Functional Design

ISO/ FDIS-IDMP DATABASE 11238

CBG-MEB: Department of Substances

Herman Diederik and Ciska G. Matai

in cooperation with

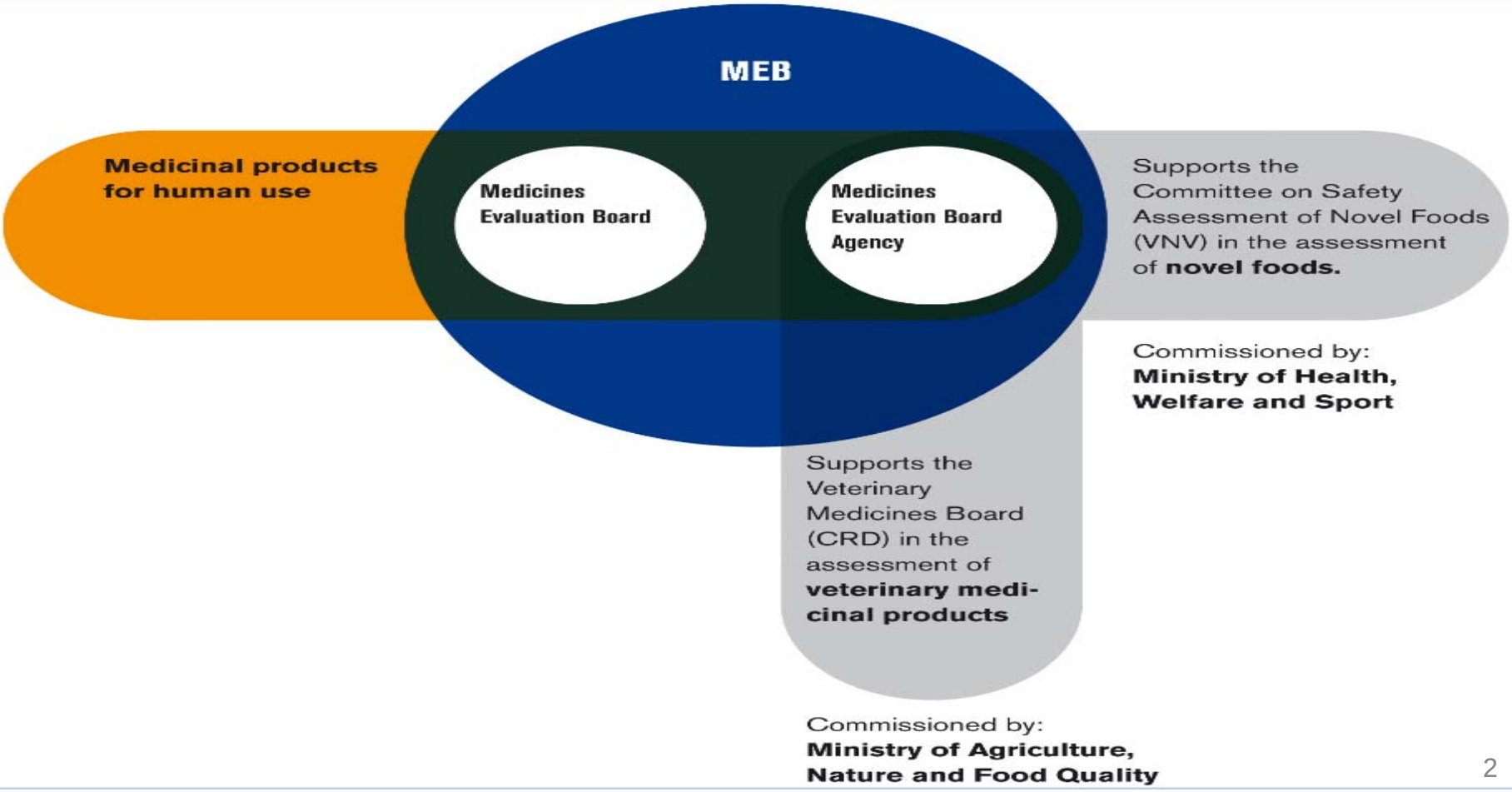
CBG-MEB: Department of Pharmacovigilance
Anja van Haren
CBG-MEB: Department of Int. Affairs/ ICH
Stan van Belkum

February, 2013

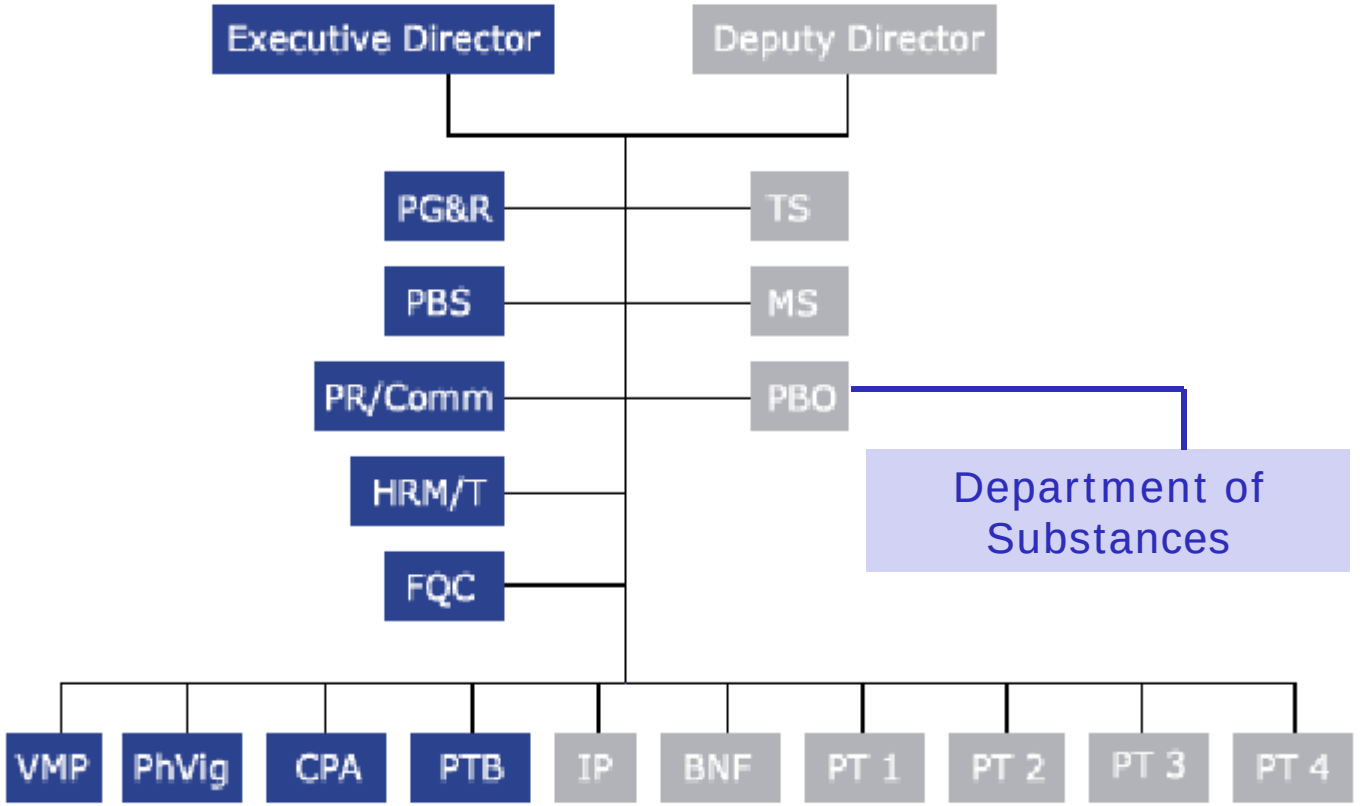
COLLEGE
TER BEOORDELING VAN
GENEESMIDDELEN

C B G
M E B

MEDICINES
EVALUATION
BOARD


MEB
Medicinal products for human use
Medicines Evaluation Board
Medicines Evaluation Board Agency
Supports the Committee on Safety Assessment of Novel Foods (VNV) in the assessment of **novel foods.**
Commissioned by: **Ministry of Health, Welfare and Sport**
Supports the Veterinary Medicines Board (CRD) in the assessment of **veterinary medicinal products**
Commissioned by: **Ministry of Agriculture, Nature and Food Quality**

