-sulfated domains.[20]
Hyaluronan	GlcUA	GlcNAc	-GlcUA***β1-3***GlcNAc***β1-4***	The only GAG that is exclusively non-sulfated

- **GlcUA** = β-D-glucuronic acid
- **GlcUA(2S)** = 2-O-sulfo-β-D-glucuronic acid
- **IdoUA** = α-L-iduronic acid
- **IdoUA(2S)** = 2-O-sulfo-α-L-iduronic acid
- **Gal** = β-D-galactose
- **Gal(6S)** = 6-O-sulfo-β-D-galactose
- **GalNAc** = β-D-N-acetylgalactosamine
- **GalNAc(4S)** = β-D-N-acetylgalactosamine-4-O-sulfate
- **GalNAc(6S)** = β-D-N-acetylgalactosamine-6-O-sulfate
- **GalNAc(4S,6S)** = β-D-N-acetylgalactosamine-4-O, 6-O-sulfate
- **GlcNAc** = α-D-N-acetylglucosamine
- **GlcNS** = α-D-N-sulfoglucosamine
- **GlcNS(6S)** = α-D-N-sulfoglucosamine-6-O-sulfate

Classification Glycoaminoglycans (GAGs)

e.g. Dermatan: Variable Epimerization and Sulfation

Dermatan sulfate	GlcUA or IdoUA or IdoUA(2S)	GalNAc or GalNAc(4S) or GalNAc(6S) or GalNAc(4S,6S)	***IdoUAα1-3GalNAcβ1-4***	Distinguished from chondroitin sulfate by the presence of iduronic acid, although some hexuronic acid monosaccharides may be glucuronic acid.[15]

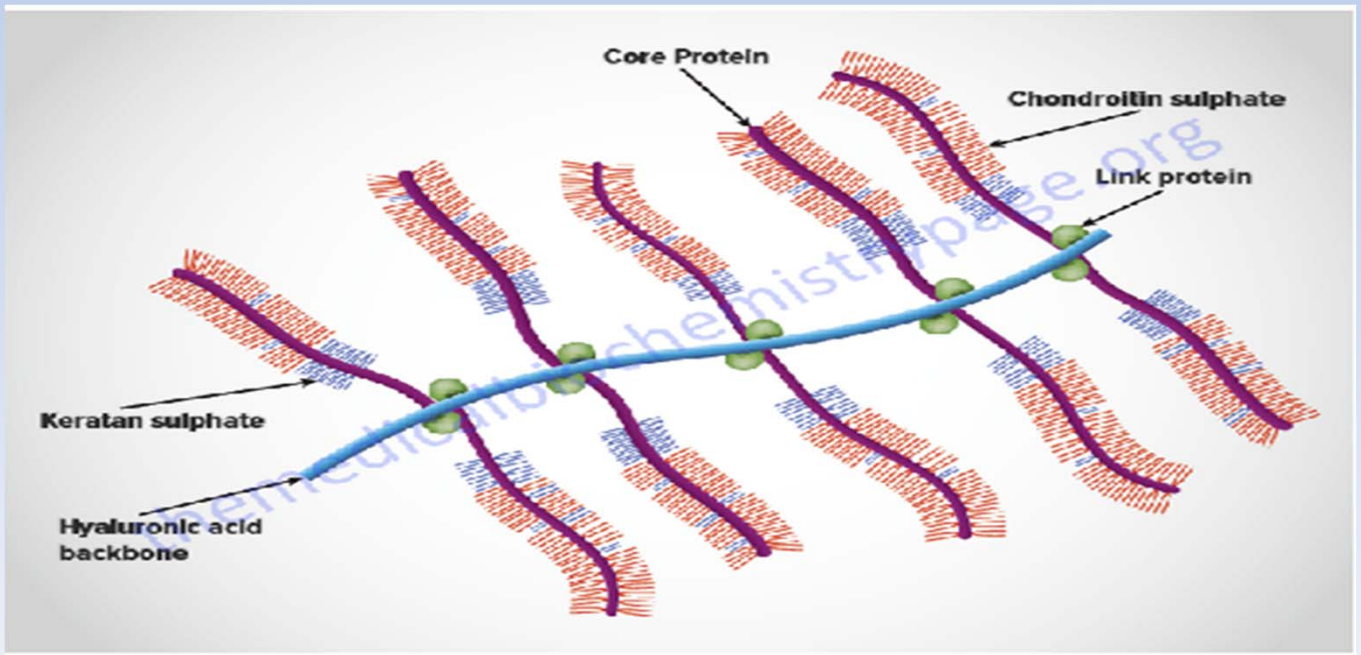


Aggrecan is also known as **cartilage-specific proteoglycan core protein** (CSPCP) or **chondroitin sulfate proteoglycan 1.**

Aggrecan is a Proteoglycan and the human form of the core protein has 2316 AAs with 4 domains: (N-G1-G2-CS-G3-C), Mol. Mass > 2.500 kDa. The core protein (210 - 250 kDa) has 100 –150 Glyco- aminonoglycan (GAG) chains attached to it.

