



National Substance Register for Medicinal Products (NSL)

Documentation for version 1.2

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Background: Companies in the EU must report human medicinal product information to the EMA

- **New regulations for pharmacovigilance are meant to increase transparency and improve cooperation in the EU regarding management of adverse reactions**
- **Medicinal product information to be reported:**
 - Information on medicinal products
 - Information on ingredients
 - Information on adverse reactions
- **Product information shall be reported in a defined format by 1 July 2012 (Article 57:2 in 726/2004)**



EMA: Format specification

- **Shall be formatted in accordance with a group of ISO-standards**
 - Together they are called IDMP – Identification of Medicinal Products
- **Product information will be stored in EudraVigilance in the Extended EudraVigilance Medicinal Product Dictionary (xEVMPD)**
 - Format published 1 July 2011 by the EMA
 - Medicinal products – [emaxevmpd.xsd](#)
 - Substances – [emaxevmpd_ssi.xsd](#)



Standards in the IDMP package (latest approved versions):



- 11238:2018** - Health informatics -- Identification of medicinal products -- Data elements and structures for the unique identification and exchange of regulated information on **substances**
- 11239:2012 - 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
- 11240:2012 - Health informatics -- Identification of medicinal products -- Data elements and structures for the unique identification and exchange of units of measurement
- 11615:2017 - Health informatics -- Identification of medicinal products -- Data elements and structures for the unique identification and exchange of regulated medicinal product information
- 11616:2017 - Health informatics -- Identification of medicinal products -- Data elements and structures for the unique identification and exchange of regulated pharmaceutical product information

Substance Information in PharmaPackage

- The requested substance information was **VERY comprehensive**
- After discussions with industry, the EMA decided (Feb 2012) that the requirement for highly detailed substance information should be delayed
- Substance information will be required from industry in the detailed format eventually (2022?)



BUT

MPA decided to use this structure already in 2012

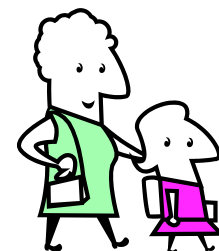
Information Structure – Basic Principles

- Based on a 2011 draft of **ISO 11238**:
Health informatics -- Identification of medicinal products -- Data elements and structures for the unique identification and exchange of regulated information on substances
- Standard interpreted by the EMA – published an XSD file in July 2011
 - [emaxevmpd_ssi.xsd](#)
 - ssi = **Structured Substance Information**



MPAs interpretation of the ISO standard

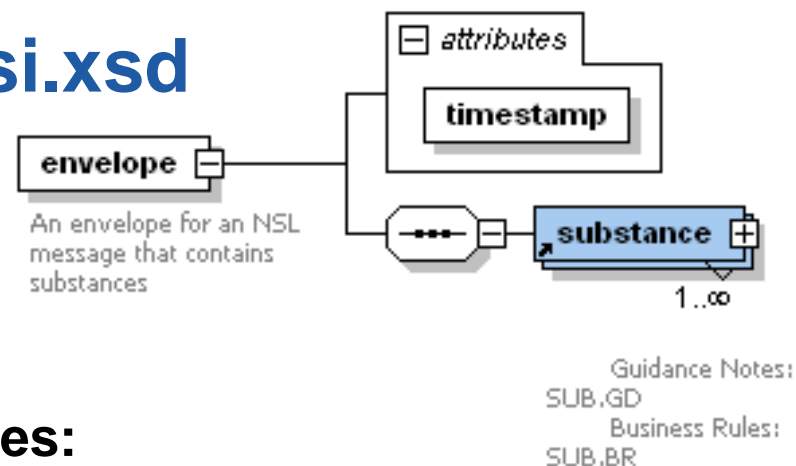
- **ISO standard is much more comprehensive than what NSL needs**
- **Cut down but the basic structure was kept**
 - [SEnsl-ssi.xsd](#) – scheme for ISO part
- **No place for specific Swedish information needed in NSL e.g. recommended Swedish name and substance relationship (parent-child relationship)**
 - Separate scheme (.xsd) to avoid breaking compatibility with the EMA
 - [SEnsl-other.xsd](#)
- **Several other files for management of pre-defined values (dictionaries) were added**



NSL package – consists of a ZIP file with 17 files

- **SEnsl-ssi.xsd and SEnsl-ssi.xml**
 - Substance data in ISO structures
- **SEnsl-other.xsd and SEnsl-other.xml**
 - Substance data for other information
- **SEnsl-lexicon.xsd**
 - Scheme for management of dictionaries
- **12 schemes with dictionaries**
 - Including Swedish translations of ATC codes:
atc-code-lx.xsd