ORGANISATION STRUCTURE



Current Substance Registration System

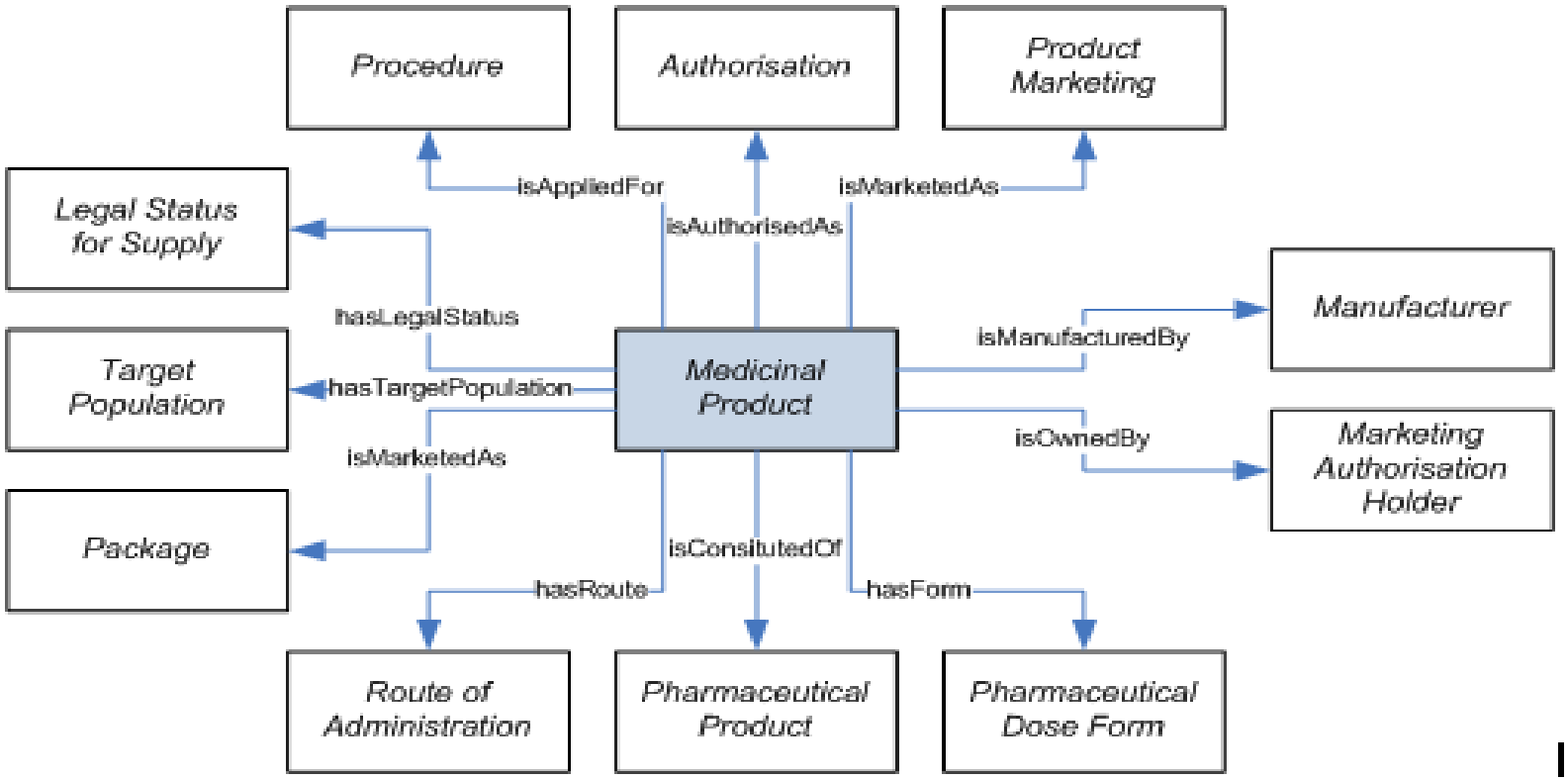


Figure 2-1: Relationships with Medicinal Product Business Concept

Current Substance Registration System

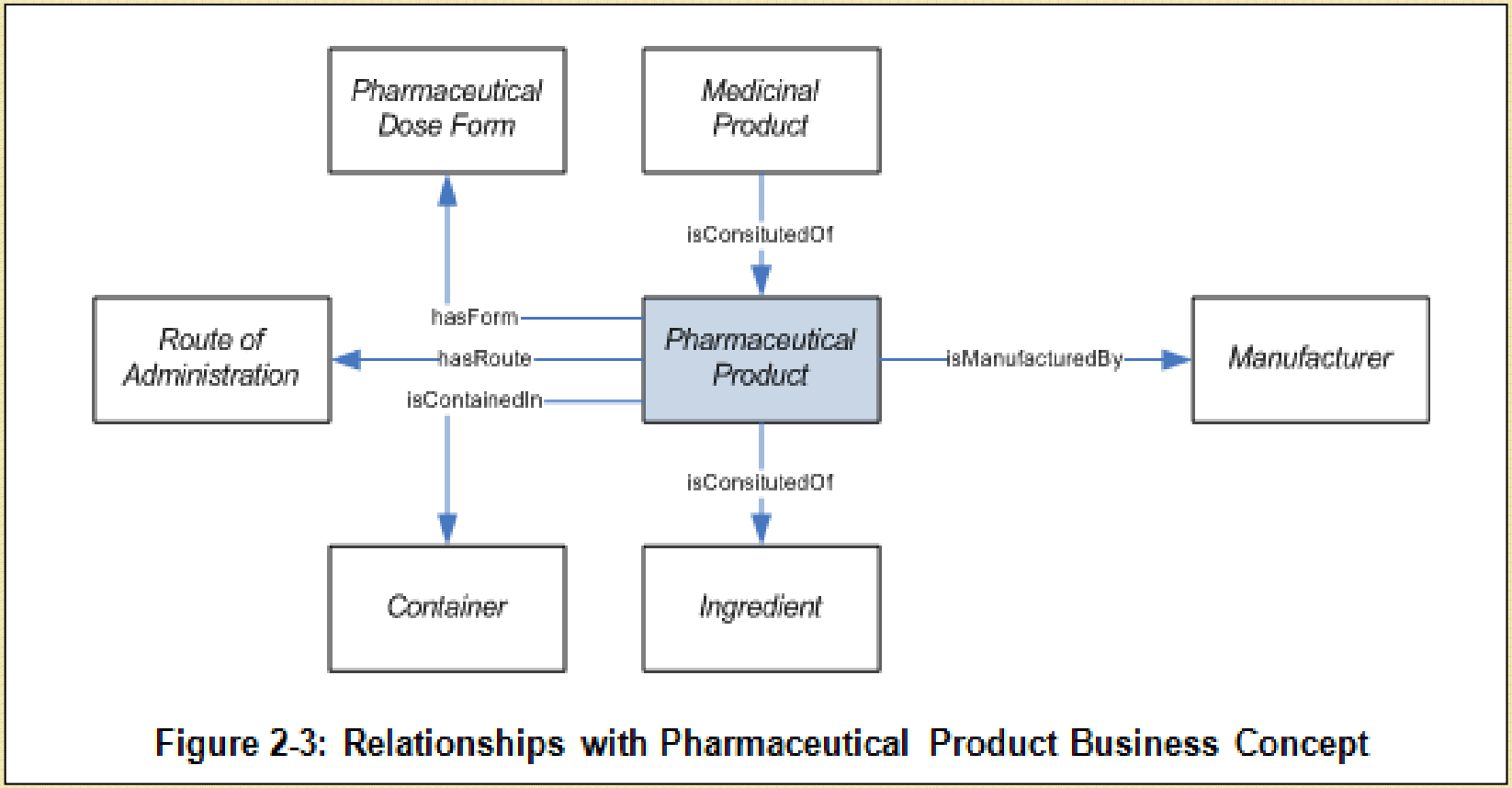


Figure 2-3: Relationships with Pharmaceutical Product Business Concept

Current Substance Registration System

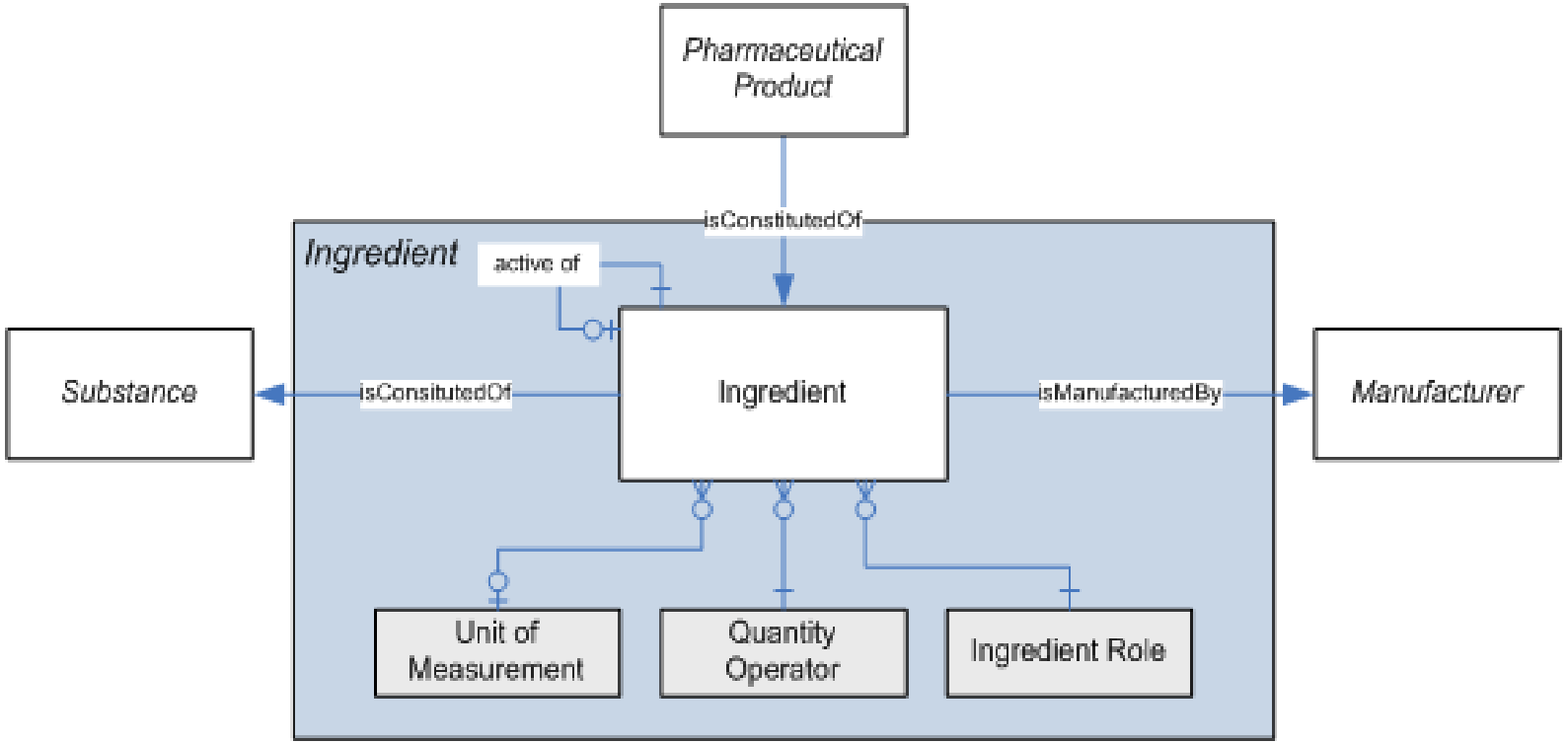


Figure 2-7: Link from Ingredient to Technical Concepts

Pharmaceutical Product Representation in “ICI”, Tablet

Filter folder for documents where: Show Advanced Criteria

Document Title contains

Apply Filter Clear

Actions Menu Items Found: 7 View: Detailed Show Items: 500

Title ▲	Quantity Value 1	Quantity Operator	Quantity Value 2	Unit	Ingredient Type	Composition Group
CELLULOSE, MICROKRISTALLIJN					Inactief bestanddeel	Samenstelling
INDAPAMIDE, 0-WATER 0,625 = mg/stuk	0,625	=		mg/stuk	Actief bestanddeel	Samenstelling
LACTOSE 1-WATER					Inactief bestanddeel	Samenstelling
MAGNESIUM STEARATE (E 470B) (RI)					Inactief bestanddeel	Samenstelling
NATRIUMWATERSTOFCARBONAAT					Inactief bestanddeel	Samenstelling
PERINDOPRIL-TERT-BUTYLAMINE 2 = mg/stuk	2,0	=		mg/stuk	Actief bestanddeel	Samenstelling
SILICIUMDIOXIDE (E 551)					Inactief bestanddeel	Samenstelling

Active Substance Representation of Pharm. Product, Tablet

Class: Ingredient

	Property	Value
	Ingredient Type:	Actief bestanddeel
*	Substance:	9999910182 - PERINDOPRIL-TERT-BUTYLAMINE Change Value
	Quantity Value 1:	2,0
	Quantity Operator:	=
	Quantity Value 2:	
	Unit:	mg/stuk Change Value Clear
*	Concerned Pharmaceutical Product:	Co-Tomil 2 mg/0,625 mg, tabletten - 103269 - Tablet Change Value
	Equivalent Substance:	- PERINDOPRIL Change Value
	Equivalent Quantity Value 1:	1,668
	Equivalent Quantity Operator:	=
	Equivalent Quantity Value 2:	
	Equivalent Unit:	mg/stuk Change Value Clear
*	Composition Group:	Samenstelling
	Notes:	

Connection between Naming Active Substance "Dutch name field" and wording in Chapter 2 of SmPC

1. NAME OF THE MEDICINAL PRODUCT

<<Product name>> 2 mg/0.625 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg perindopril tert-butylamine equivalent to 1.67 mg perindopril and 0.625 mg indapamide.

Excipient:
Each tablet contains 33.74 mg lactose.
For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Oblong, white, slightly biconvex tablets with bevelled edges.

Connection between Naming Active Substance "Dutch name field" and wording in Chapter 6 of Patient Information Leaflet / Package Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

<<Product name>> 2 mg/0.625 mg tablets

perindopril tert-butylamine/indapamide

Read this leaflet carefully before you start taking this medicine.

6. FURTHER INFORMATION

What <<Product name>> tablets contain

- The active substances are perindopril tert-butylamine and indapamide. Each tablet contains 2 mg perindopril tert-butylamine equivalent to 1.67 mg perindopril and 0.625 mg indapamide.

- The other inactive substances are microcrystalline cellulose, lactose monohydrate, sodium hydrogen carbonate, colloidal anhydrous silica, magnesium stearate.

Connection between Naming Active Substance "Dutch name field" and wording in Marketing Authorization License

registratienummer	RVG 103269	
naam van het geneesmiddel	Perindopril tert-butylamine/Indapamide 2/0,625 A tabletten 2/0,625 mg	
farmaceutische vorm	Tablet	
werkzame stoffen en hoeveelheid per doseringseenheid of de concentratie	INDAPAMIDE 0-WATER	0.625 mg/stuk
	PERINDOPRIL-TERT-BUTYLAMINE	2.0 mg/stuk
	OVEREENKOMEND MET PERINDOPRIL	1.668 mg/stuk
naam en adres houder van de handelsvergunning	Apothecon B.V. Nijverheidsweg 3 3771 ME Barneveld	
datum van afgifte	6 april 2009	
datum van verlenging voor onbepaalde tijd	11 januari 2012	
afleverstatus	Uitsluitend recept	
wettelijke grondslag	Art 10(1), Directive 2001/83/EC, generic application	

Utrecht, 02 augustus 2012

Deze pagina('s) vormt (vormen) samen met de laatst goedgekeurde versie van de samenvatting van de productkenmerken de handelsvergunning.

Active Substance Record Representation

Custom Object: 9999910182 - PERINDOPRIL-TERT-BUTYLAMINE

Close

Class: *Substance (readonly)*

Property	Value
CBG Number:	9999910182
CAS Number:	0107133368
Dutch Name:	PERINDOPRIL-TERT-BUTYLAMINE
Homeopatic Name:	
Preferred Term As Inactive Ingredient:	
Quantity Indicator Inactive Ingredient:	
P RMS:	
Harmonised Substance Data Lock Point:	
Active Ingredient Synonym:	"BUTYL(TERT)AMINOPERINDOPRIL"; "PERINDOPRIL TERT-BUTYLAMINE SALT"; "PERINDOPRILBUTYLAMINE (TERT)"; "S 9490-3"; "TERT-BUTYLAMINOPERINDOPRIL"; "1H-Indole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro(2S,3aS,7aS)-comp.with 2-methyl-2propanamine (1:1)"; "Coversyl"; "2-Methylpropan-2-amine (2S,3aS,7aS)-1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1H-indole-2-carboxylate."; "Perindopril erbumine"
Origin:	
Latin Name:	PERINDOPRILUM TERT-BUTYLAMINUM
INN Name:	PERINDOPRIL-tert-BUTYLAMINE
English Name:	PERINDOPRIL-tert-BUTYLAMINE
Inactive Ingredient Name:	
Notes:	Mol. Gew.: 441,60 Mol. Form.: C19 H32 N2 O5 . C4 H11 N Polymorphism: De stof kan bestaan in een amorfe vorm (Manufactorer LEK) of in diverse crystallijne vormen; Alpha criystallijne vorm: Krka

Path: **Object Stores > Nice > Medicinal Products > M > ME > Menopur--Dr. Fisher Farma B.V. > Menopur 75 IE, poeder en oplosmiddel voor oplossing voor injectie - 102479 > V004 - Herstelzaak humaan - Approved > Pharmaceutical Products > Poeder voor oplossing voor injectie > Ingredients**

Get Info | Bookmark | Add To Shortcuts | Printable View

Filter folder for documents where: Show Advanced Criteria

Document Title contains

Apply Filter Clear

Actions Menu Items Found: 8 View: Detailed Show Items: 500

Title ▲	Quantity Value 1	Quantity Operator	Quantity Value 2	Unit	Ingredient Type	Composition Group
FOLLIKEL-STIMULEREND HORMOON 75 = IE/flacon	75,0	=		IE/flacon	Actief bestanddeel	Samenstelling overeenkomend met
LACTOSE 1-WATER					Inactief bestanddeel	Samenstelling
LUTEÏNISEREND HORMOON 75 = IE/flacon	75,0	=		IE/flacon	Actief bestanddeel	Samenstelling overeenkomend met
MENOPAUZEGONADOTROFINE 2000 >= IE/mg	2000,0	>=		IE/mg	Actief bestanddeel	Samenstelling
NATRIUMHYDROXIDE					Inactief bestanddeel	Samenstelling
NITROGEN (HEAD SPACE) (E 941) (RI)					Inactief bestanddeel	Samenstelling
POLYSORBAAT 20					Inactief bestanddeel	Samenstelling
ZOUTZUUR					Inactief bestanddeel	Samenstelling

Background

Pharmacovigilance

- Identification of the medicinal product involved in the adverse event report is critical:
  - Specificity within an adverse event/reaction report
  - Clear and accurate communication across jurisdictions (countries & regions)

- More specificity leads to more accuracy in analysis

European Commission Estimation

- 5% of all hospital admissions due to ADRs
- 5% of all hospital patients experience an ADR
- ADRs 5th most common cause of hospital death
- 197,000 deaths per year in EU caused by ADRs
- Total societal cost €79 billion

Better protecting the patients

Be aware of the system and your role

ICH Background

ICH M5 Objective:

Develop harmonized standards building on the regulatory and technical processes established in the 3 ICH regions and observer countries

- Standardize terminology/controlled vocabulary concepts and models related to medicinal products
- Standardize the exchange format of regulated medicinal product information

ISO IDMP Standards (1)

Set of 5 International Standards:

- prEN ISO 11615 Health informatics — Identification of medicinal products - Data elements and structures for the unique identification and exchange of regulated medicinal products

- prEN ISO 11616 Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated pharmaceutical product information