Biosynthesis Glycoaminoglycans (GAGs)/ Structures, e.g

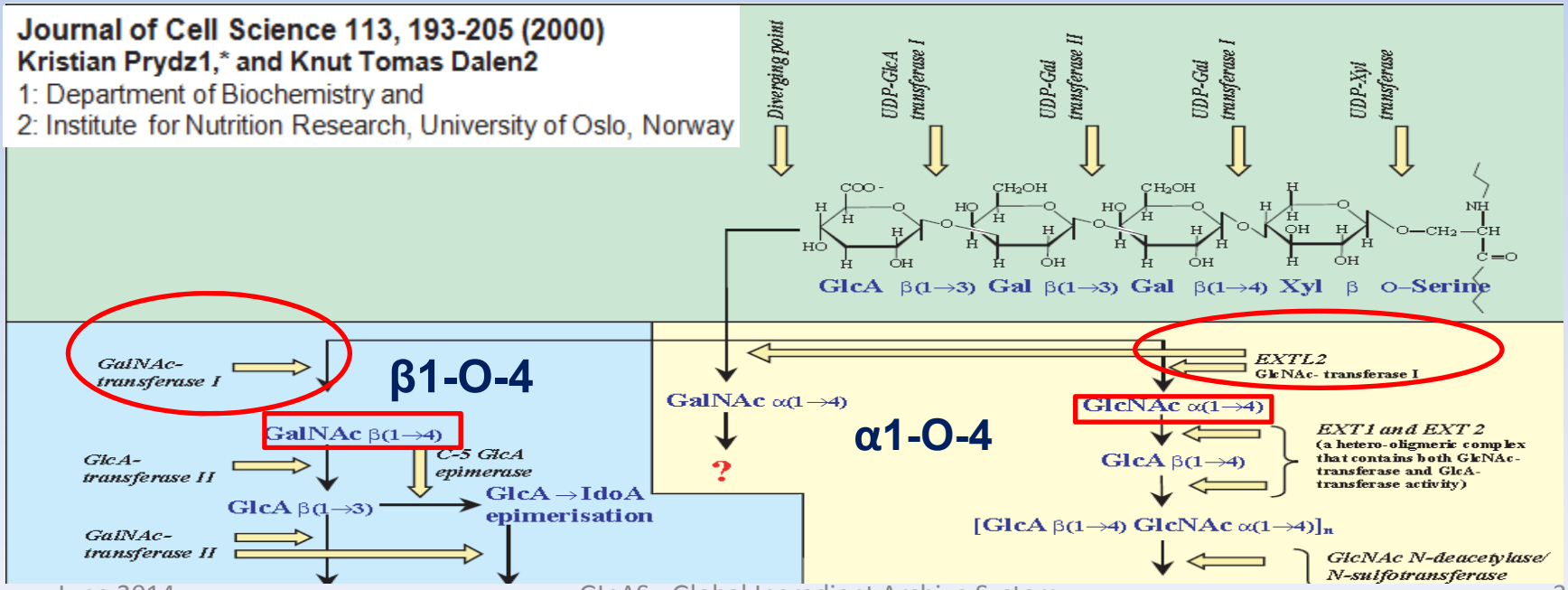
HSGAG and CSGAG modified proteoglycans first begin with a consensus **Ser-Gly/Ala-X-Gly motif in the core protein. (Ser-Gly)*n=3* starts HSGAG; (Ala-Ser-Gly)*n=3* influence the choice for CSGAG.**