Basic structure: SEnsl-ssi.xsd

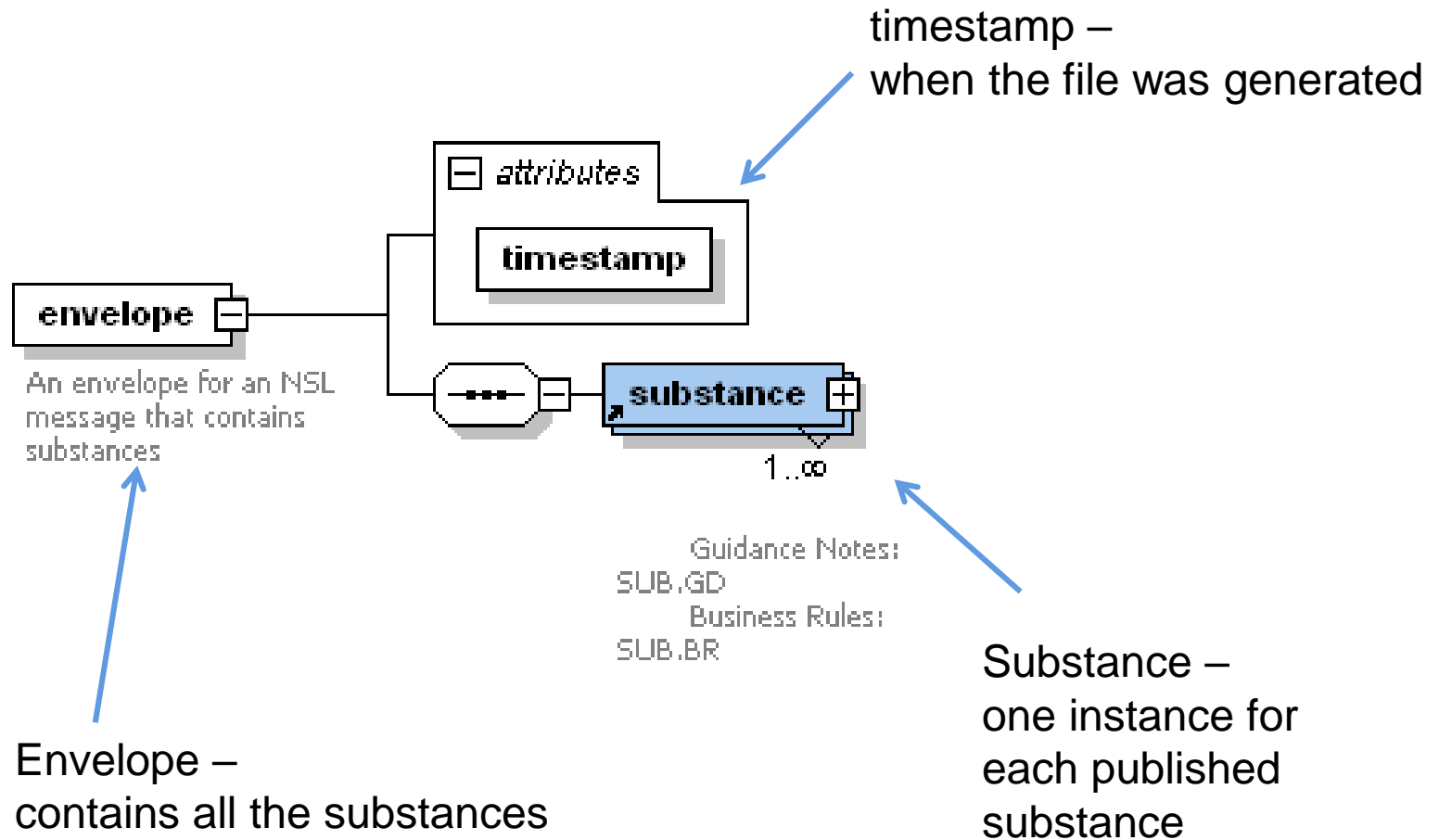


Guidance Notes and Business Rules: Chapter 4: Structured substance information

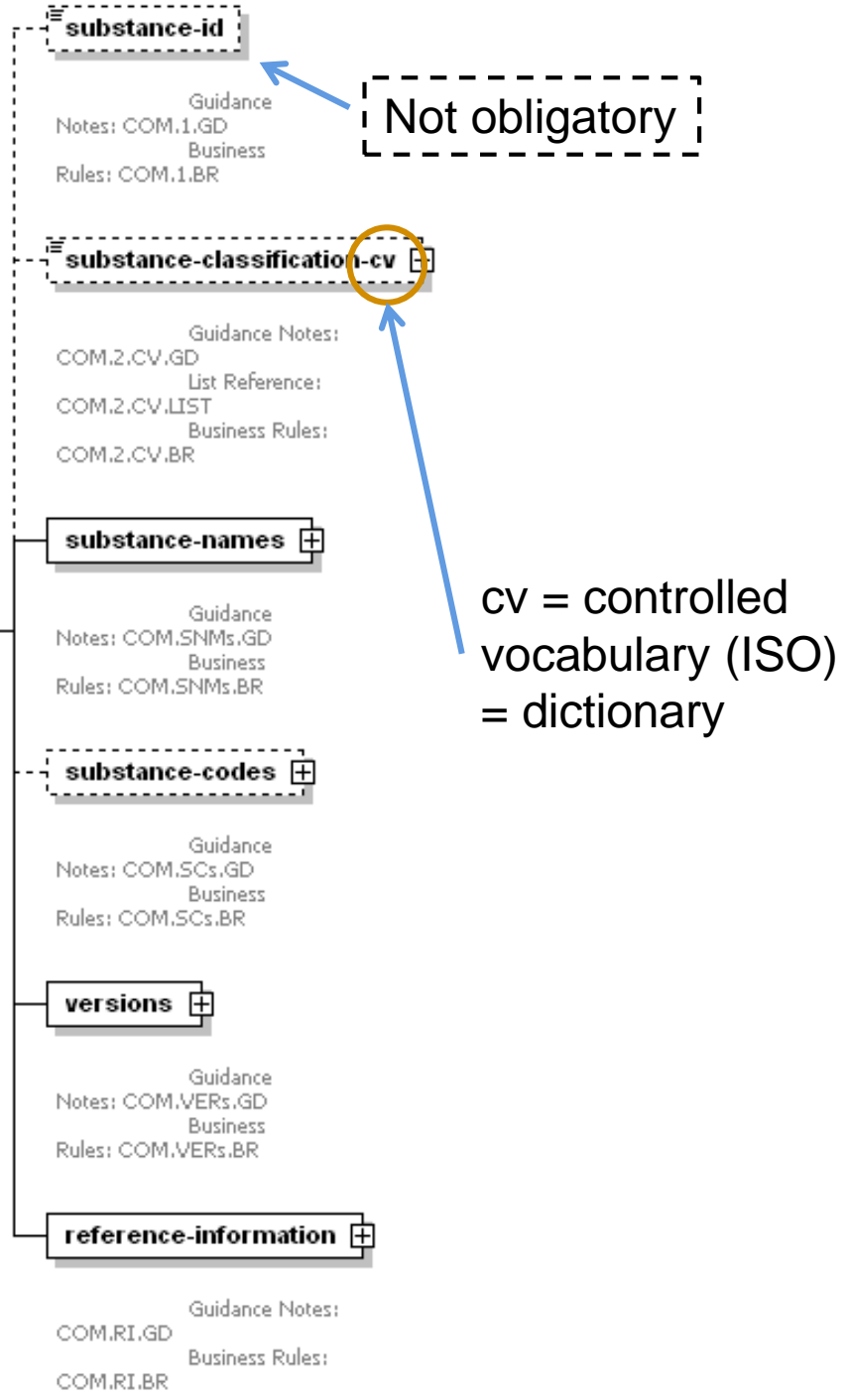
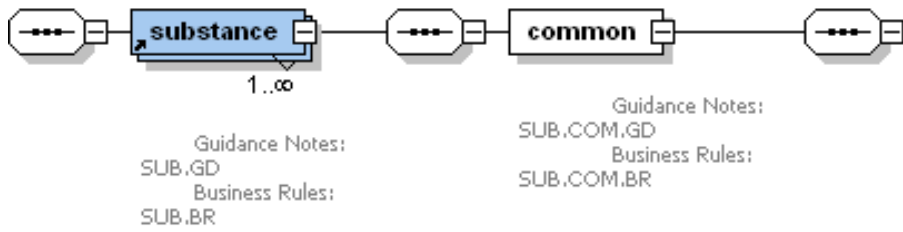
Detailed guidance on the electronic submission of information on medicinal products for human use by marketing authorisation holders to the European Medicines Agency in accordance with Article 57(2), second subparagraph of Regulation (EC) No. 726/2004
Version 2.0 (1 sep 2011)

Document removed from EMAs website 5 March 2012 but is available on nsl.mpa.se. Read the examples – they are easier to understand than the guidance notes.