18

ISO IDMP Standards (2)

- prEN ISO 11238 Health Informatics — Identification of medicinal products — Data elements and structures Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on substances and specified substances
- prEN ISO 11239 Health Informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging
- prEN ISO 11240 Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of units of measurement

Scope

Together, these five standards:

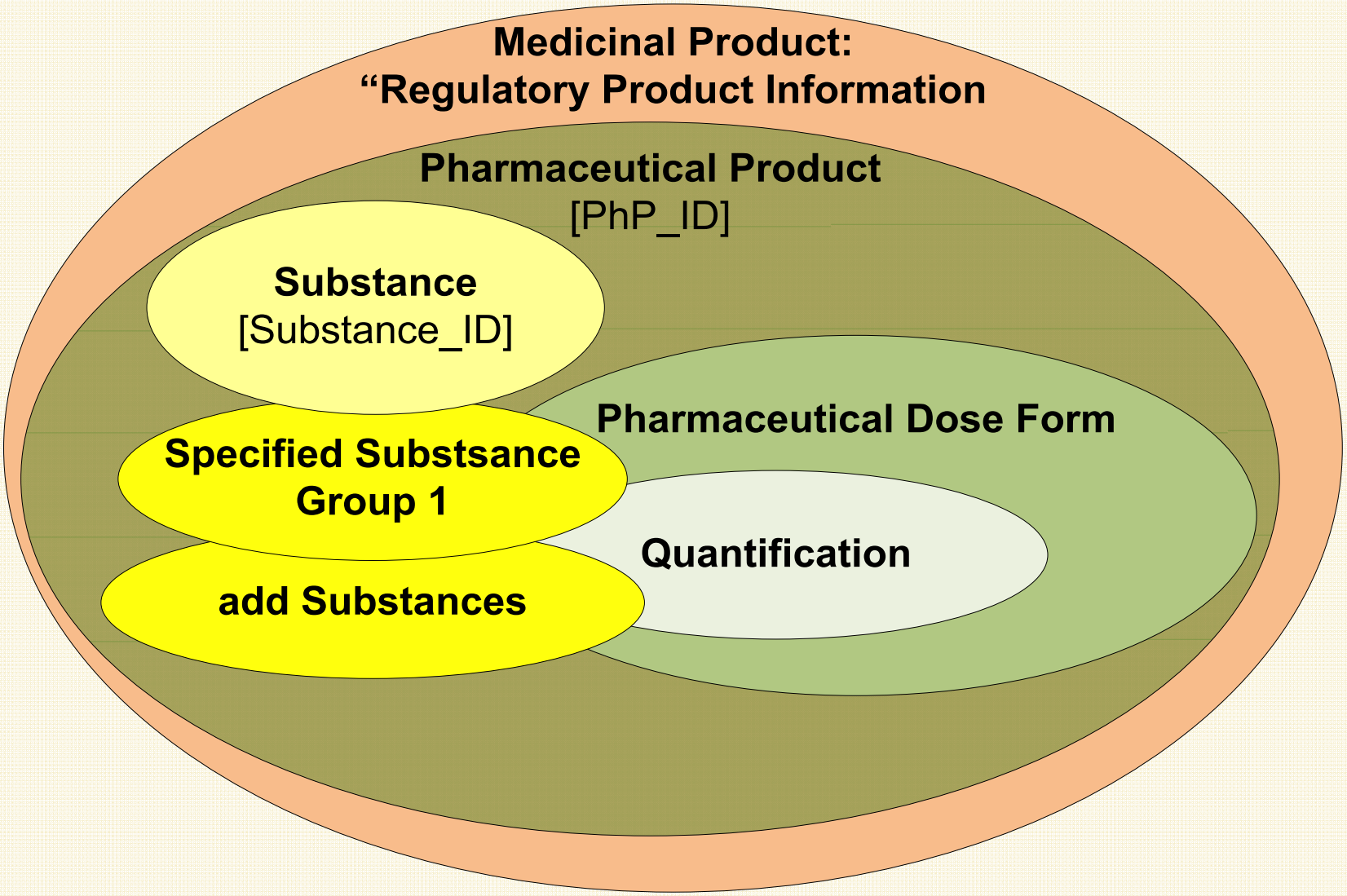
- Define
- Characterize
- Uniquely identify

regulated medicinal products for human use

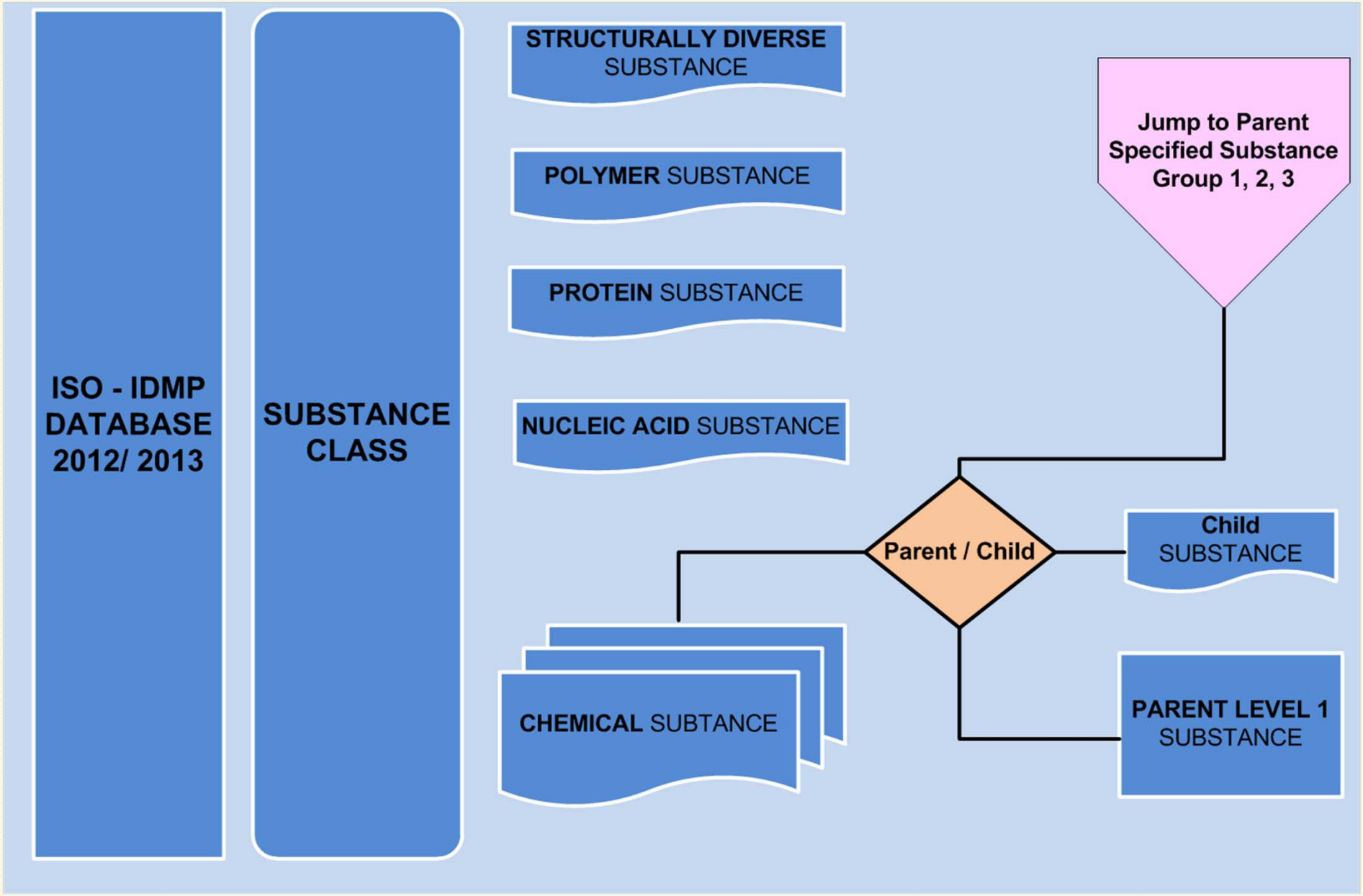
Support the entire product life cycle management:

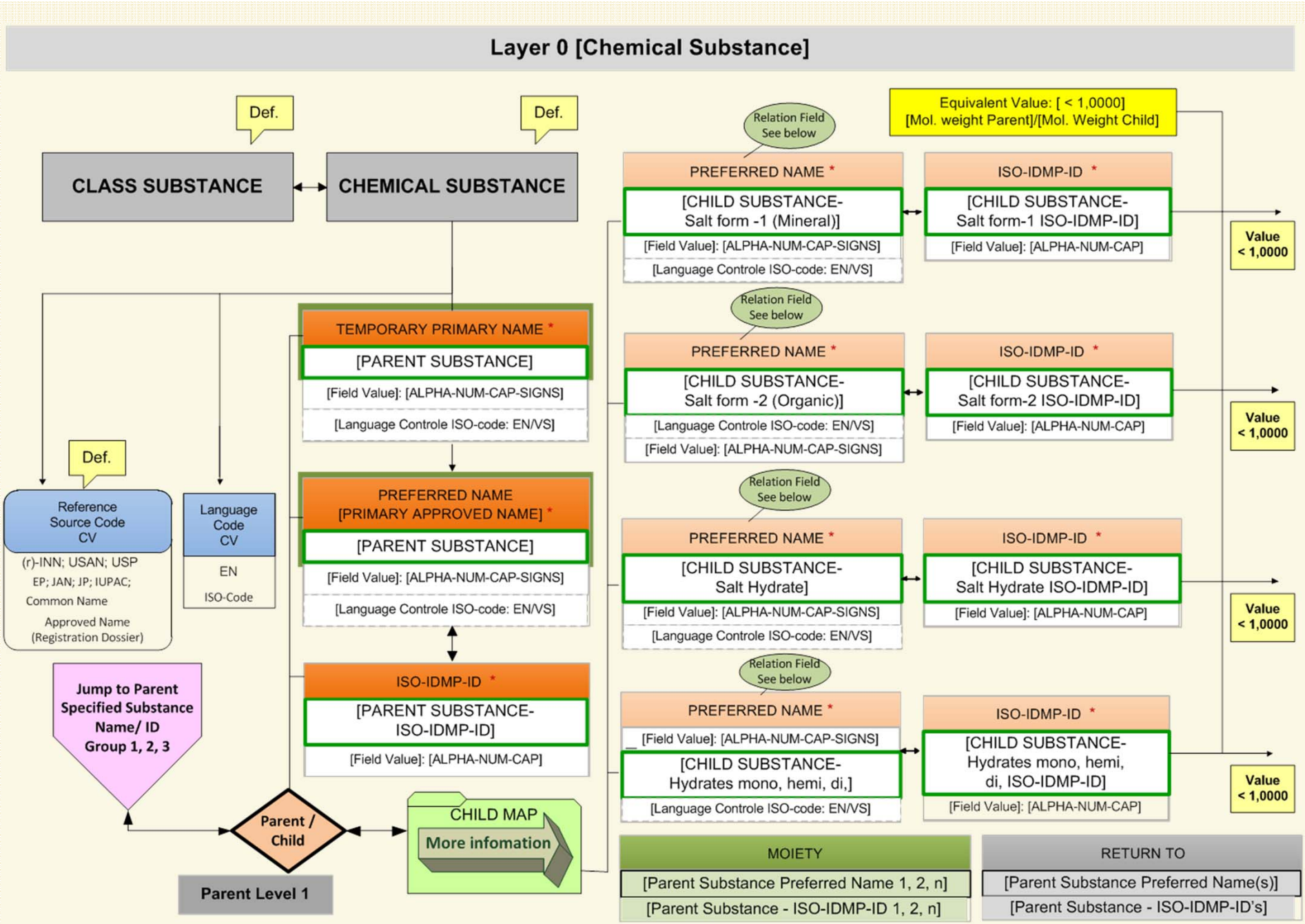
- Development
- Authorization (approval)
- Post-marketing
- Renewal or withdrawal as applicable

ISO-IDMP SUBSTANCE DATABASE APPROACH



CLASSIFICATION SUBSTANCE ISO-IDMP-DATABASE

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Def.
CLASS SUBSTANCE
CHEMICAL SUBSTANCE
Def.
Reference Source Code CV
(r)-INN; USAN; USP
EP; JAN; JP; IUPAC;
Common Name
Approved Name
(Registration Dossier)
Language Code CV
EN
ISO-Code
TEMPORARY PRIMARY NAME *
[PARENT SUBSTANCE]
[Field Value]: [ALPHA-NUM-CAP-SIGNS]
[Language Controle ISO-code: EN/VS]
PREFERRED NAME [PRIMARY APPROVED NAME] *
[PARENT SUBSTANCE]
[Field Value]: [ALPHA-NUM-CAP-SIGNS]
[Language Controle ISO-code: EN/VS]
ISO-IDMP-ID *
[PARENT SUBSTANCE-ISO-IDMP-ID]
[Field Value]: [ALPHA-NUM-CAP]
Jump to Parent Specified Substance Name/ ID Group 1, 2, 3
Parent / Child
Parent Level 1
CHILD MAP
More infomation
Equivalent Value: [< 1,0000]
[Mol. weight Parent]/[Mol. Weight Child]
Relation Field See below
PREFERRED NAME *
[CHILD SUBSTANCE-Salt form -1 (Mineral)]
[Field Value]: [ALPHA-NUM-CAP-SIGNS]
[Language Controle ISO-code: EN/VS]
ISO-IDMP-ID *
[CHILD SUBSTANCE-Salt form-1 ISO-IDMP-ID]
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Relation Field See below
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[CHILD SUBSTANCE-Salt form -2 (Organic)]
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ISO-IDMP-ID *
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RETURN TO
[Parent Substance Preferred Name(s)]
[Parent Substance - ISO-IDMP-ID's]

CLASSIFICATION SUBSTANCE ISO-IDMP-DATABASE LAYER DEFINITION

Layer 0.0: FLOW CHART CHEMICAL SUBSTANCE

Layer 0 [Chemical Substance] PREFERRED NAME and ISO-IDMP-ID (*Parent Substance*)