Structure of an aggrecan-type complex proteoglycan

Biosynthesis Glycoaminoglycans (GAGs)/ Structures, *e.g HSGAG en CSGAG*

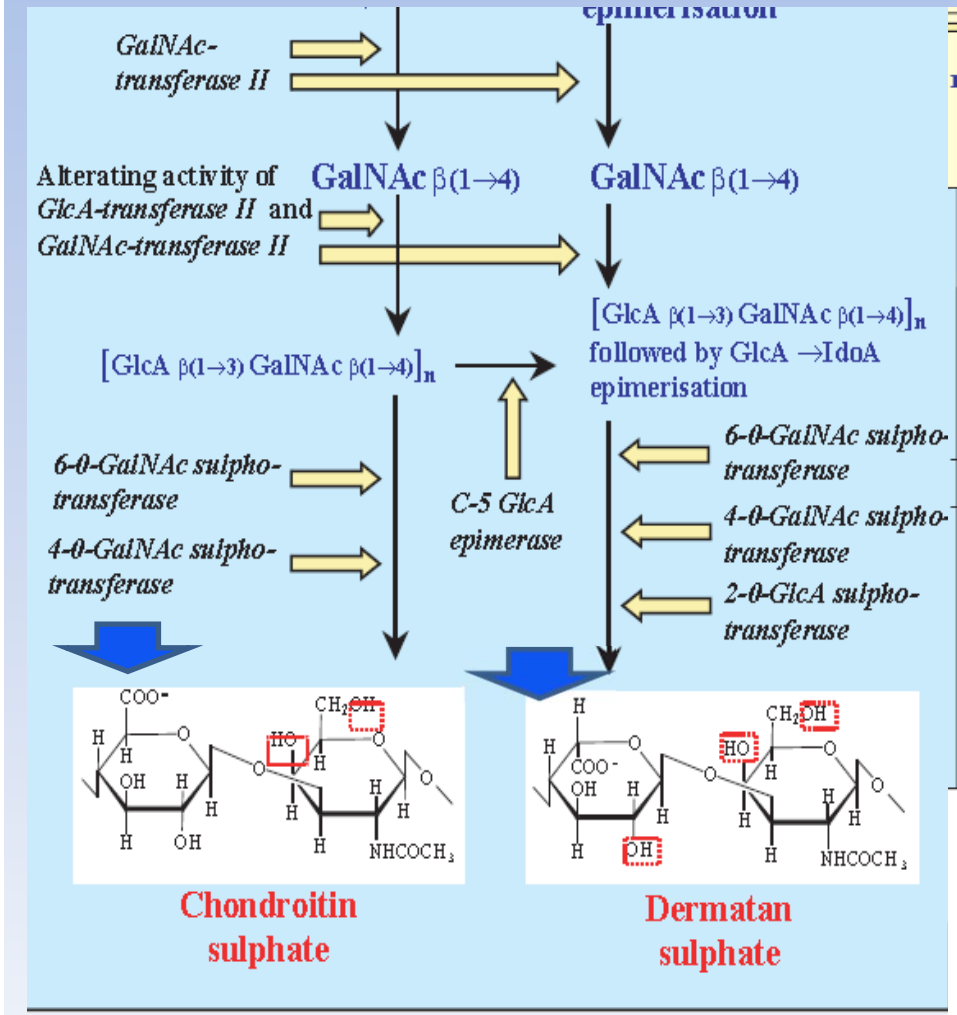
1. **HSGAG and CSGAG** modified proteoglycans first begin with a consensus **Ser-Gly/Ala-X-Gly motif in the core protein. (Ser-Gly)*n=3* starts HSGAG; (Ala-Ser-Gly)*n=3* influence the choice for CSGAG.**
2. **Construction of a tetrasaccharide linker that consists of -GlcAβ1–3Galβ1–3Galβ1–4Xylβ1-O-(Ser)-**
3. **The first modification of the tetrasaccharide linker determines whether the HSGAGs or CSGAGs will be formed. Addition of a GlcNAc promotes the formation of HSGAGs while addition of GalNAc to the tetrasaccharide linker promotes CSGAG development by *beta*-GalNAcT1.**
   ***alpha*-GlcNAcT-I transfers GlcNAc to the tetrasaccharide linker**, which is distinct from glycosyltransferase GlcNAcT-II, the enzyme that is utilized for elongation to build HSGAGs.
4. HSGAG/ CSGAGs, are differentiated from each other by the presence of beta-D-Glycuronic acid (GlcA) and alpha L-Iduronic acid (IdoA) **epimers** respectively.