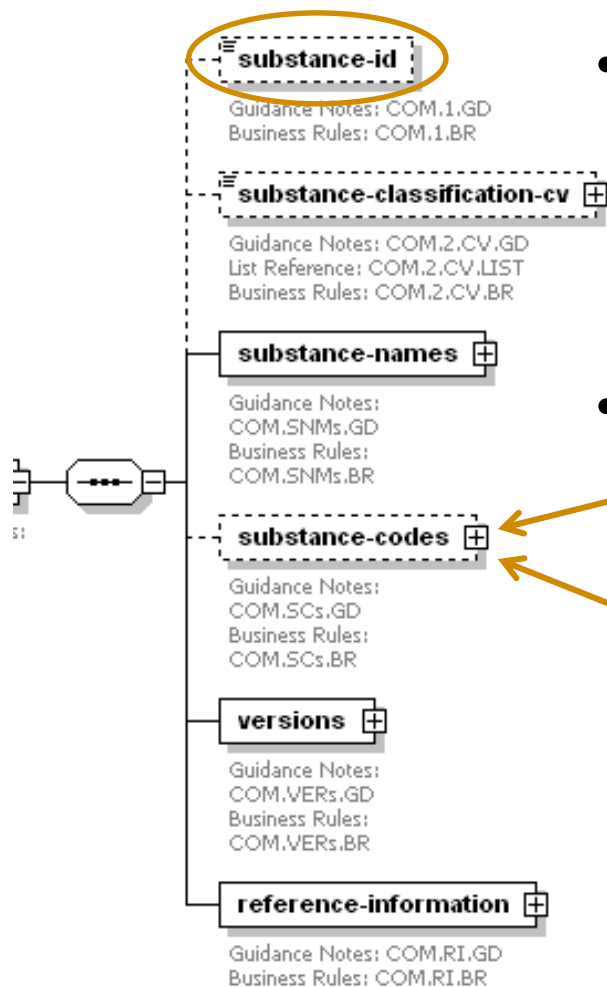
Basic structure for ISO compatible information in SEnsl-ssi.xsd



Basic structure for ISO-compatible information in SEnsl-ssi.xsd



SEnsl-ssi.xsd



- **Substance-id – place for a common EU-id**

– NOT used today

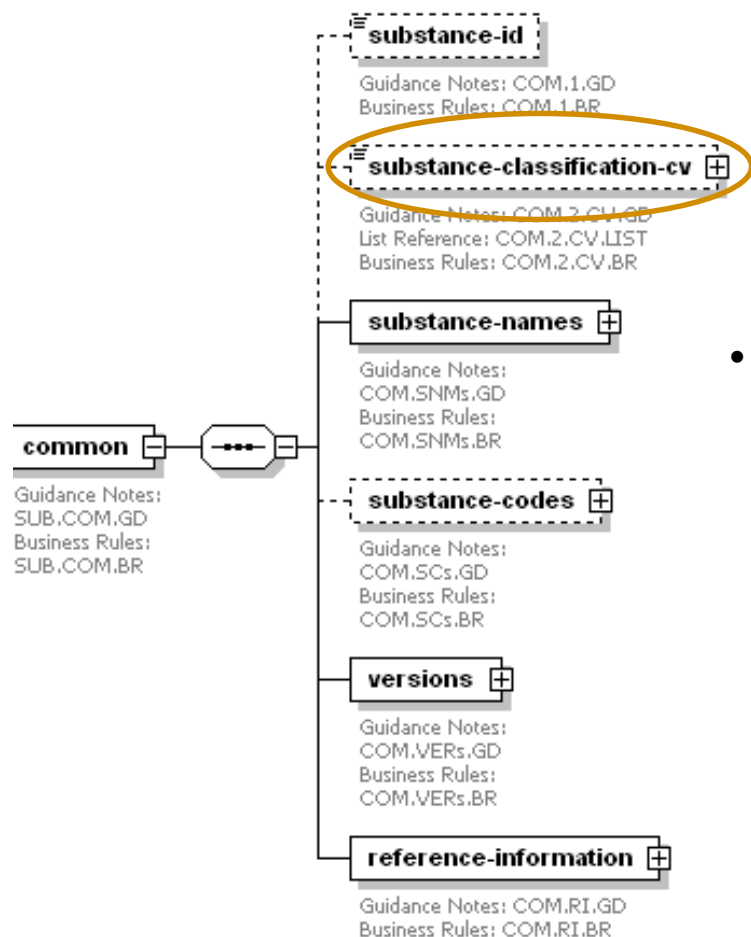
- **SE national ID (SeNSLid) for the substance is under substance-codes**

– same ID as in NPL

SEnsl-ssi.xsd

- **Classification of substances according to the ISO standard – [subst-class-iso-lx.xsd](#)**

- Single
- Mixture
- Specified substance

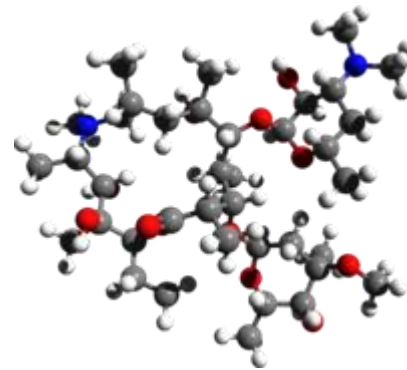


- **Definitions are in: Chapter 6: Definitions** | Detailed guidance on the electronic submission of information on medicinal products for human use by marketing authorisation holders to the European Medicines Agency in accordance with Article 57(2), second subparagraph of Regulation (EC) No. 726/2004 (Ref 2)

Substance-classification-cv (ISO)

– Single substance

**"Refers to a substance that can be described by a single representation or set of descriptive elements. A single substance can be described using one or more of five types of elements; chemical, protein, nucleic acid, polymer and structurally diverse substances."
(Ref 2).**



Substance-classification-cv

– Mixture substance



- a type of polydisperse substance that is **a combination of single substances isolated together or produced in the same synthetic process**. Single substances of diverse origin that are brought together and do not undergo a chemical transformation can be defined as multi-substance materials (Group 1 specified substances) and not as mixture substances.
- **Gentamicin** can be defined as a **mixture substance** of Gentamicin C1A, Gentamicin C1, and Gentamicin C2.
- **Simethicone** which consists of dimethicone and silicon dioxide should not be defined as a mixture substance since these are **diverse materials** brought together to form a product – **Specified substance**

(Ref 2)

Substance-classification-cv

– Specified substance

- **Refers to groups of elements which describe multi-substance materials and specify further information on substances and multi-substance materials relevant to the description of medicinal products**
 - There are three groups (group 1, 2 & 3)

(Ref 2)

Specified substance – group 1

- **Material that contains multiple substances, solvents used in the preparation of herbal or allergenic extracts, specific marker or signature substances present in materials derived from biological matrices**
- **This grouping of constituents allows for the definitions of many materials in commerce that are used in the formulation of medicinal products**
 - Paracetamol with 3 % povidone
 - Insulin human isophane

(Ref 2)

Specified substance – group 2



- Refers to the manufacturer of either a substance or a specified substance group 1, along with minimal manufacturing information
- Group 2 elements would allow the tracking of the substance to the manufacturer, e.g. biosimilar products, synthetic vs recombinant peptides
- *May be used in NSL – e.g. for biotechnological and herbal substances*