Parent/ Child Specified Substance Name/ ID Group 1, 2, 3

Child Substance Name/ ID and Equivalent Value *Child Substance/ Parent Substance*

Layer 1 [Chemical Substance] [Naming and Coding of *Parent/ Child Substance*]

Layer 2 [Chemical Substance] [Molecular Formula, Molecular Weight, Molecular Structure] [*Parent/ Child Substance*]

Chemical Substance Role Classification of Isomers/ Impurities/ Degradant/ etc:

Chemical Name (*Parent Substance* and Sructural Related Substance; Molecular Structure an Molecular Weight

Layer 3 [Chemical Substance] [Naming and Coding of *Parent/ Child Substance*] ***Specified Substance Group 1***

Parent/ Child Substance Specified Substance Group 1 **Constituents** (Name and ISO-IDMP-ID)

Constituent Role and Properties/ Notes Field

CLASSIFICATION SUBSTANCE ISO-IDMP-DATABASE LAYER DEFINITION *continue*

↓

Layer 4 [Chemical Substance] [Naming and Coding of *Parent/ Child Substance*] or

[Naming and Coding of *Parent/ Child Substance Specified Substance Group 1*]

***Specified Substance* Group 2**

Addition MANUFACTURER(s)

↓

Parent/ Child Substance Specified Substance Group 2 Manufacturer Name and ID-Code

Production Site and GMP Inspection, Inspection date

↓

Layer 5 [Chemical Substance] [Naming and Coding of *Parent/ Child Substance*] or

[Naming and Coding of *Parent/ Child Substance Specified Substance Group 1*]

***Specified Substance* Group 3**

Addition Grade

↓

Type or Description of Grade
Measurement of Technical Grade
Definition of Fineness of Powder
Expression of Particle Size Distribution Specification
Notes Field

↓

CLASSIFICATION SUBSTANCE ISO-IDMP-DATABASE LAYER DEFINITION *continue*

↓

Layer 6 [*Parent/ Child Substance*] **Documentation**

Public Domain

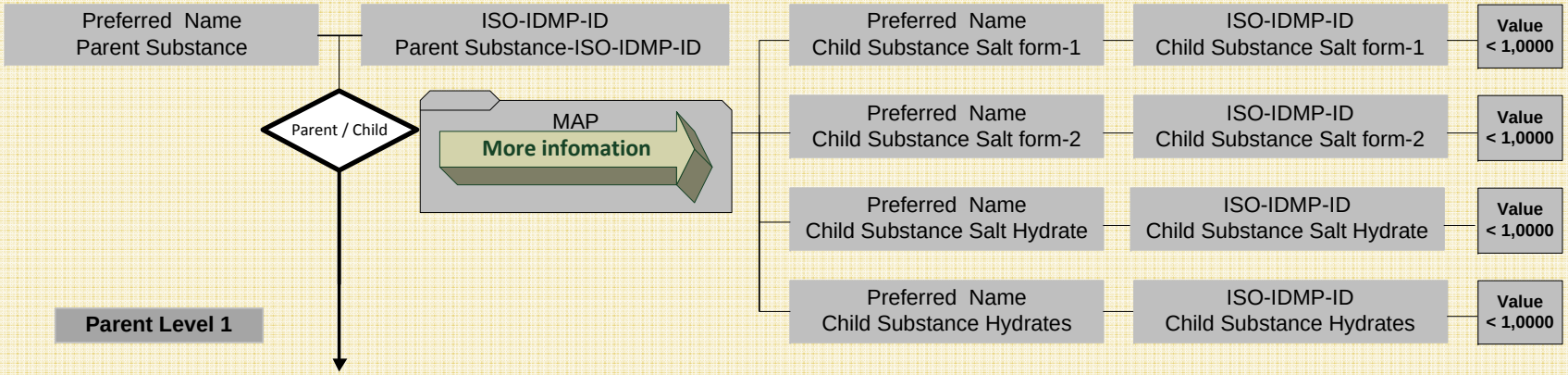
Restricted Domain Part I
(Competent Registration Authority Only)

Restricted Domain Part II
(Competent Registration Authority, Edetorial Reviewer Only)

↓

Layer 7 [Chemical Substance] **LEGEND**

Layer 1 [Chemical Substance]



Layer 1 [Naming and Coding of Parent (Child) Substances]

MANDATORY OFFICIAL NAMES

Def.

Jump To STN

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CA Index Name	EN ISO-Code	[CA INDEX NAME]
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Def.

Jump to WHO list

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INN NAME *
[RECOMMENDED INN ENGLISH]
[Field Value]: [ALPHA-CAP]

MANDATORY CODES

Jump To STN

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ISO-Code CAS Registry number	[NUMBER]
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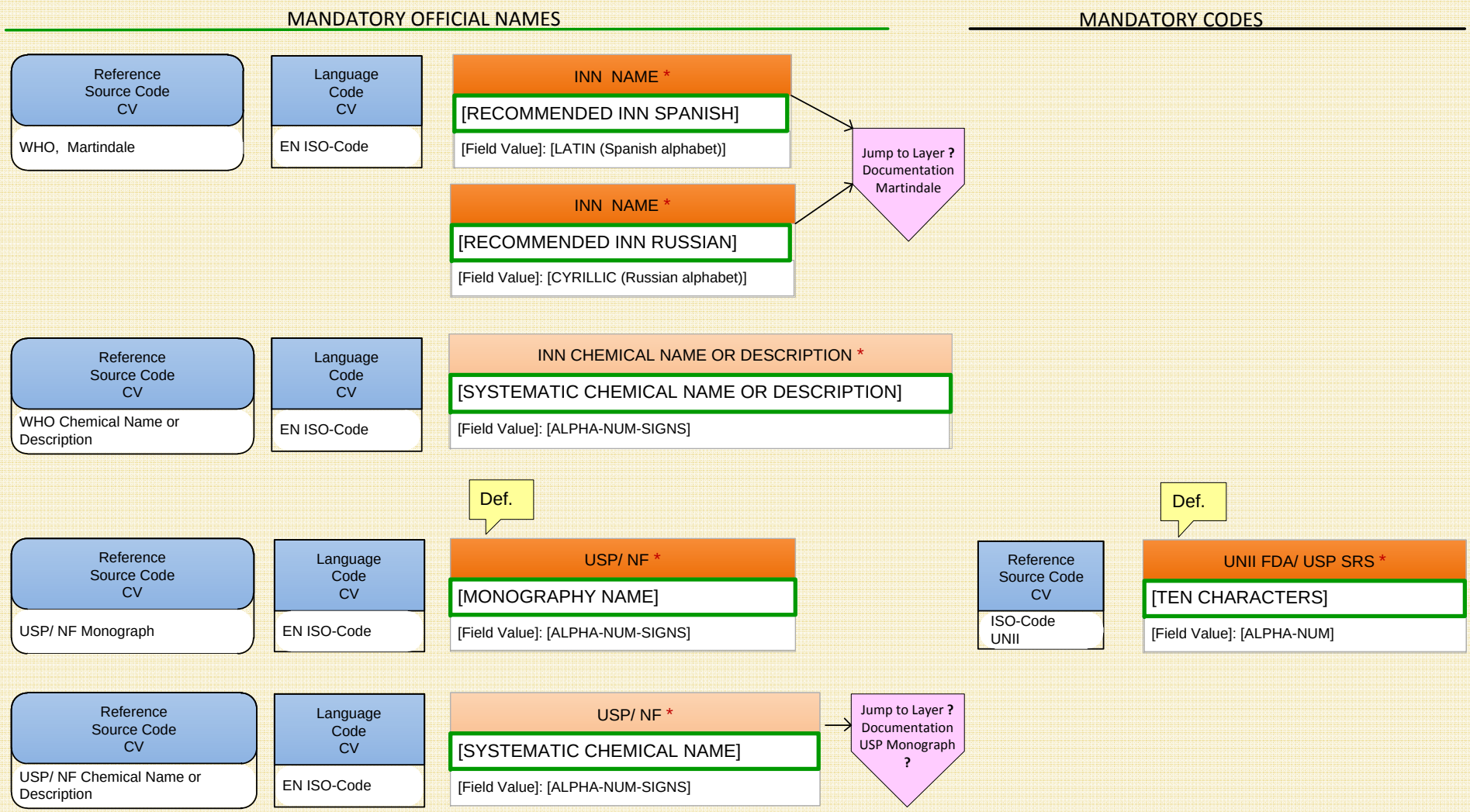
Jump to WHO list

Reference Source Code CV	WHO Drug Information *
WHO	[vol. number]; [number]; [year]; [list number]
	[Field Value]: [NUM-SIGNS]

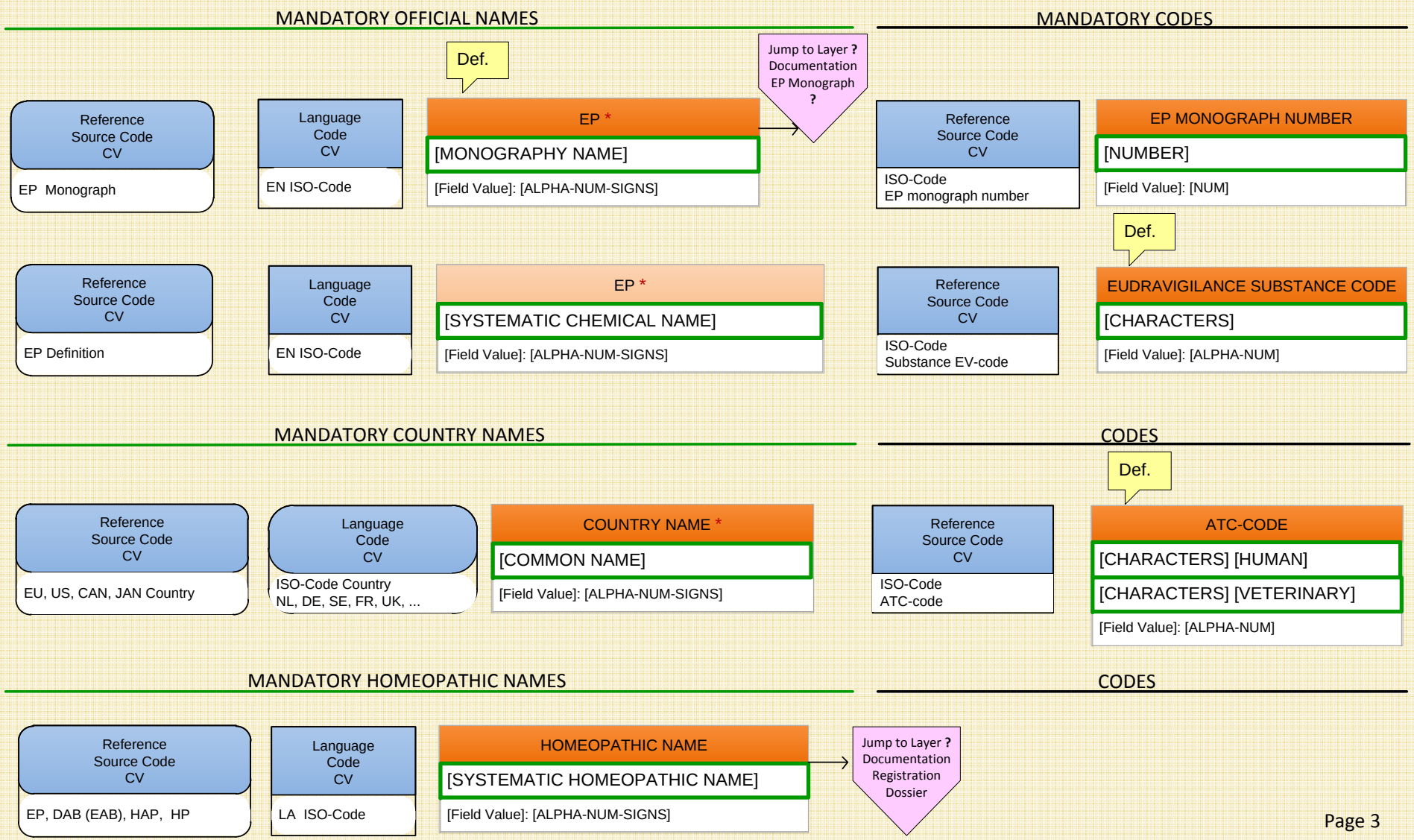
Layer 1 [Chemical Substance]

Layer 1 [Naming and Coding of Parent (Child) Substances] *continue*

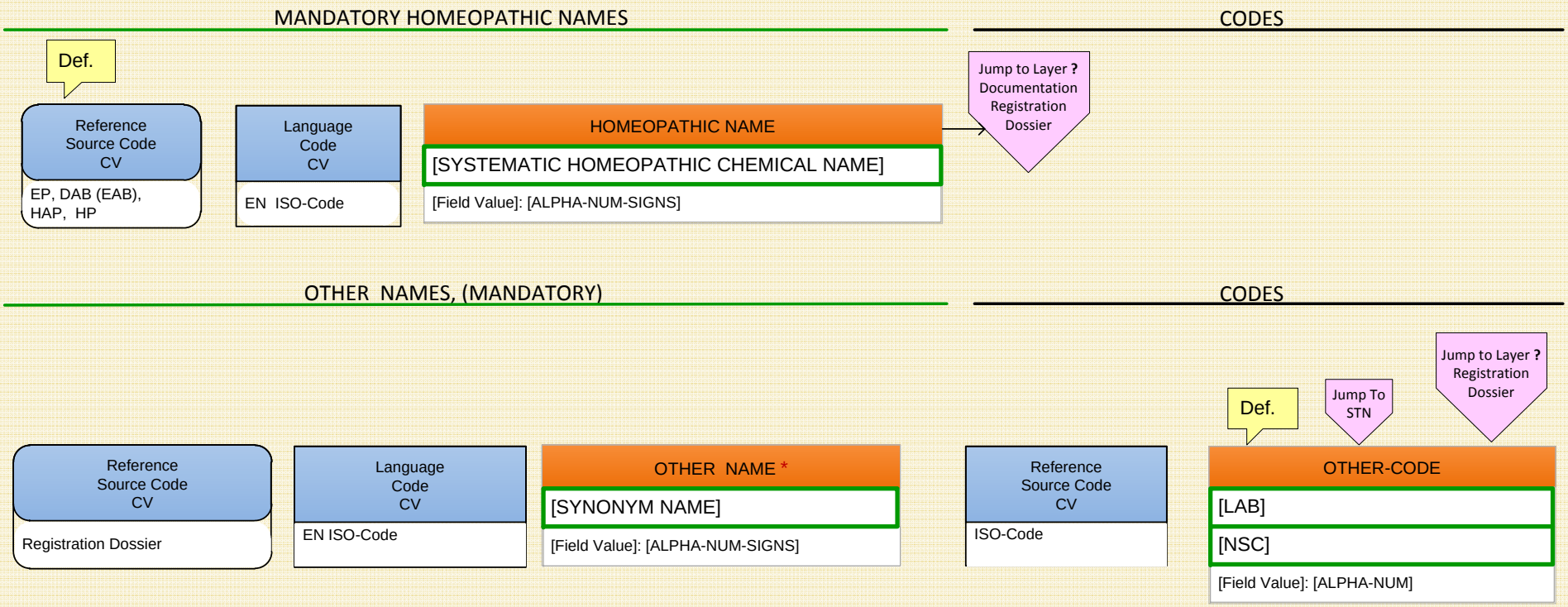


Layer 1 [Chemical Substance]