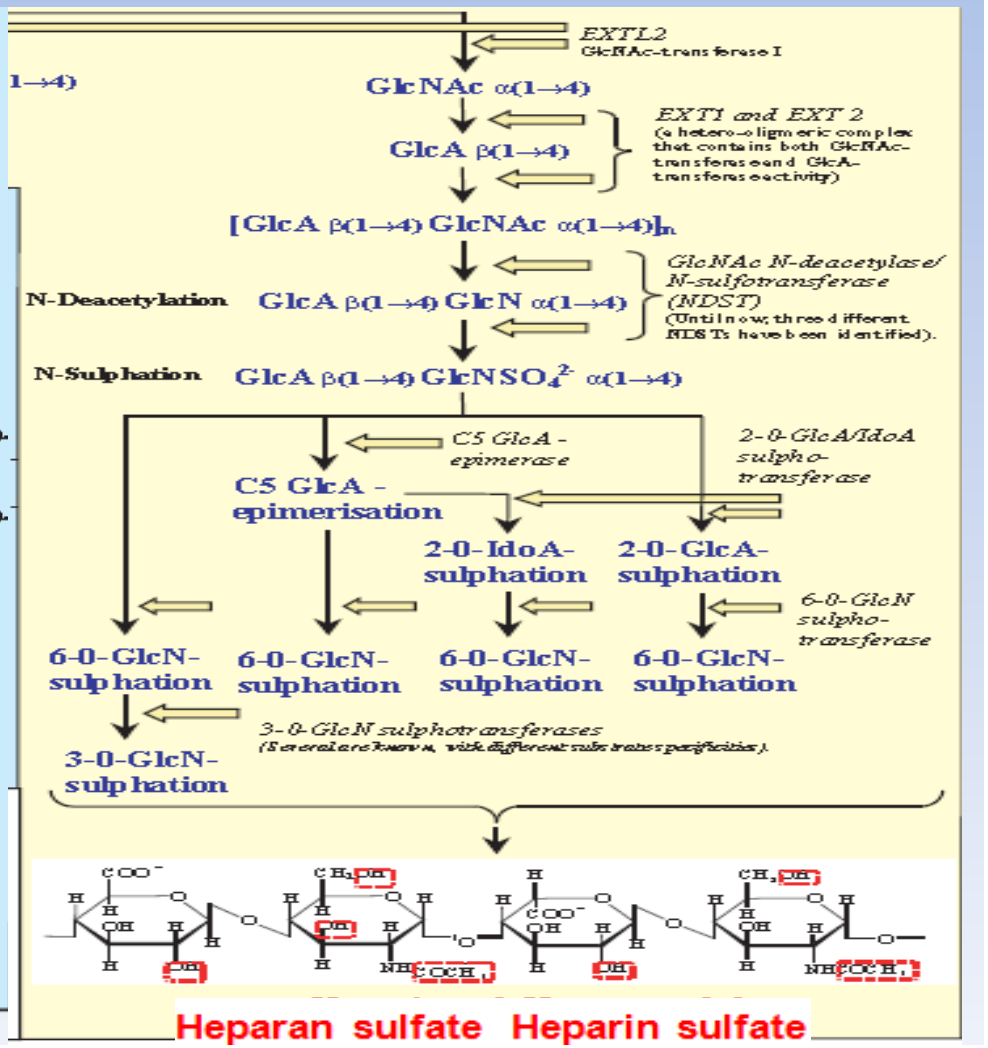


Biosynthesis Glycoaminoglycans (GAGs)/ Structures, *e.g HSGAG en CSGAG*

CSGAGs, are differentiated from each other by the presence of GlcA and IdoA epimers respectively. Similar to the production of HSGAGs, C-5 uronyl epimerase converts d-GlcA to L-IdoA to synthesize dermatan sulfate. ***For CSGAG epimerization occurs before sulfation.***

Three sulfation events of the **CSGAG** chains occur: 4-*O* and/or 6-*O* sulfation of GalNAc and 2-*O* sulfation of uronic acid. ***For HSGAG first N-deacetylation occurs and than sulfation of the Amino function,***. **$GlcNH_2$** residues have been found in heparin and some species of HS.



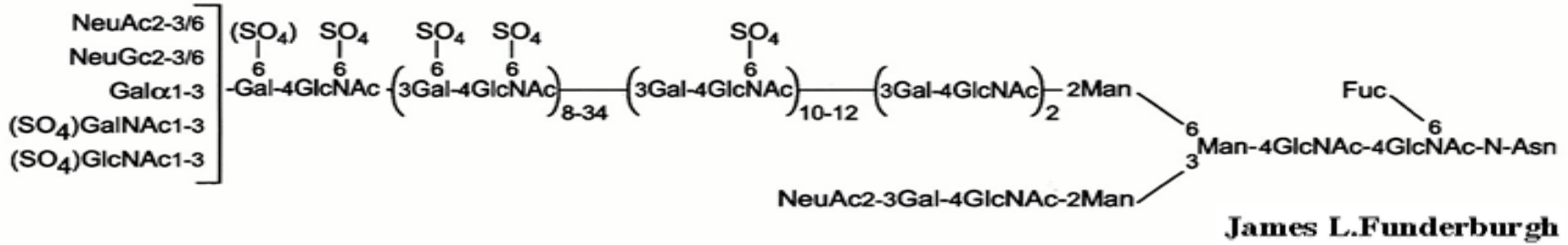


Biosynthesis Glycoaminoglycans (GAGs)/ Structures, *e.g KS types*

- **Keratan sulfate GAGs: KS classes: KS I; KS II; KS III**
- **Originally** the designations KSI and KSII were based on **differences** between KS from **cornea and that of cartilage. Corneal KS is N-linked to Asn residues in the core protein, whereas cartilage KS is O-linked to Ser or Thr residues**. These linkage structures, however, are not tissue-specific in their localization.
- **The class designations currently are employed with respect to the linkage structure**, **not tissue localization**. Thus, the term **KSI** includes all N-**Asn-linked** KS molecules, and **KSII** is used to refer to all KS linked to protein through **GalNAc-O-Ser/Thr.**
  A third type of KS linkage **(Man-O-Ser)** has been identified that might be considered **KSIII**