(Ref 2)

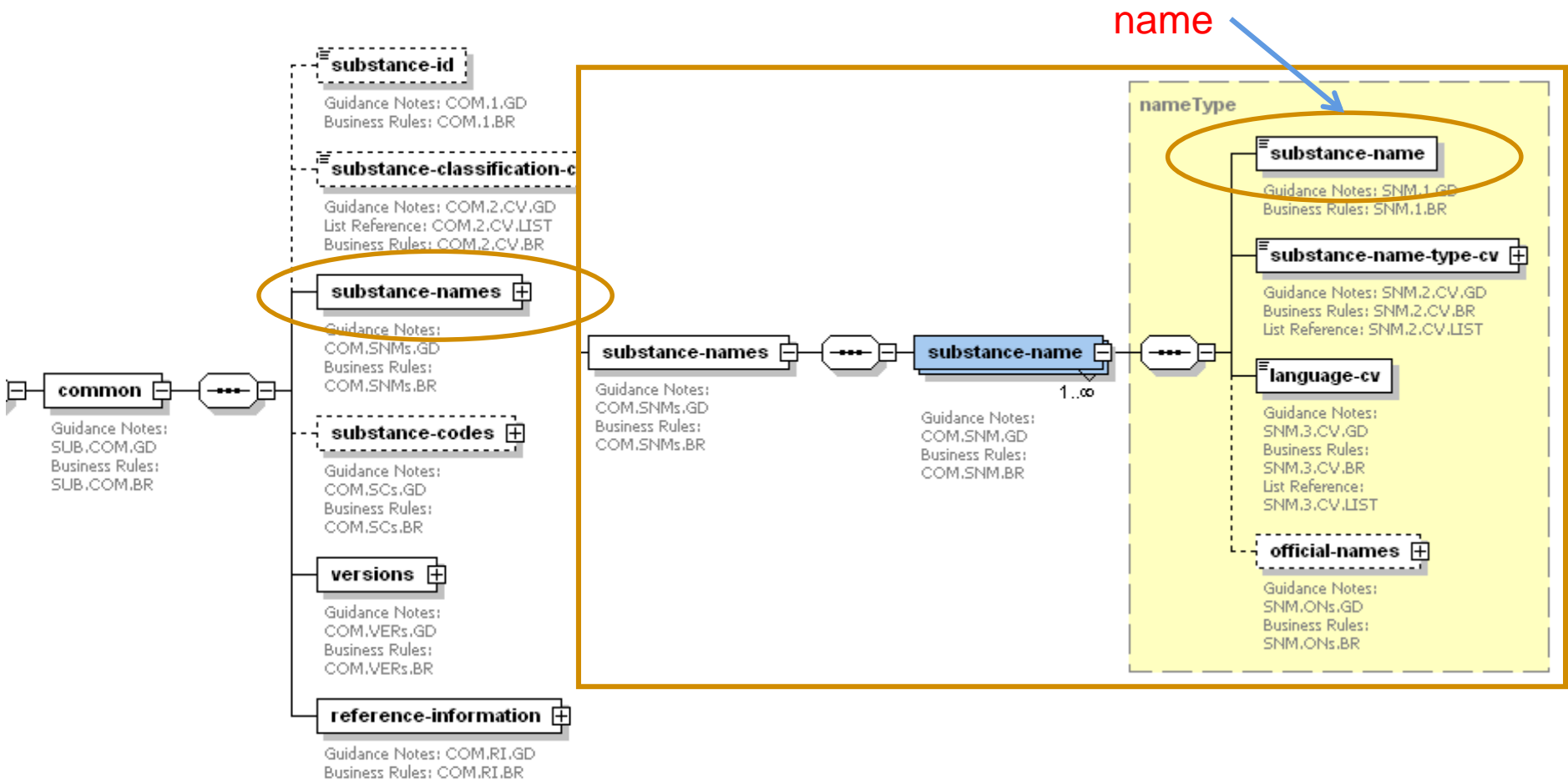
Specified substance – group 3

- Refers to the grade of the material along with the source that defines the given grade
- Group 3 elements shall be used to distinguish specific pharmacopoeial and technical grades of material, e.g. *Sterile Water for Injection USP*
- *Will not be used in NSL – too detailed*



(Ref 2)

SEnsl-ssi.xsd – name of the substance including synonyms



1:many relation – there must be at least one but may occur as many times as necessary

Substance-name-type-cv (ISO)

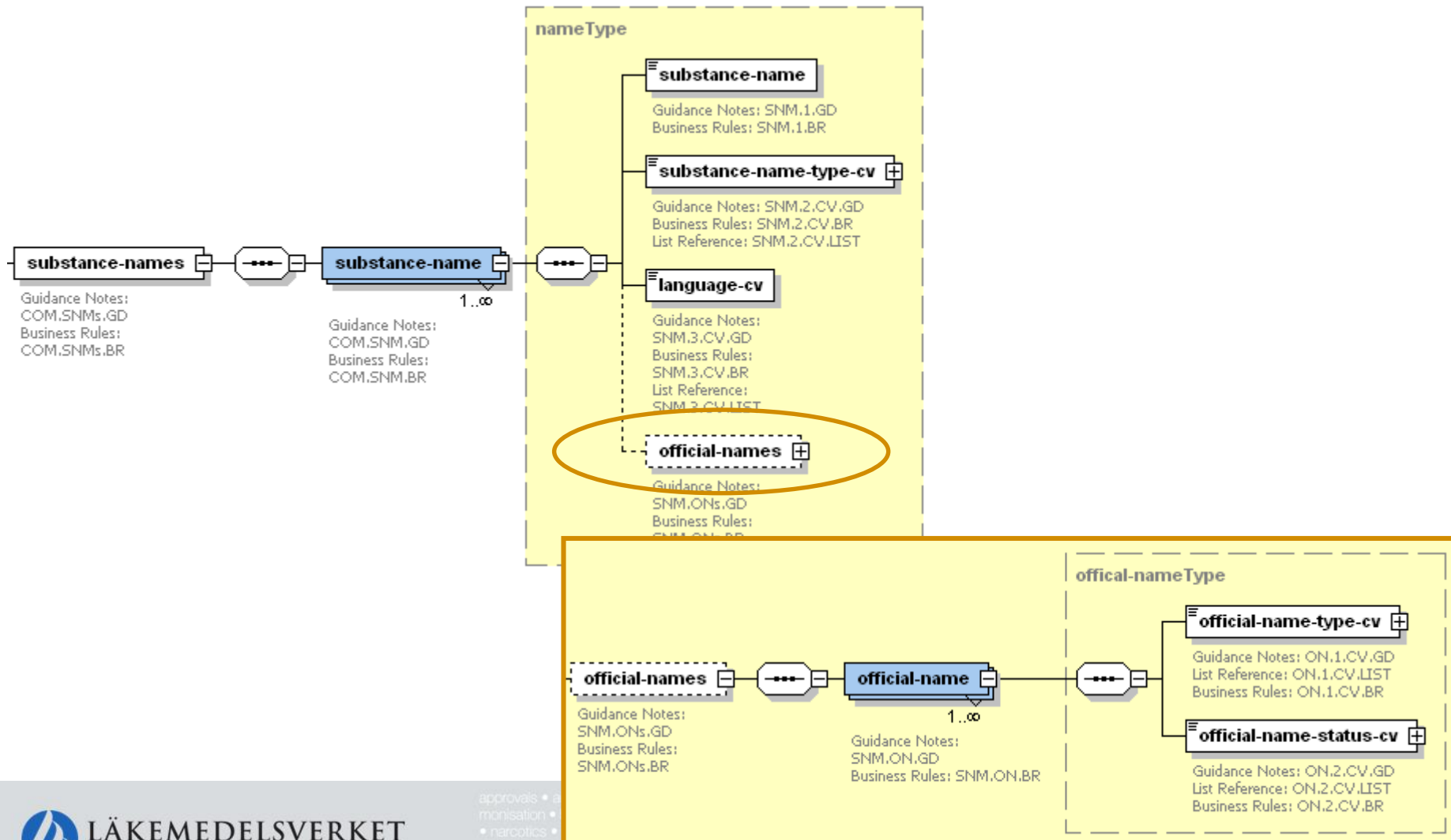
- Code
- Official Name
- Other Name
- Translation