Layer 1 [Naming and Coding of Parent (Child) Substances] *continue*



Layer 1 [Naming and Coding of Parent (Child) Substances] *continue*



PREFERRED NAME:

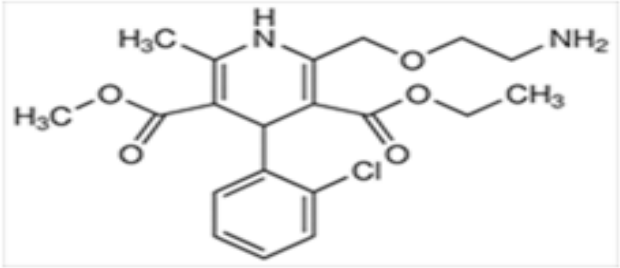
USP: AMLODIPINE BESYLATE; EP: AMLODIPINE BESILATE;

INN: Amlodipini Besilas [rINNM (la)

INN: Amlodipine Besilate [rINNM (en)]

INN: Besilato de amlodipino [rINNM (es)]

INN: Амлодипина Безилат [rINNM (ru)]



CHEMICAL NAME:

CAS: **3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, benzenesulfonate (1:1) (CA INDEX NAME)**

USP: **3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (±)-, monobenzenesulfonate.**

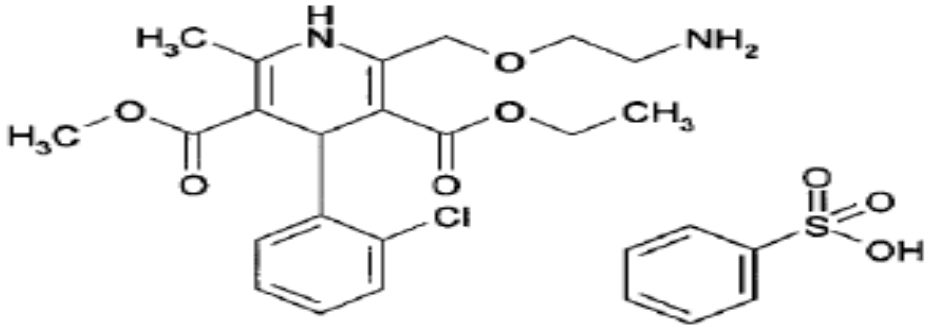
EP: **3-Ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-l,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate.**

Martindale Parent Substance AMLODIPINE:

3-Ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate

APPLICANT:

. Structural formula:



. Molecular formula: $C_{20}H_{25}ClN_2O_5$, $C_6H_6O_3S$

. Relative molecular mass: 567.1 (408.882 + 158.178)
The conversion factor for the salt to the base is 0.721.

. Amlodipine corresponds to the racemic mixture (one asymmetric carbon).

MOLECULAR FORMULA/ Weight:

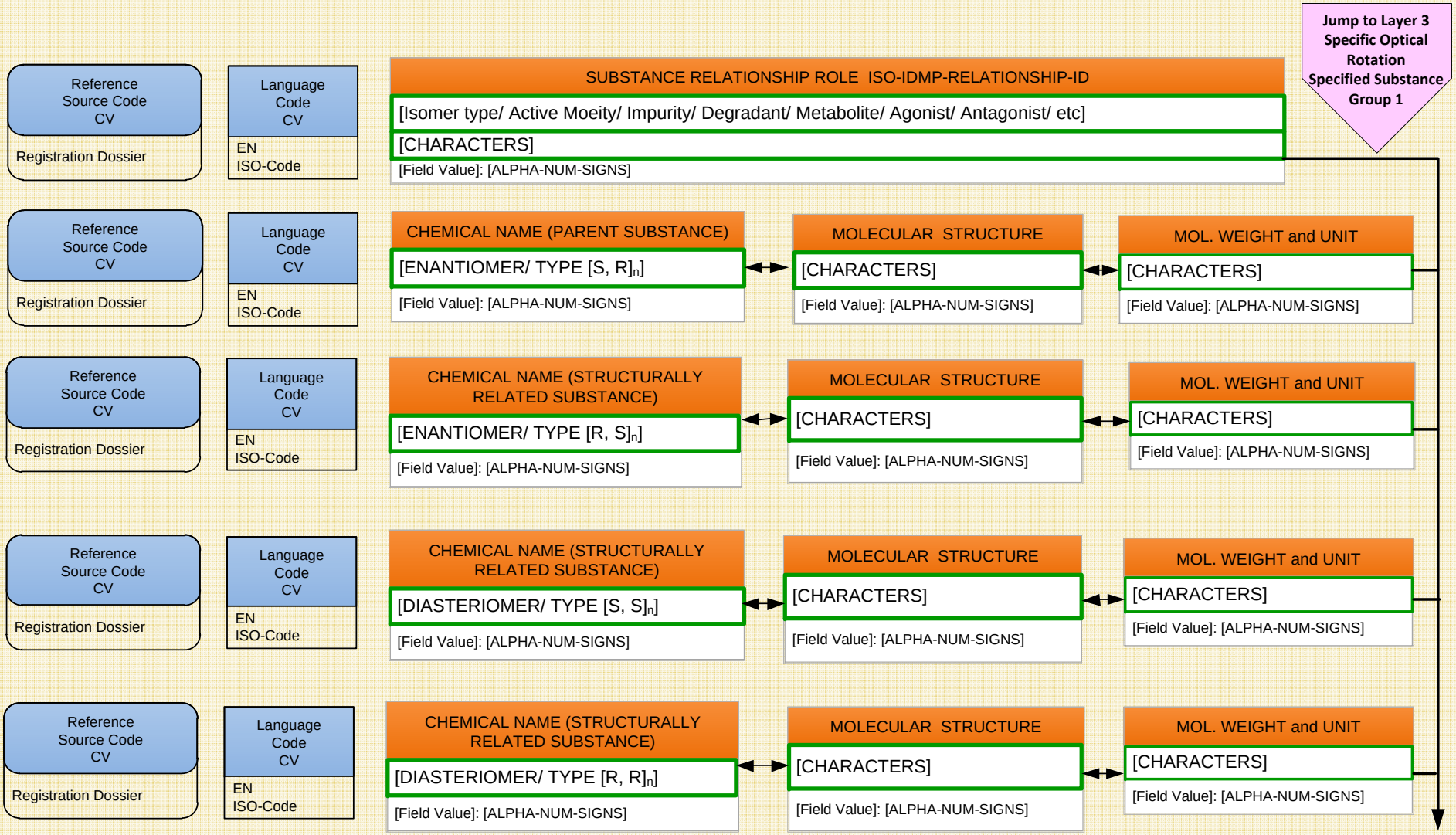
USP: $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$; **567.05**

EP: $C_{26}H_{31}ClN_2O_8S$; **567,1**

CAS: C20 H25 Cl N2 05 . C6 H6 03 S; No presentation of Mol. Weight.

Martindale: $C_{20}H_{25}ClN_2O_5, C_6H_6O_3S$ **=567.0**

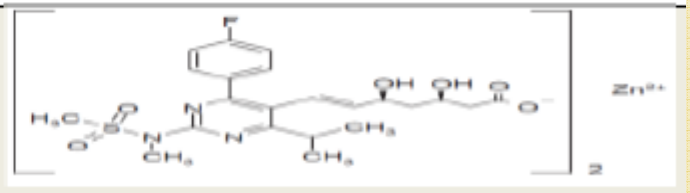
Layer 2 [Naming and Coding of Parent Substance or Child Active Moeity Structural Relationship] *continue*



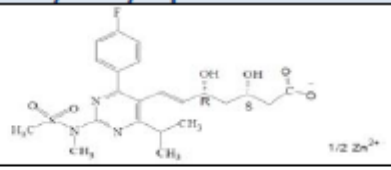
Rosuvastatin Zinc

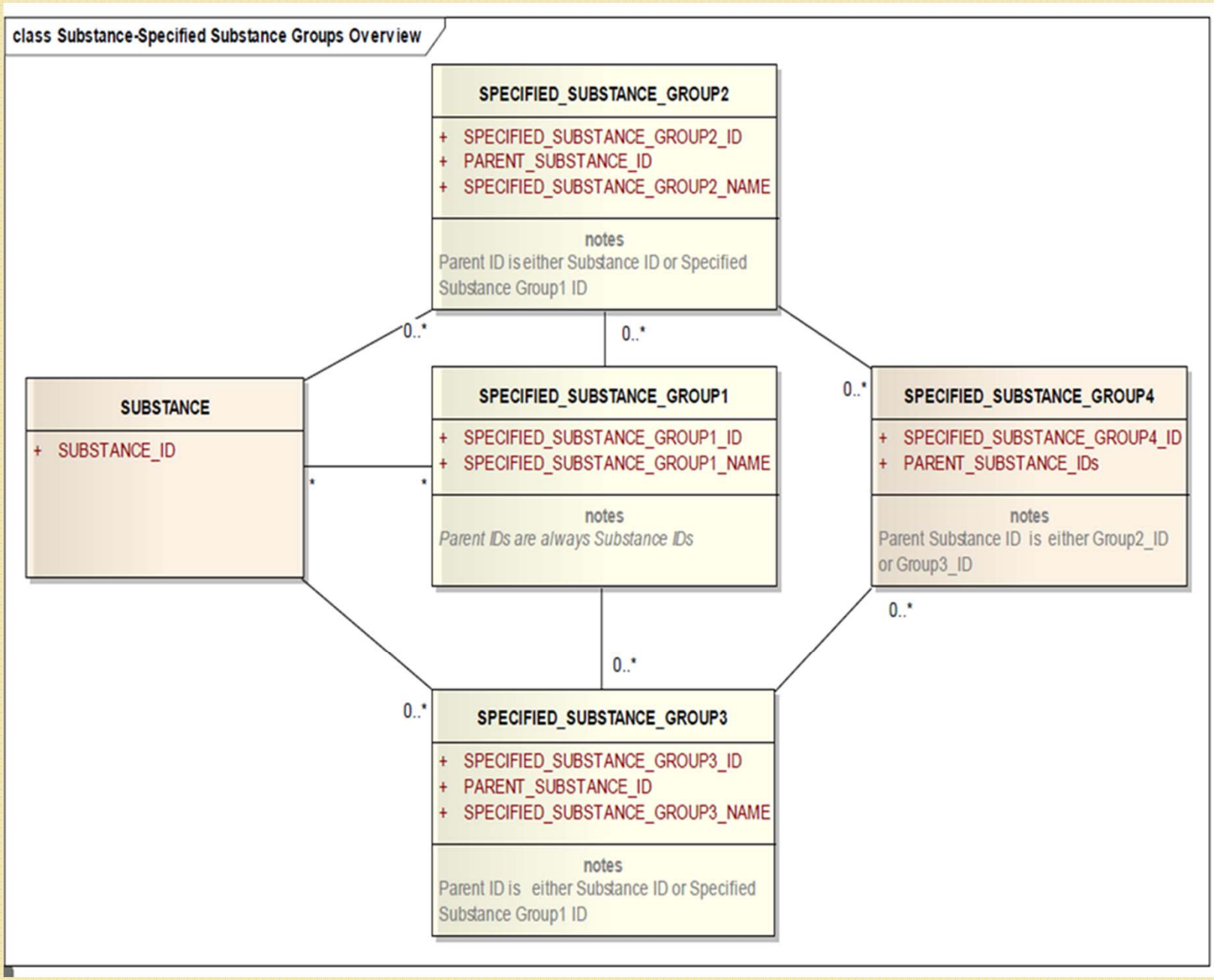
Field Name	Source/ Reference Name	Role Substance/ Choice list value	SOURCE VALUE
		LAYER 0	
		PARENT SUBSTANCE	
PREFERRED NAME	INN; USAN; USP; EP; JAN; JP; IUPAC; Common Name; Approved Name **Registration Dossier**		**ROSUVASTATIN**
ISO-IDMP-ID	Generated		**Generated**
		CHILD SUBSTANCE	
PREFERRED NAME Salt form 1 (mineral)	INN; USAN; USP; EP; JAN; JP; IUPAC; Common Name; Approved Name **Registration Dossier**		**ROSUVASTATIN ZINC**
ISO-IDMP-ID salt form 1	Generated		**Generated**
EQUIVALENT VALUE	< 1,0000		**0,9381**
COUNTRY NAME CHEMICAL SUBSTANCE	Country Name and Name Chem. Subst. in Language Nl, De,Se,Fr,Uk, US, Can, Jan, etc.	**Dutch Name (NL)**	**ROSUVASTATINE ZINK**
ATC-CODE	ATC-CODE Human/ Veterinary		**Human: C10AA07**