A. Corneal KSI

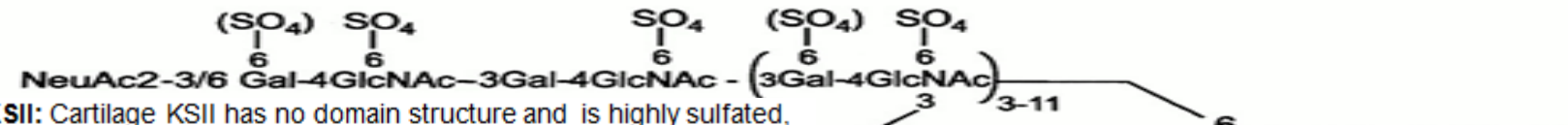
KSI: Complex-type biantennary oligosaccharide N-linked to Asn.
Only the C6-branch is extended. The C3-branch is terminated with a single lactosamine capped by sialic acid (NeuAc2).



James L.Funderburgh

B. Articular Cartilage KSII

Glycobiology vol. 10 no. 10 pp. 951–958, 2000



KSII: Cartilage KSII has no domain structure and is highly sulfated, consisting of almost completely of disulfated monomers interrupted occasionally by single monosulfated lactosamine monomers.
Sialylation of Gal linked to the C3 of the linkage GalNAc is only partial.

Thank you for your attention

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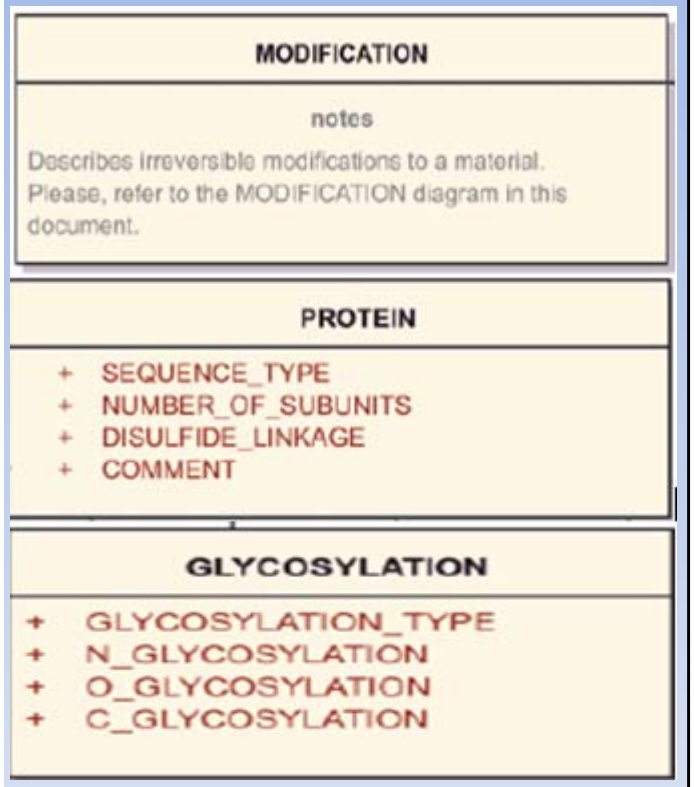
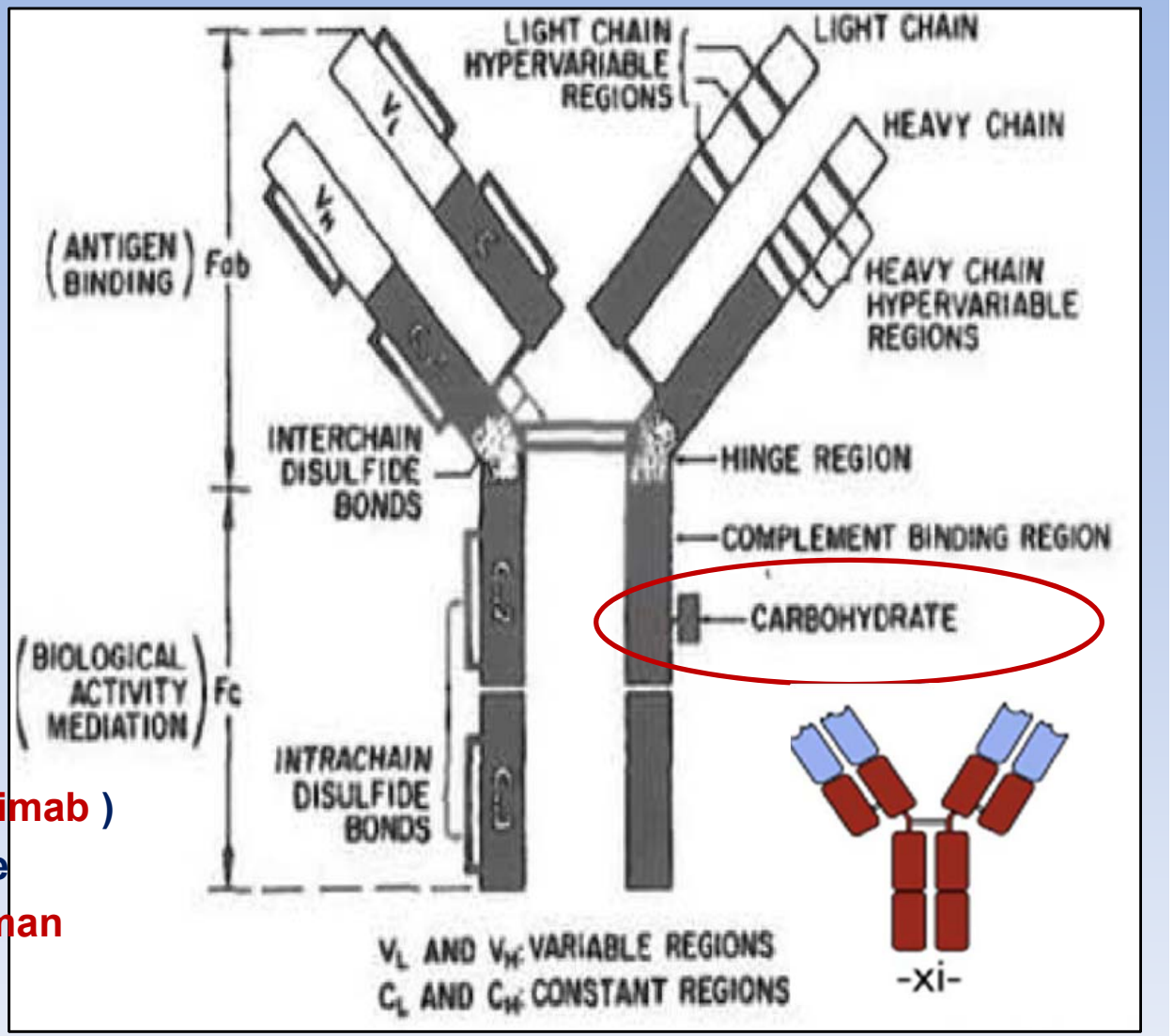
Back up Slides