Language-cv (ISO)

- SWE
- ENG
- ZXX for no language – used when the name is a code or a proprietary name

SEnsl-ssi.xsd – official name: when the name comes from an official source e.g. Ph.Eur.

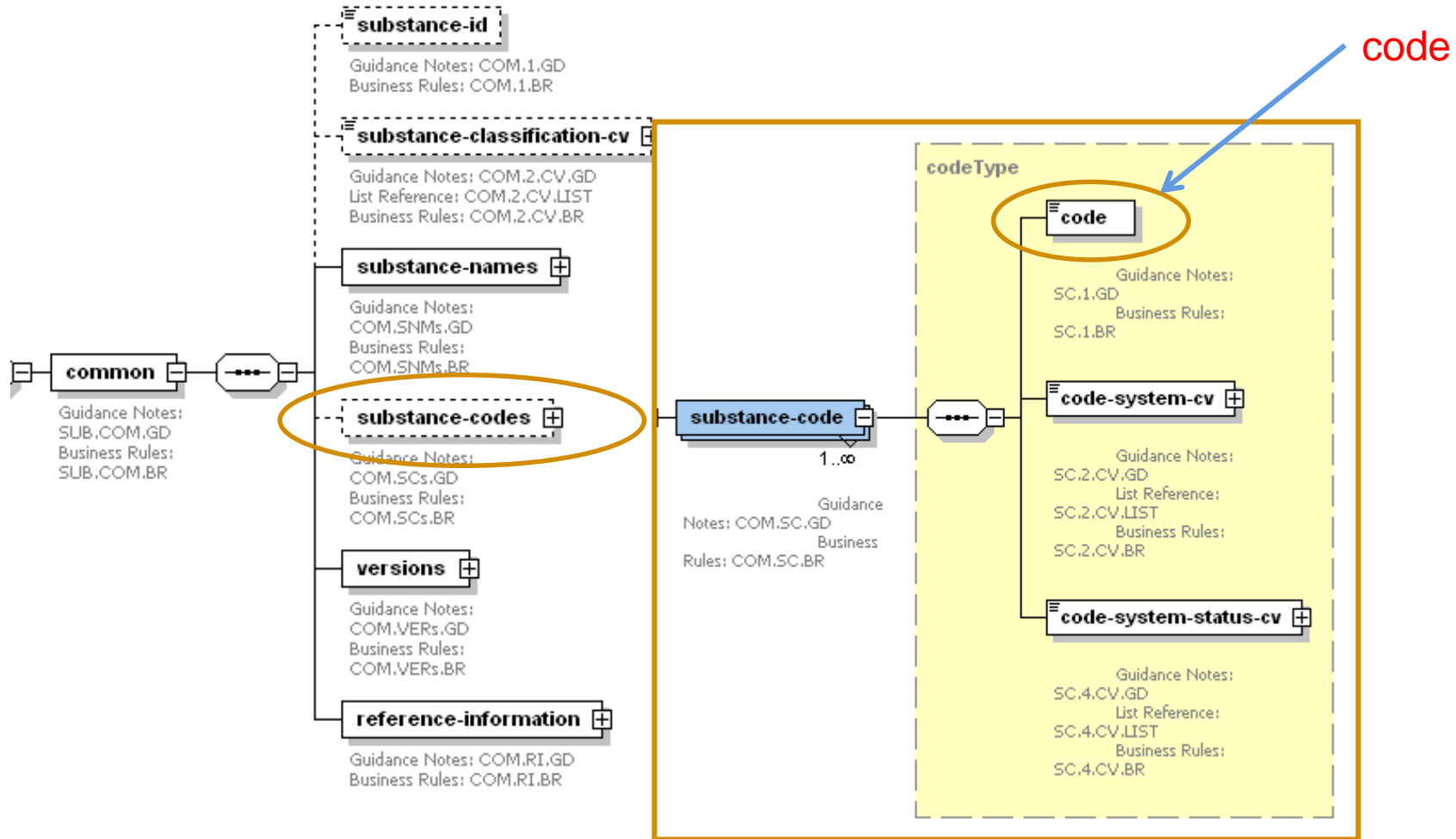


Official name

- **If the name is official, then more details are provided**
 - Official-name-type-cv (ISO): e.g. INN
 - Official-name-status-cv (ISO): e.g. Current, superceded