Rosuvastatin Zinc

Field Name	Source/ Reference Name	Role Substance/ Choice list value	SOURCE VALUE
HOMEOPATIC CHEMICAL NAME	Systematic Chemical Homeopathic Name; EP, DAB, HAP, HP		
OTHER NAME REGISTRATION DOSSIER	Synonym Name (s)	7-[4-(4-Fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl] -3,5-dihydroxy-(3R,5S,6E)-6-heptenoic acid zinc salt (2:1); (3R,5S,6E)-7-{4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid zinc salt	
OTHER CODE REGISTRATION DOSSIER	Registration Dossier; Lab-Code; NSC		
LAYER 2			
PARENT/ CHILD SUBSTANCE MANDATORY Mol. Formula; Mol. Weight; Mol. Structure			
MOLECULAR FORMULA	Registration Dossier; STN; EP; USP; Martindale		$(C_{22}H_{27}FN_3O_6S)_2 \cdot Zn$
MOLECULAR WEIGHT	Registration Dossier; EP; USP; Martindale		1026.46 Da $[(480.5)_2 + 65.38]$
INCHI CODE and INCHI KEY	Generated value		
MOLECULAR STRUCTURE	Registration Dossier; EP; USP; Martindale; STN		

Rosuvastatin Zinc

Field Name	Source/ Reference Name	Role Substance/ Choice list value	SOURCE VALUE
Racemic Mixture [+/-]	Registration Dossier; EP; USP; Martindale	No, Chiral Substance	**Two chiral centers [3*R*, 5*S*]**
Molecular Structure	Registration Dossier; EP; USP; Martindale		
Molecular Weight	Registration Dossier; EP; USP; Martindale		
Chemical Name (Structurally Related Substance)	Registration Dossier; EP; USP; Martindale	Impurity: Enantiomer type 3S,5R	**(3S,5R,6E)-7-{4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid zinc salt**
Molecular Structure	Registration Dossier; EP; USP; Martindale		
Molecular Weight	Registration Dossier; EP; USP; Martindale		**513.19 Da**
Chemical Name (Structurally Related Substance)	Registration Dossier; EP; USP; Martindale	Impurity: RVA-IMP CH_{ac} (Lactone)	**N-[4-(4-fluorophenyl)-5-{(E)-2-[(2S,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethenyl}-6-(1-methylethyl)pyrimidin-2-yl]-N-methylmethanesulfonamide**
Molecular Structure	Registration Dossier; EP; USP; Martindale		
Molecular Weight	Registration Dossier; EP; USP; Martindale		
Chemical Name (Structurally Related Substance)	Registration Dossier; EP; USP; Martindale	Impurity: RVA-IMP 1 Diasteriomer type [3R,5R]	**(3R,5R,6E)-7-{4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid zinc salt**


class Substance-Specified Substance Groups Overview
SPECIFIED_SUBSTANCE_GROUP2
+ SPECIFIED_SUBSTANCE_GROUP2_ID
+ PARENT_SUBSTANCE_ID
+ SPECIFIED_SUBSTANCE_GROUP2_NAME
notes
Parent ID is either Substance ID or Specified Substance Group1 ID
SUBSTANCE
+ SUBSTANCE_ID
SPECIFIED_SUBSTANCE_GROUP1
+ SPECIFIED_SUBSTANCE_GROUP1_ID
+ SPECIFIED_SUBSTANCE_GROUP1_NAME
notes
Parent IDs are always Substance IDs
SPECIFIED_SUBSTANCE_GROUP4
+ SPECIFIED_SUBSTANCE_GROUP4_ID
+ PARENT_SUBSTANCE_IDs
notes
Parent Substance ID is either Group2_ID or Group3_ID
SPECIFIED_SUBSTANCE_GROUP3
+ SPECIFIED_SUBSTANCE_GROUP3_ID
+ PARENT_SUBSTANCE_ID
+ SPECIFIED_SUBSTANCE_GROUP3_NAME
notes
Parent ID is either Substance ID or Specified Substance Group1 ID
0..*
0..*
0..*
0..*
0..*
0..*
*
*

Documentation Layer

Field Name	Source/ Reference Name	Role Substance/ Choice list value	SOURCE VALUE
LAYER 6			
[PARENT (CHILD) Substances] DOCUMENTATION			
DOMAINS			
PUBLIC DOMAIN			
Scientific Information	Articles/ Textbook		NO
Definitions of Substances/ Monograph	Official Monograph USP/ EP		NO
Data view of Chemical Abstract Register	STNEasy Database, Karlsruhe, Germany		YES
Martindale	Monograph		NO
RESTRICTED DOMAIN; Authorized Persons Competent Authority			
Restricted Domain PART I			
CTD Quality Modules			
Module M2 2.3.S Quality Overall Summary (Substance)	CTD M2		YES
CTD Quality Modules			
Module M3 3.2.S.1: General Properties - Nomenclature - Structure	CTD M3		YES
Module M3 3.2.S.2 Manufacturing - Manufacturer(s) and Sites; - Process and Controls	CTD M3		YES

Linaclotide, Public domain

WHO: WHO Drug Information, Vol. 21, No. 3, 2007 **Recommended** INN: List 58

linaclotidum
linaclotide [9-L-tyrosine]heat-stable enterotoxin (*Escherichia coli*)-(6-19)-peptide

linaclotide [9-L-tyrosine]entérotoxine thermostable (*Escherichia coli*)-(6-19)-peptide

linaclotida [9-L-tirosina]enterotoxina termoestable (*Escherichia coli*)-(6-19)-péptido

C59 H79 N15 O21 S6

H Cys Cys Glu Tyr Cys Cys Asn Pro
Ala Cys Thr Gly Cys Tyr OH

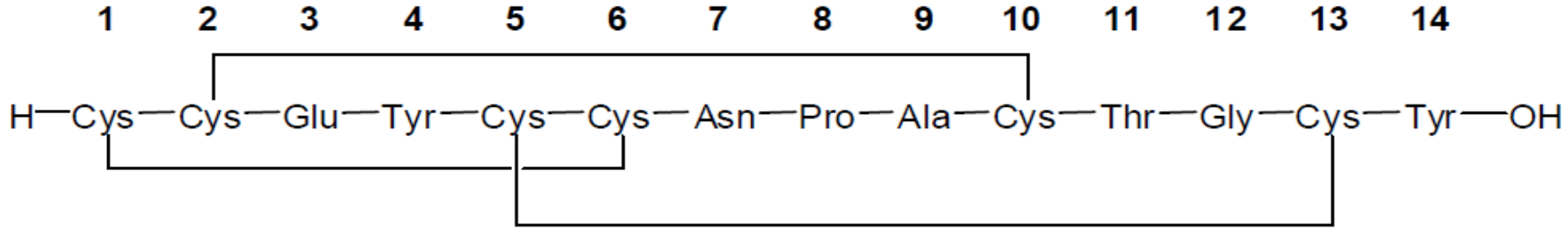
Small Notes ICI:

Mol. Gew,:1.526,8 Da;

Mol. Form.: C59 H79 N15 O21 S6

Linaclotide is a 14-amino acid synthetic peptide with 3 disulfide bonds. All amino acid are of L-configuration. Linaclotide contains three disulfide bridges between Cys^{1} and Cys^{6}, Cys^{2} and Cys^{10}, and Cys^{5} and Cys^{13}. The chemical structure is shown in the following figure:

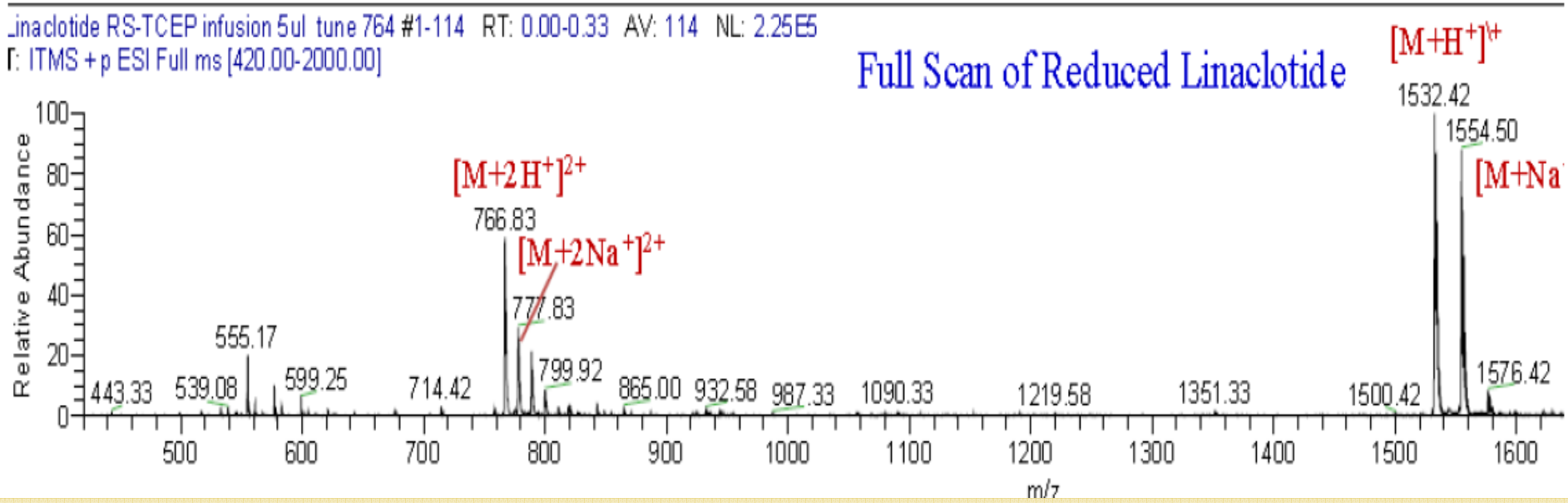
Figure 1: Chemical structure of linaclotide



Physically, linaclotide is an amorphous, white to off-white powder, soluble in water and aqueous sodium chloride (0.9%). Sequence length: 14; Sequence: 1 CCEYCCNPAC TGCY; The ES+-data therefore confirms the expected primary sequence of linaclotide: Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (CCEYCCNPACTGCY). Electrospray mass spectrometry shows a monoisotopic mass of 1524.8 Da, in good agreement with the expected value of 1525.4 ± 1 Da for linaclotide.

Linaclotide, Restricted Domain

Linaclotide, is a potent and selective guanylate cyclase-C (GC-C) receptor agonist, which is locally acting within the gastrointestinal (GI) tract. This first-in-class, orally administered peptide is structurally related to the guanylin peptide family, which is involved in the regulation of intestinal fluid homeostasis and bowel function. The guanylin family of peptides includes the hormones guanylin and uroguanylin.



CBG MEB

THANK YOU FOR YOUR ATTENTION

Postal address: P.O. Box 8275 , 3503 RG Utrecht,
The Netherlands

Miss Ing. C.G. Matai, Chemist <cg.matai@cbg-meb.nl>

Drs. H. Diederik, Pharmacist <h.diederik@cbg-meb.nl>

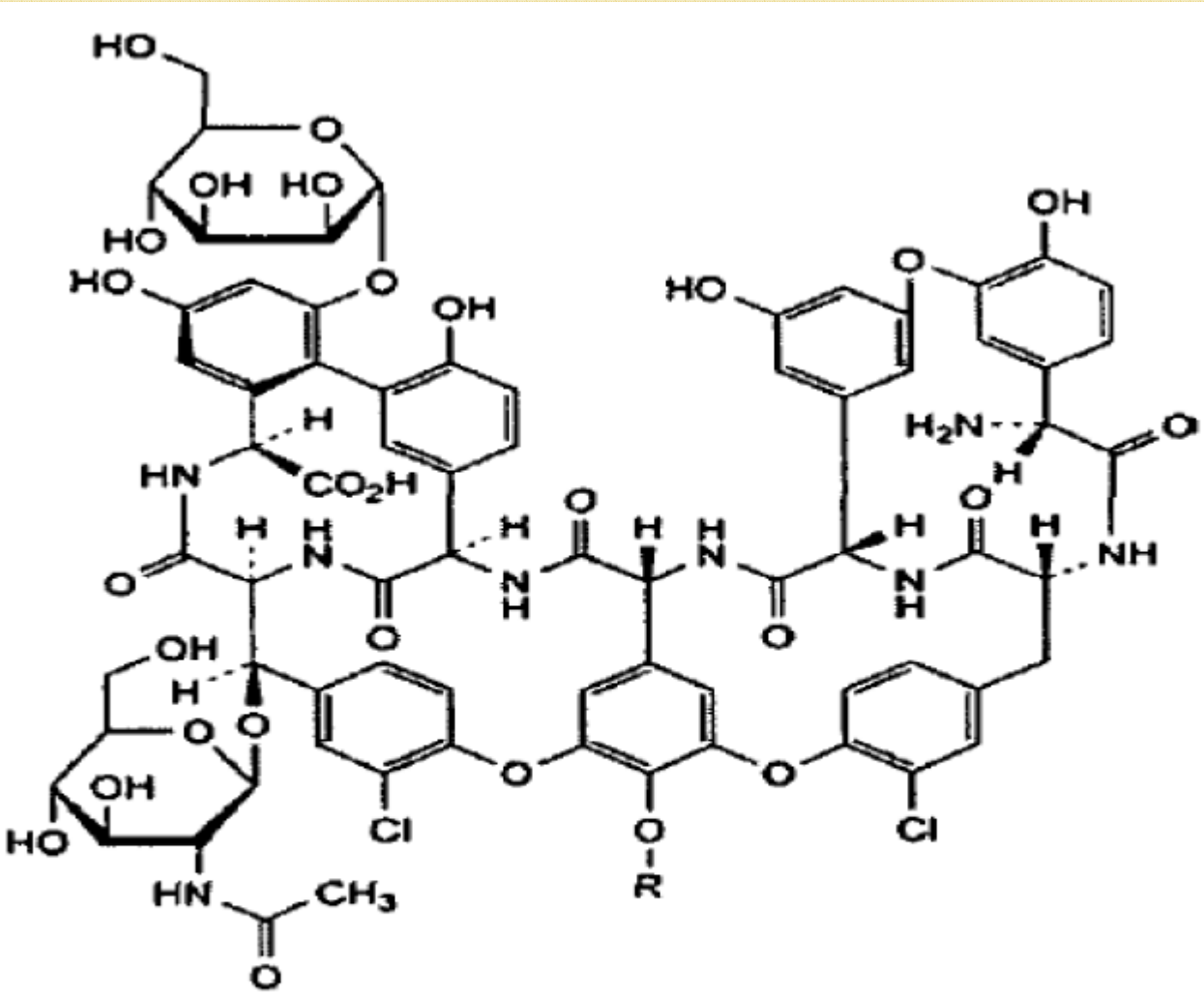
Question 1:

What is the classification of Teicoplanin according to the ISO-IDMP-11238 Standard

- **Answer** : **The substance is a mixture of components isolated together** or produced in the same synthetic process. (The mixture of components appear as an amorphous powder.)