Glycan structures formed by Post Translational Modifications in Proteins (*e.g.* MAB) captured in the ISO/IDMP M3 11238 Substance Implementation Guide Modification Group





Chimeric antibodies (suffixes –ximab) are composed of murine variable regions (in blue) fused onto human Constant regions (in brown)

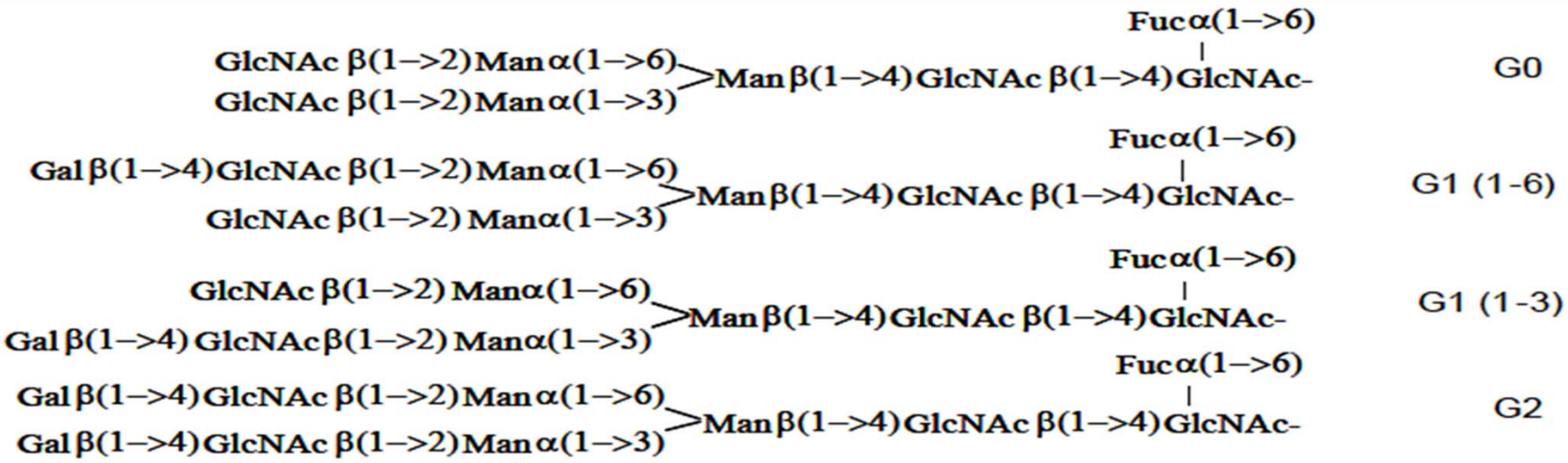
Human gene sequences taken from the kappa light chain and the heavy IgG1 heavy chain, results in antibodies that are approx. 65% human. This reduces immunogenicity, and thus increases serum half life as do Carbohydrate Glycans