SEnsl-ssi.xsd – different codings for the substance

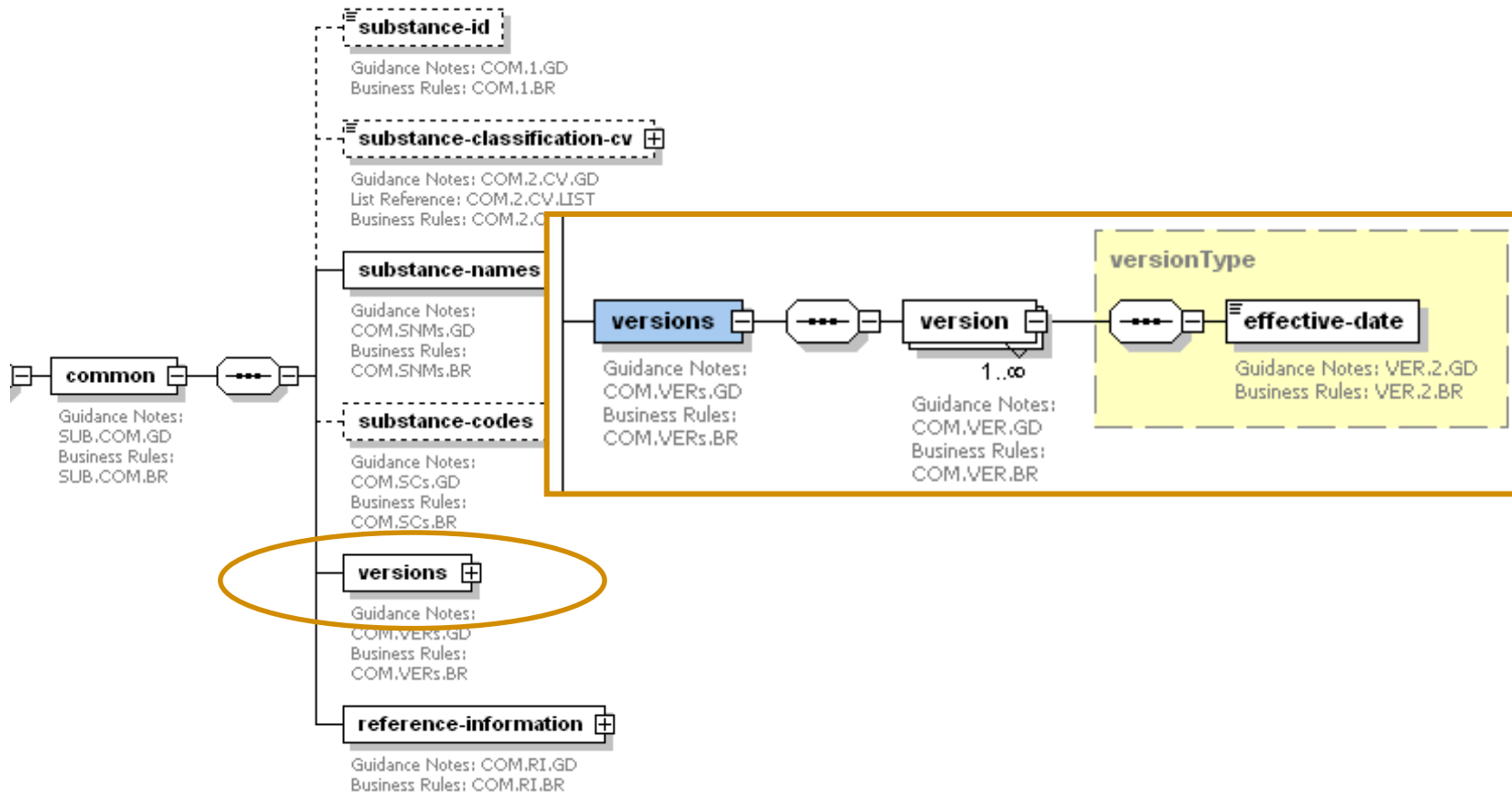


There must always be at least one since our SeNSLid is stored there.

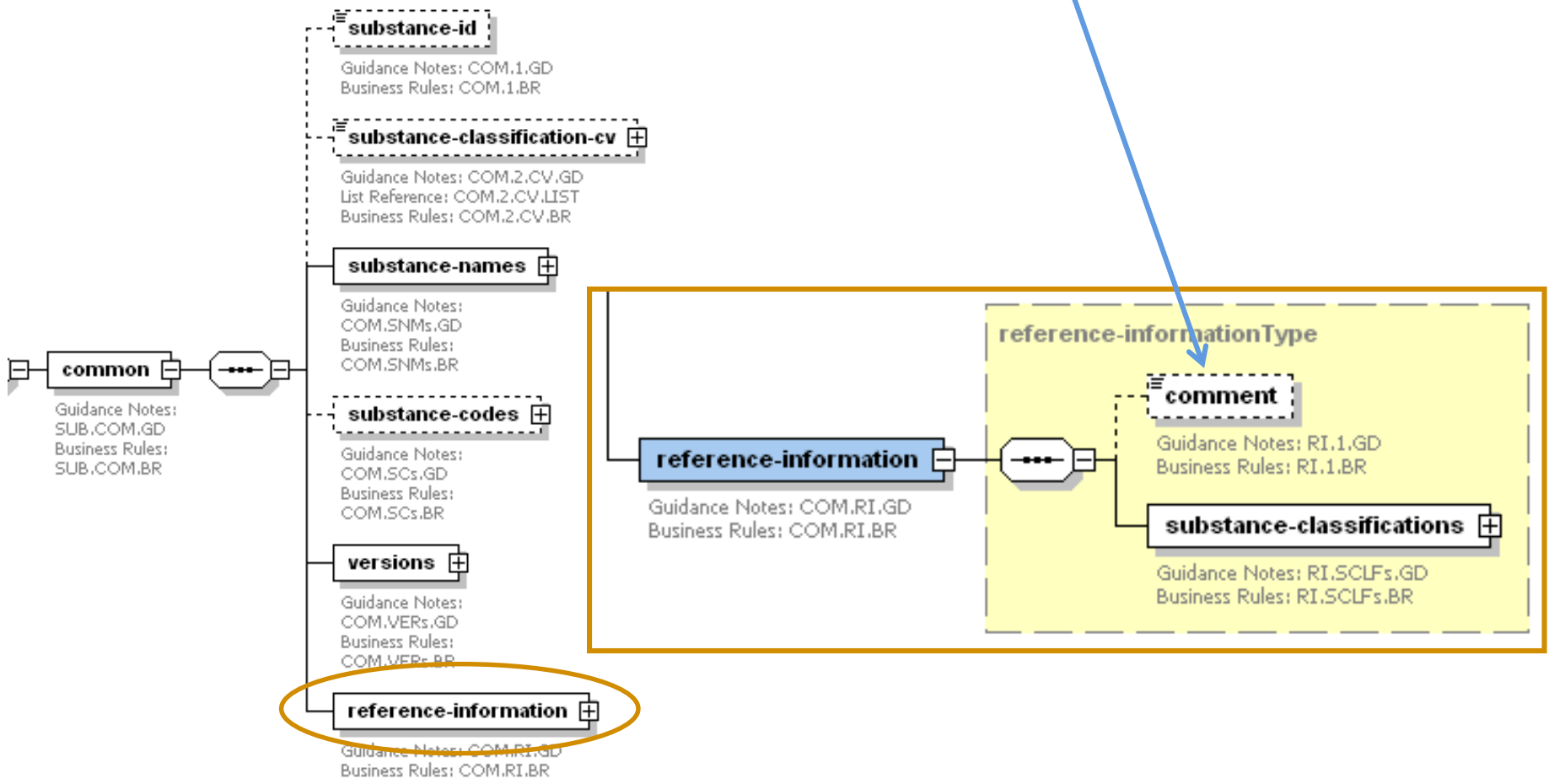
Code-system-cv (ISO) in NSL

- ATC
- CAS
- FDA's **Unique Ingredient Identifier (UNII)** from their **Substance Registration System (SRS)**
- Snomed-CT
- EUTCT – code EMA's EUTCT code system
- **Swedish National Drug Substance Registry ID**
 - The code used in NPL - SeNSLid