- **Conclusion: The substance Teicoplanin will be classified as a Mixture substance, having a Parent Substance ISO-IDMP-ID.**

- **This mixture substance contains as active multiple active components containing two pairs of constitutional isomers having the same chiral conformation.**



The chemical structure consists of 6 components of glycopeptides, which are composed of a hepta peptide core of 7 amino acids connected with 3 sugars (N-acetylglucoamine, α-mannitose and the glucose substituted by different N-acylamino).

Question 2:

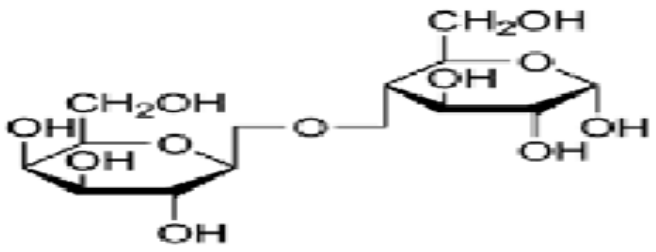
Can Lactose monohydrate be considered as the "Child" Substance of the "Parent" Substance Lactose anhydrous?

- **Answer 2: YES.**
- **The monohydrate of lactose can be referred to the anhydrate despite the conformational difference for the alpha or beta isomer of the glucose unit.**

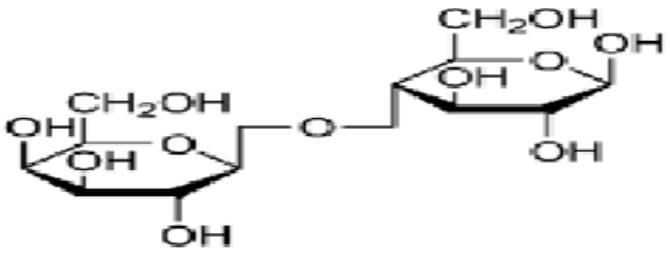
- **Chiral difference will be captured in the relationship between parent and child substance as defined, e.g. any salt, any salt-hydrate or hydrate form will be related to the parent moiety base or acid form or anhydrate.**

Lactose anhydrous consist of:

(β-D-Galactose) (α-D-Glucose) (β-D-Galactose) (β-D-Glucose)



Anhydrous α-lactose



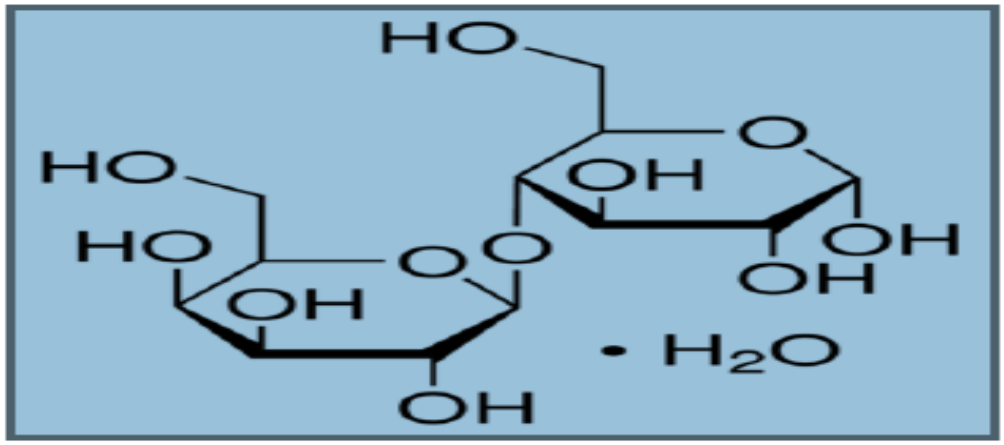
Anhydrous β-lactose

The PhEur 7.4 and USP35–NF30 describe anhydrous lactose as *O*-β-D-galactopyranosyl-(1 to 4)-β-D-glucopyranose; or as a mixture of

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

Definition: Lactose monohydrate is the monohydrate of *O*-β-D-galactopyranosyl-(1 to 4)-α-D-glucopyranose

Synonym: D-(+) Lactose monohydrate (99,0%) or α-Lactose monohydrate.



Question 4:

How do we classify the complex substance Paclitaxel-Albumin in the medicinal product Abraxane?

- **Answer 4: The product is presented as a sterile, pyrogen-free, white-to-yellow lyophilized cake formulation of nanoparticles of 100 mg paclitaxel "bound" by 800 mg human albumin.**
- **The Paclitaxel nanoparticles and the Albumin are substances of diverse origin that are brought together but do not undergo a chemical transformation.**
- **Therefore the Paclitaxel – Albumin complex can be defined as multi-substance materials and are placed in accordance with the standard in**

Specified Substance Group 1.

Question 5: How do we classify the complex VEMURAFENIB non crystalline co-precipitate with Hypromellose acetate succinate (30 : 70)?

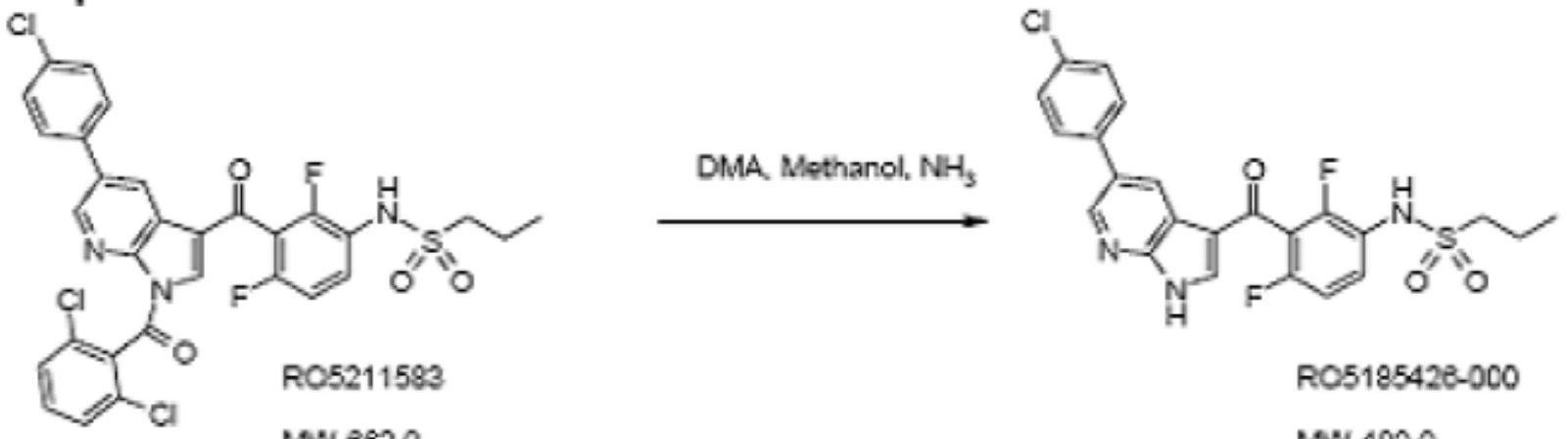
Definitions:

RO5185426 = unmilled crystalline API Vemurafenib: 1-Propanesulfonamide, N-[3-[[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]carbonyl]-2,4-difluorophenyl]- ; (Mol. Form.: $C_{23}H_{18}ClF_2N_3O_3S$; Mw = 489,9 Da, Polymorphy: Crystalline form II, Mp = Approx. 271 °C)

RO5185426-006 = milled non-crystalline co-precipitate containing Vemurafenib (RO5185426) and HPMC-AS polymer.

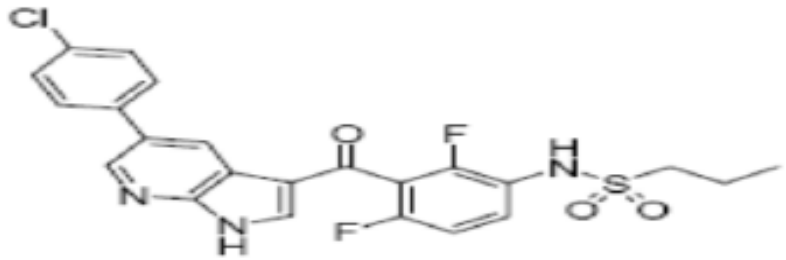
Manufacturing method:

Step 4: RO5185426-000



DMAP: 4-Dimethylaminopyridine

Steps 5 and 6: RO5185426-004 and RO5185426-006

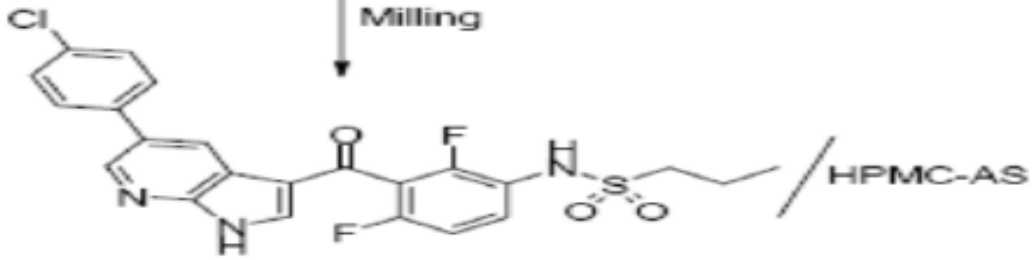


RO5185426-000

HPMC-AS
DMA
HCl, H_2O

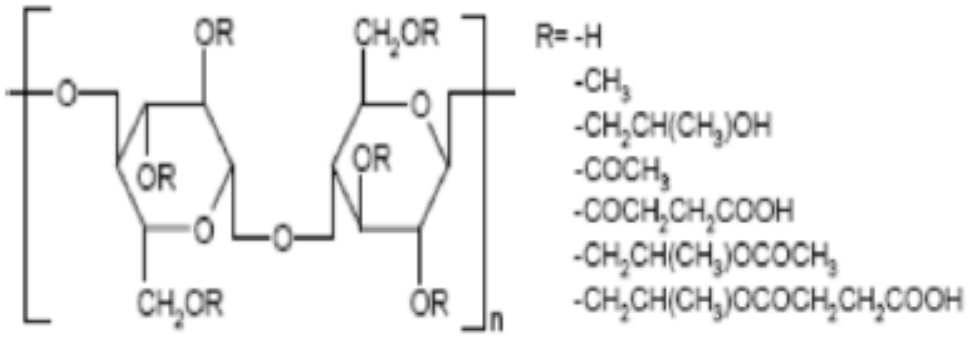
RO5185426-004

Milling



RO5185426-006

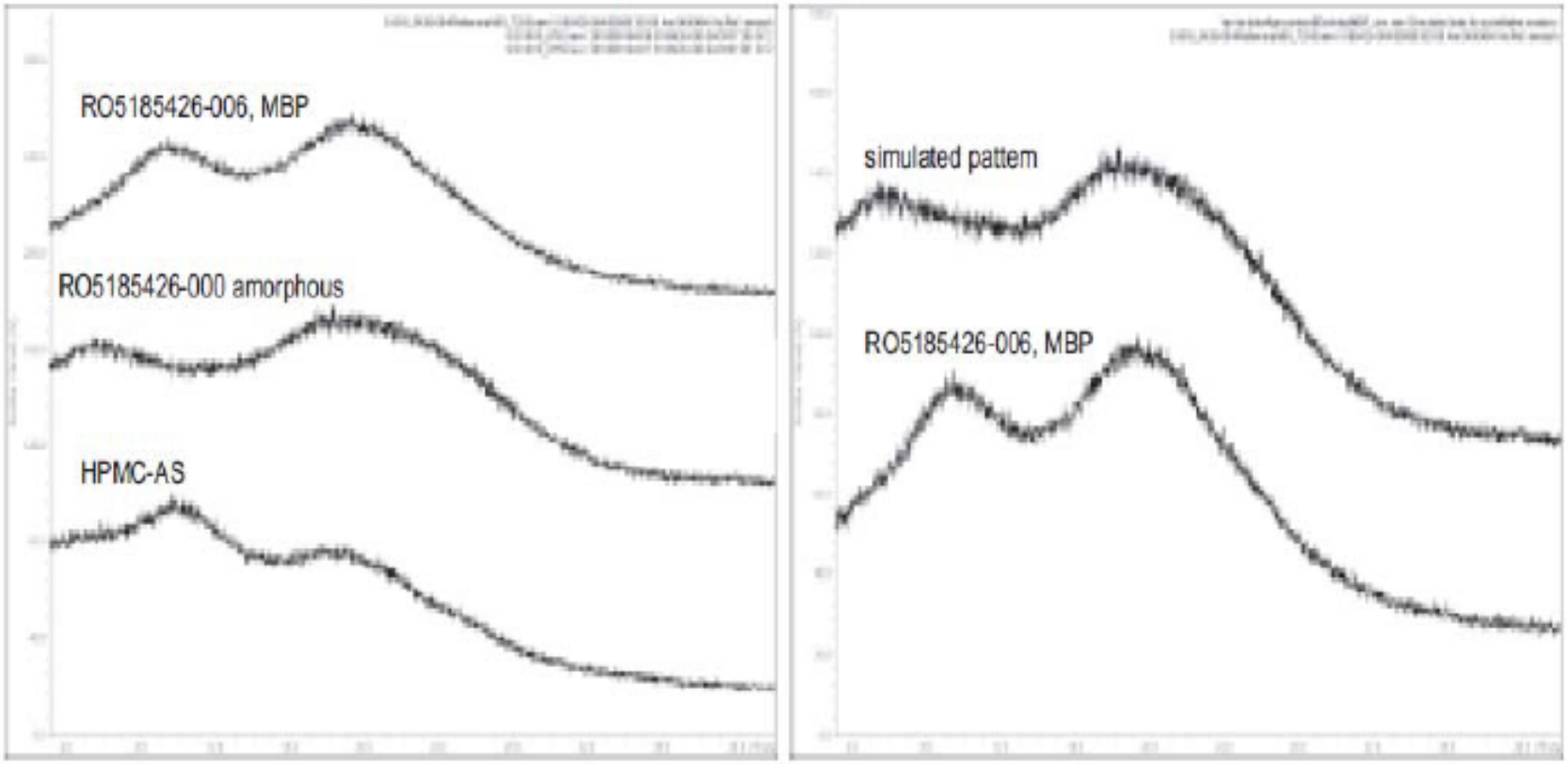
Specification Hydroxypropyl methylcellulose- acetate-succinate:

Hydroxypropyl methylcellulose acetate succinate	**Shin-Etsu Chemical Co. Ltd.**
	28-1, Nishifukushima, Kubiki-ku Joetsu-shi, Niigata, Japan
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.