BRENTUXIMAB (Recombinant chimeric immunoglobulin G1 [IgG1], anti-CD30 monoclonal antibody produced by rDNA technology in Chinese Hamster ovary cells)

Glycosylation site, Monosaccharide Composition Glycan Distribution

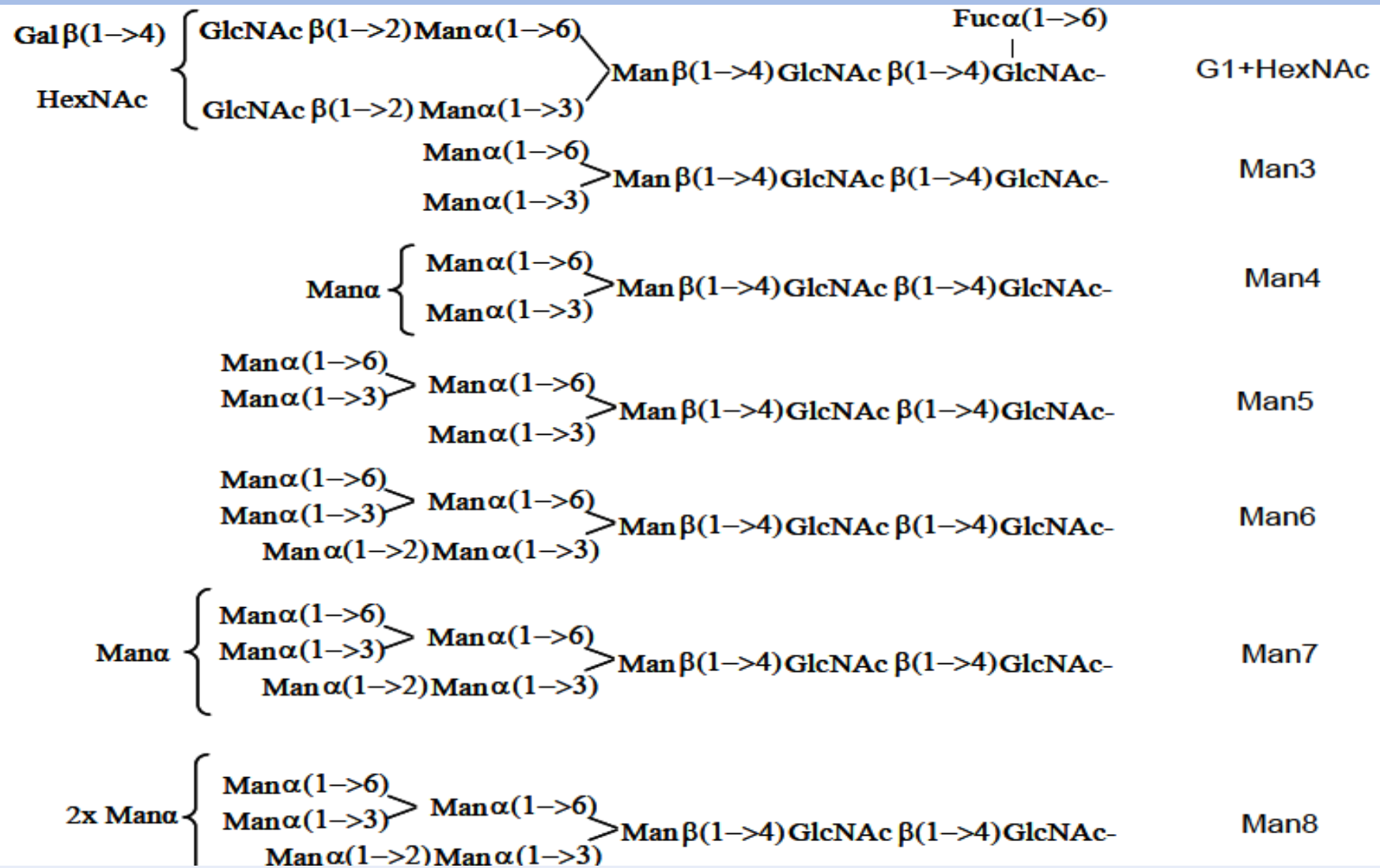
- **N-glycosylation sites: 297, 297"**
  There is one N-glycosylation site on the heavy chain (Asn297), and it is predominantly occupied with a core fucosylated biantennary glycan, typically found with monoclonal antibodies produced by CHO (Chinese Hamster Ovary) cells, **with 0, 1 or 2 terminal galactose residues.**
- **Glycosylation Occupancy:** Asn297 is occupied for 97%.
- **Monosaccharide Composition: Neutral monosaccharides** (fucose, galactose, glucose and mannose); **Basic monosaccharides** (galactosamine, glucosamine) and **sialic acid** was released from the antibody using acid hydrolysis.
- **N-Glycan Distribution:** The predominant N-linked glycoforms detected are core fucosylated biantennary glycans with 0, 1, and 2 terminal galactose residues (G0, G1, and G2).
- **Together, these forms comprise 88% of the N-linked glycans detected.**