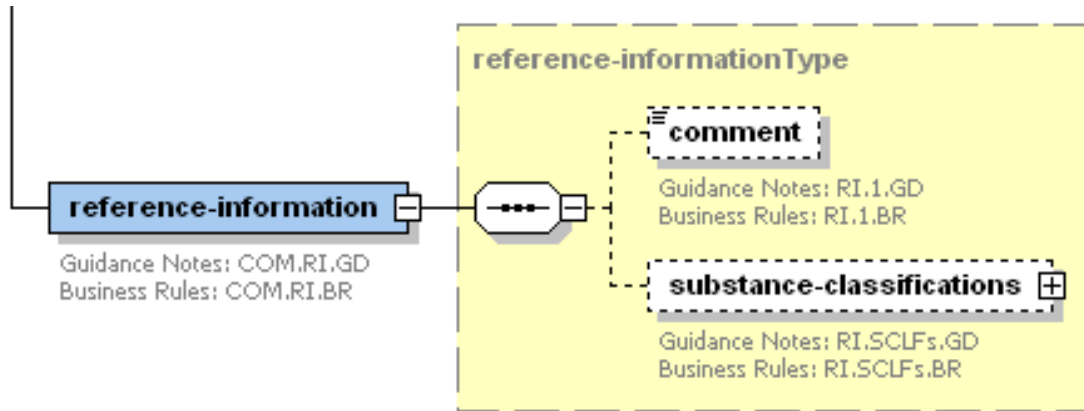
SEnsl-ssi.xsd – version: latest update date



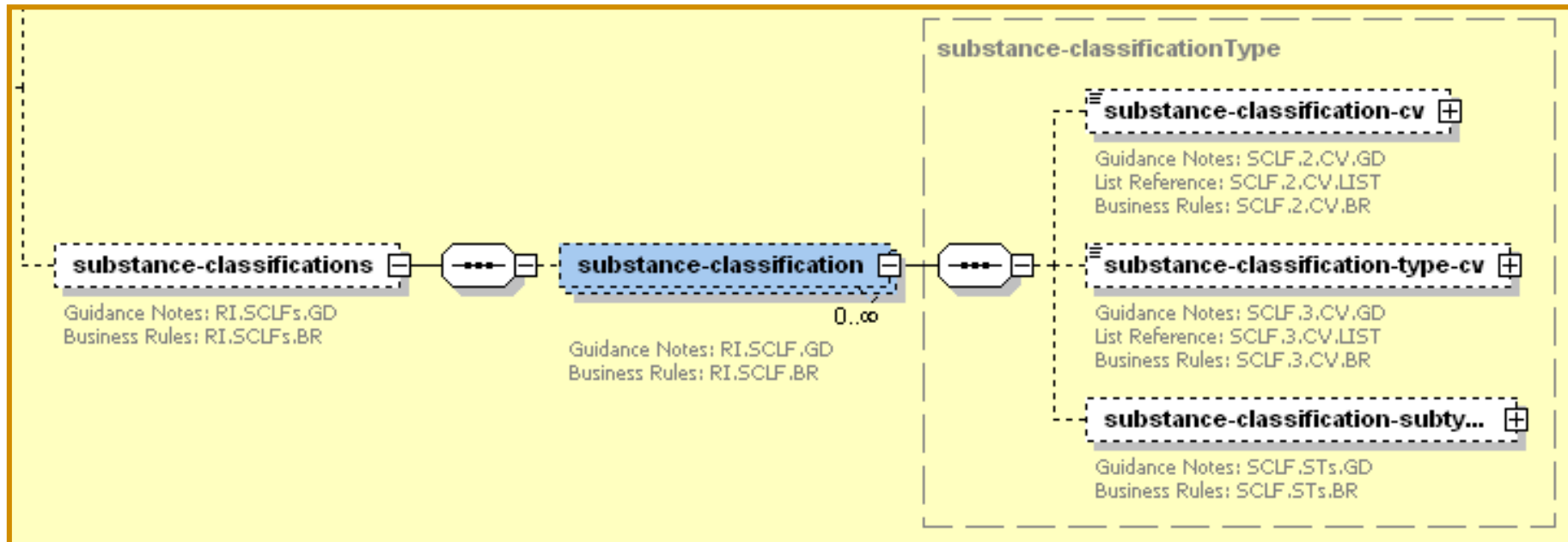
SEnsl-ssi.xsd – Reference information: allows a comment and further classification



SEnsl-ssi.xsd – more ISO classification

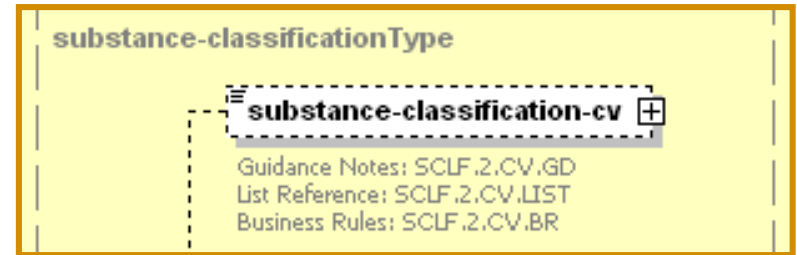


Will not be used for now



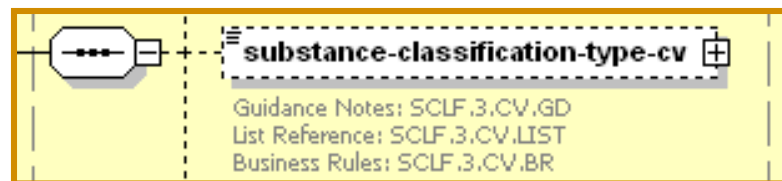
Substance-classification-cv (ISO)

- **Same as previously**
 - Single substance
 - Mixture substance
 - Specified substance



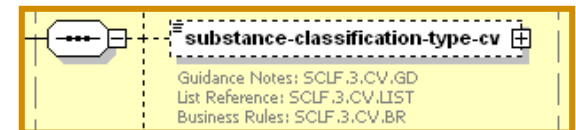
Substance-classification-type-cv (ISO)

- When substance-classification is **Single** or **Mixture**, substance-classification-type comes from **Substance Type CV**
 - Chemical
 - Nucleic Acid
 - Protein
 - Polymer
 - Structurally Diverse
 - Mixture
 - When substance-classification is **Specified substance**, substance-classification-type comes from **Specified Substance Type CV**
 - Specified Substance Level 1
 - Specified Substance Level 2
 - Specified Substance Level 3
- See ch 4, p 26 in Ref 2 for more details