Answer 5:

The manufacturing of the Vemurafenib- HPMC-AS polymer –co-precipitate start with dissolution of both Vemurafenib and HPMC-AS polymer in NN-Dimethylacetamide in which the Vemurafenib is very soluble till a clear solution upon heating to max. 80 °C. The warm RO5185426-HPMC-AS solution is gradually mixed with a cold dilute aqueous hydrochloric acid at 0 – 7 °C causing RO5185426-000 and polymer to co-precipitate. The co-precipitate (RO5185426-004) is isolated by centrifugation and washed with dilute aqueous hydrochloric acid and water.

Left: Overlay of XRPD patterns of HPMC-AS, amorphous RO5185426-000 and RO5185426-006 (MBP)	*Right: Simulated pattern (Least squares fit) and experimental pattern physical mixture*



Conclusion:

The Vemurafenib-HPMC-AS polymer co-precipitate/ complex complies with the ISO-IDMP 11238 definition for "Mixture Substance" :
"A Substance that is a combination of single substances isolated together or produced in the same synthetic process" So that:

A: - Vemurafenib is the parent substance name and,
Vemurafenib, polymorph crystalline form II, is the
Specified parent substance group 1 name

B: Vemurafenib-HPMC-AS-polymer (co-precipitate or complex) is to be considered as the related child substance.
The equivalent value is equal to (240/ 800) = 0,30.

(RO5185426-006 the active substance in Zelboraf filmcoated tablets contains 30% RO5185426-000 (corresponding to 240.000 mg) and 70% hypromellose acetate succinate (NF) (corresponding to 560.000 mg).

Phytochemical Record Presentation

Custom Object: **RHAMNUS FRANGULA SCHORS, GEPOEDERD**

Class: *Substance*

	Property	Value
	CBG Number:	
	CAS Number:	
*	Dutch Name:	RHAMNUS FRANGULA SCHORS, GEPOEDERD

"Rhamnus Frangula bark consist of the dried, whole or fragmented bark of the stems and branches of Rhamus frangula L. (Fangula alnus Miller)"; "Rhamnus frangula schors, gepoederd"; "Rhamnus frangulae Cortes, pulv." Change Value

English Name: RHAMNUS FRANGULA BARK, POWDERED

The bark contains NLT 7,0 pCt of glucofragulins, expressed as glucofrangulin A and calculated with reference of the dried drug: Mol. Form.: C27 H30 O14; Mol. Gew.: 578,5;
The main constituens of the dried bark are glucofrangulins A and B (= emodin-6-O-alpha-L-rhamnosyl-8-O-beta-D-glucoside and emodin-6-O-beta-D-apiosyl-8-O-beta-D-glucoside), frangulins A, B and C (= emodin-6-O-alpha-L-rhamnoside, emodin-6-O-beta-D-apioside and emodin-6-O-beta-D-xyloside), and emodin-8-O-beta-D-glucoside, together with small amounts of other anthraquinone glycosides, dianthrones and aglycones.

Veterinary Pharmaceutical Product; SPC Composition Record

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

SUISENG

Suspension for injection for swine.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition per dose (2 ml) :

Active substances:

F4ab fimbrial adhesin of *E. coli*	≥65% ER_{60} *
F4ac fimbrial adhesin of *E. coli*	≥78% ER_{70}
F5 fimbrial adhesin of *E. coli*	≥79% ER_{50}
F6 fimbrial adhesin of *E. coli*	≥80% ER_{25}
LT Enterotoxoid of *E. coli*	≥55% ER_{70}
Toxoid *Clostridium perfringens*, type C	≥35% ER_{25}
Toxoid *Clostridium novyi*, type B	≥50% ER_{120}

*% ERx: Percentage of immunized rabbits with a X serological EIA response

Adjuvants:

Aluminium hydroxide gel	0.5 g
Ginseng	4 mg

6.1 List of excipients

Aluminium hydroxide gel

Ginseng

Benzyl alcohol

Simethicone

PBS solution

Veterinary Pharmaceutical Product Representation

	BENZYLALCOHOL					Inactief bestanddeel
	CLOSTRIDIUM Novyi TYPE B, alpha toxoid 3,5 >= E/flacon	3,5	>=		E/flacon	Actief bestanddeel
	CLOSTRIDIUM Perfringens TYPE C, beta toxoid 10 >= E/flacon	10,0	>=		E/flacon	Actief bestanddeel
	DIMETICON					Inactief bestanddeel
	DINATRIUMWATERSTOFFOSFAAT 12-WATER					Inactief bestanddeel
	ESCHERICHIA Coli,Gewimperd aanhechtsel F4ab 13,12 = E/flacon	13,12	=		E/flacon	Actief bestanddeel
	ESCHERICHIA Coli, Gewimperd aanhechtsel F4ac 13,12 = E/flacon	13,12	=		E/flacon	Actief bestanddeel
	ESCHERICHIA Coli, Gewimperd aanhechtsel F5 500 = E/flacon	500,0	=		E/flacon	Actief bestanddeel
	ESCHERICHIA Coli, Gewimperd aanhechtsel F6 1100 = E/flacon	1100,0	=		E/flacon	Actief bestanddeel
	ESCHERICHIA Coli, LT enterotoxoid 1280 = E/flacon	1280,0	=		E/flacon	Actief bestanddeel
	KALIUMCHLORIDE					Inactief bestanddeel
	KALIUMDIWATERSTOFFOSFAAT					Inactief bestanddeel
	NATRIUMCHLORIDE					Inactief bestanddeel
	SILICIUMDIOXIDE (E 551)					Inactief bestanddeel
	WATER					Inactief bestanddeel

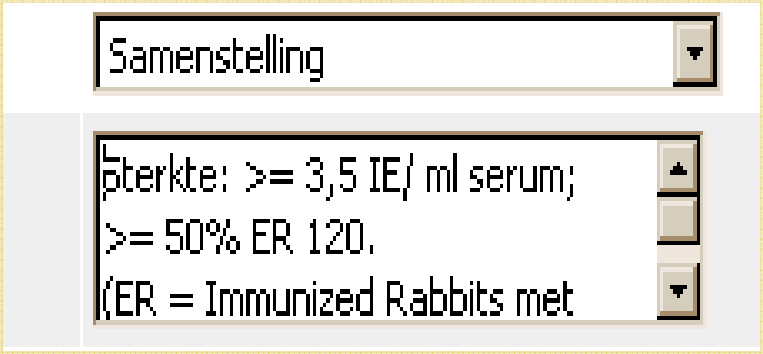
Veterinary Pharm. Product; Active substance Representation

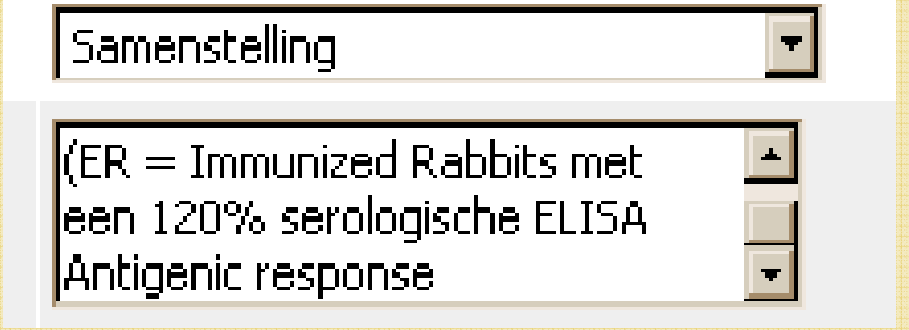
Custom

English Name:	CLOSTRIDIUM Novyi TYPE B, alpha toxoid
Inactive Ingredient Name:	
Notes:	Antigen dat een actieve en specifieke response produceert tegen de productie van a-toxine van Clostridium novyi

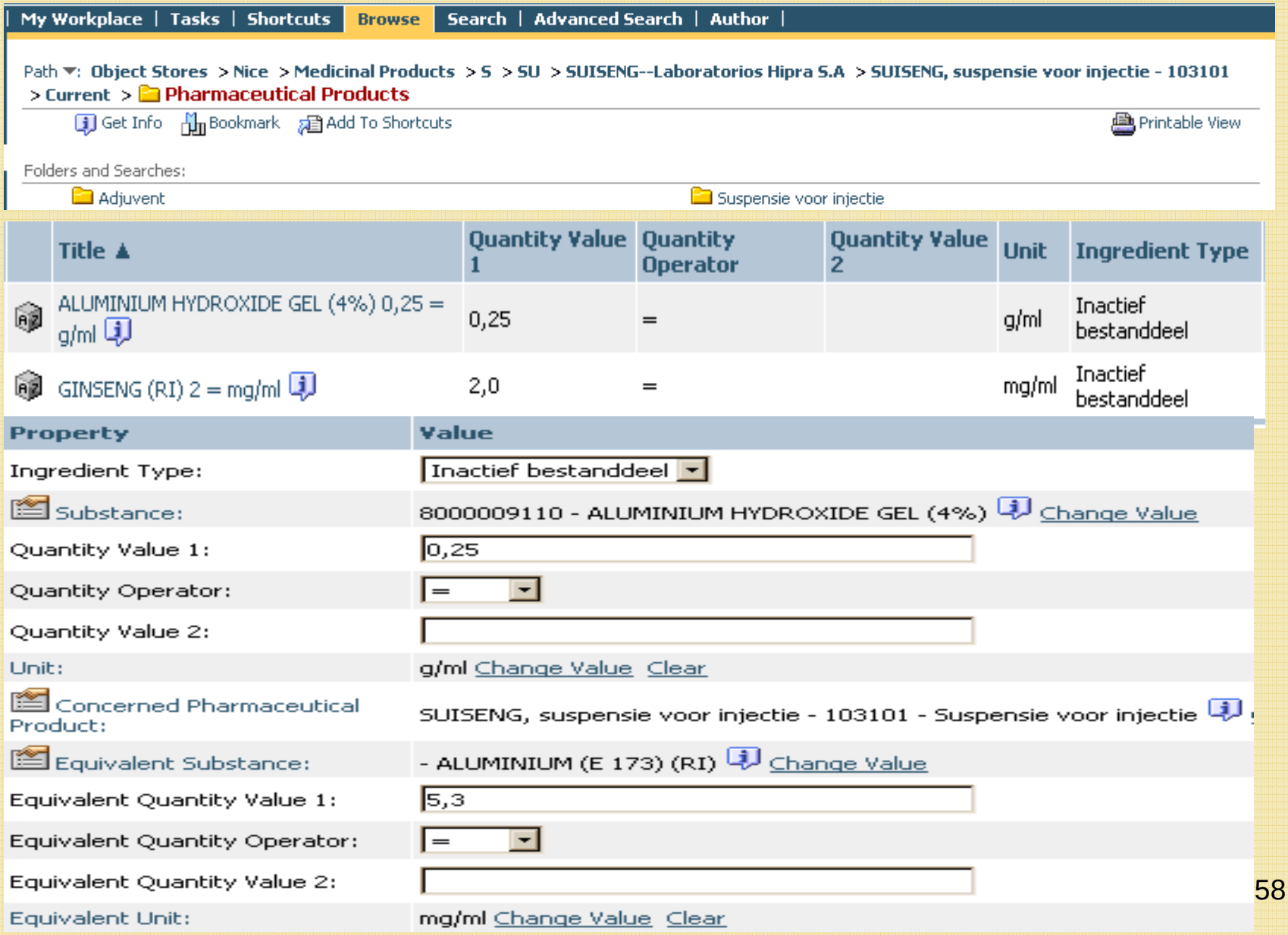
Class: Ingredient

	Property	Value
	Ingredient Type:	Actief bestanddeel
*	Substance:	311 - CLOSTRIDIUM Novyi TYPE B, alpha toxoid Change Value
	Quantity Value 1:	3,5
	Quantity Operator:	=
	Quantity Value 2:	
	Unit:	IE/flacon Change Value Clear
*	Concerned Pharmaceutical Product:	SUISENG, suspensie voor injectie - 103101 - Suspensie voor injectie Change Value





Veterinary Pharm. Product; Adjuvant Representation



Custom Object: **164 - CALCAREA PHOSPHORICA DIHYDROS (HO)**

Apply

Close

Class: *Substance*

	Property	Value
	CBG Number:	164
	CAS Number:	0007789777
*	Dutch Name:	CALCAREA PHOSPHORICA DIHYDROS (HO)
	Homeopatic Name:	CALCAREA PHOSPHORICA
	Preferred Term As Inactive Ingredient:	
	Quantity Indicator Inactive Ingredient:	
	P RMS:	
	Harmonised Substance Data Lock Point:	Clear (d-MM-yy)
	Active Ingredient Synonym:	"Calcium phosphate"; "Calcium hydrogen phosphate dihydrate"; "Calcarea phosphorica" Change Value
	Origin:	
	Latin Name:	CALCAREA PHOSPHORICA DIHYDROS
	INN Name:	CALCIUM HYDROGEN PHOSPHATE
	English Name:	CALCIUM HYDROGEN PHOSPHATE DIHYDRAT
	Inactive Ingredient Name:	Select Value
	Notes:	CALCAREA PHOSPHORICA DIHYDROS = Calciumwaterstoffosfaatdihydraa
*	Deprecated:	False