{A-(non) fucosylated G0 (G0-F) and oligomannose structures (Man3, Man5, Man6, and Man8); G0 lacking a terminal N-acetylglucosamine (G0-1) are not shown }



Brentuximab

Schematic depiction of identified N-linked glycans



Biopolymers, Structural representation, Glycosidic Bond

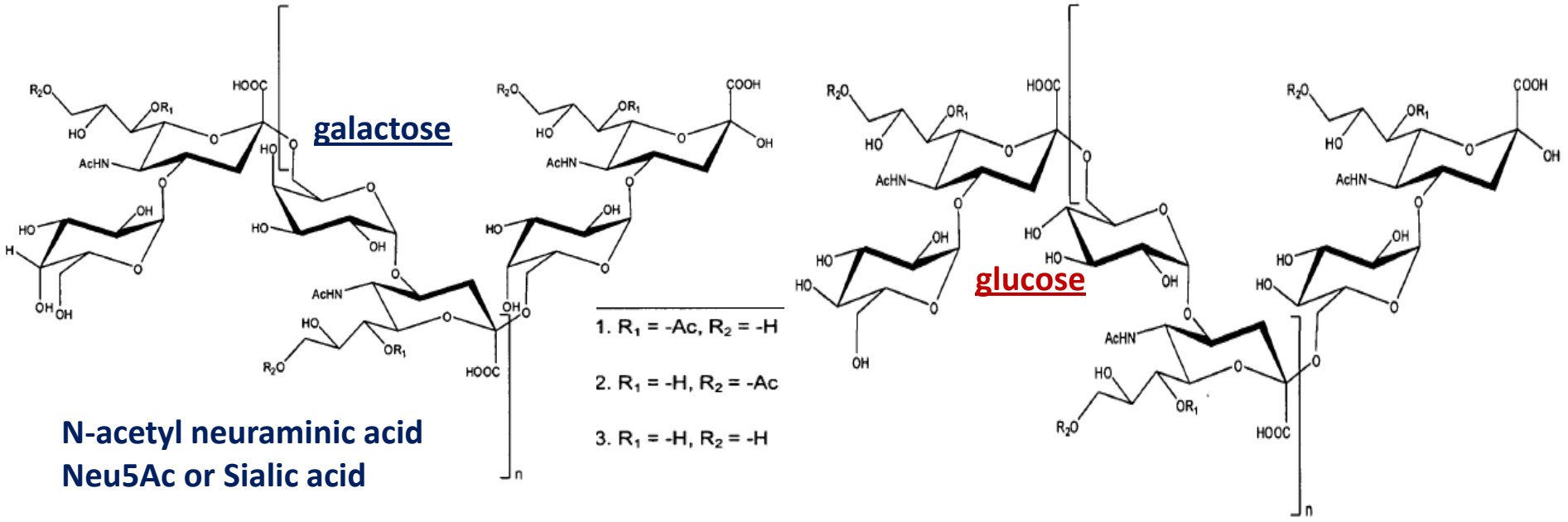
Structures of MenW and MenY Polysaccharide of Meningococcal ACWY conjugate vaccine (MenACWY)

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→4)-α-D-Neu*p*NAc-(2→).

MenY: The partly O-acetylated structure is: -6)-α-D-Glc(1→4)-α-D-Neu*p*5NAc-(2→).

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



N-acetyl neuraminic acid
Neu5Ac or Sialic acid

[Men W, SRU: —»4)-D-Neu*p5*NAc(7/9 OAc)-α-(2—>6) -D-Gal-α-(l—>,].

[MenY, SRU: —»4)-D-Neu*p5*NAc(7/9 OAc)-α-(2—>6) -D-Glc-α-(l—>,].