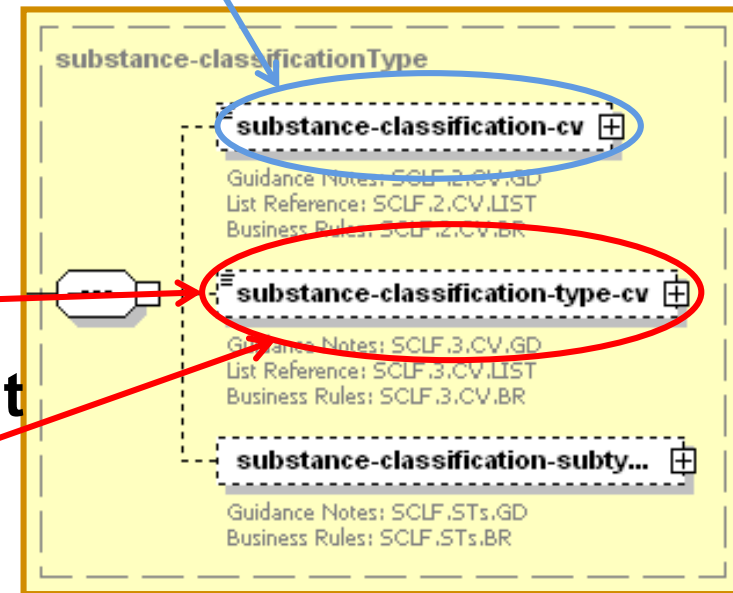
Structurally Diverse Substance

- A type of polydisperse substance isolated from a single source that is a complex mixture which cannot be described as a mixture of a limited number of single substances
- Protein mixtures containing a large number of diverse sequences such as polyclonal immunoglobulins shall be defined as structurally diverse substances
- **Examples:**
 - Vaccine
 - Immunoglobulin
 - Blood derived
 - Herbal
 - Allergen
 - Cell therapy
 - Other



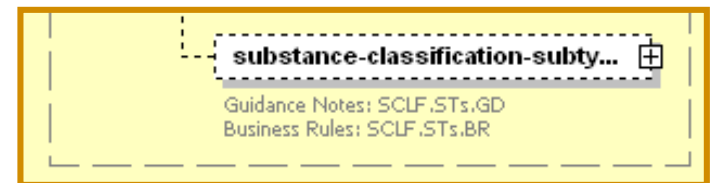
substance-classification = Mixture

- When the substances in a **Mixture** are of the same type, then **substance-classification-type** should be the same as the substances
 - E.g. two Chemicals
 - type= Chemical
- If the substances are of different types
 - E.g. chemical and protein
 - type = Mixture



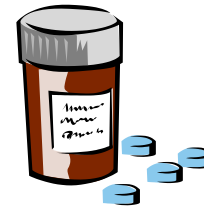
Substance-classification-subtype-cv (ISO)

- Allergen
- Blood Derived
- Cell Therapy
- Gene Therapy
- Herbal
- Monoclonal Antibody
- Multiple Substances
- Not Applicable
- Other
- Polyclonal Immunoglobulin
- Tissue Engineered
- Vaccines



Additional file - SEnsl-other.xsd

- **Contains information not in the ISO standard**
 - Recommended Swedish name
 - Alternative recommended Swedish name
 - Selected English name in Sweden
 - National Swedish narcotic classification
 - If the substance is a biological substance
 - Substance relationship(s) (parent–child)

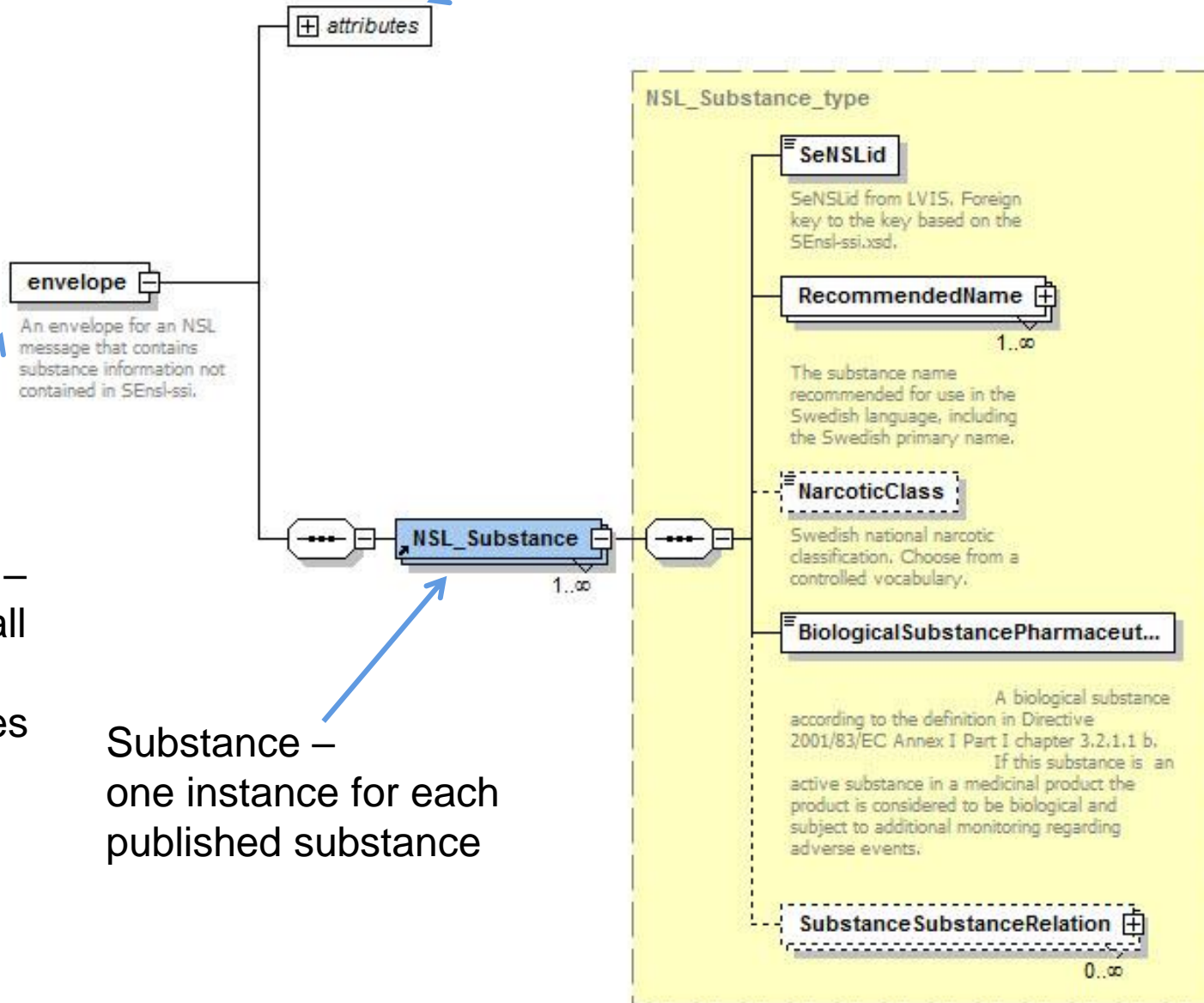


SEnsl-other.xsd

timestamp –
when the file was generated

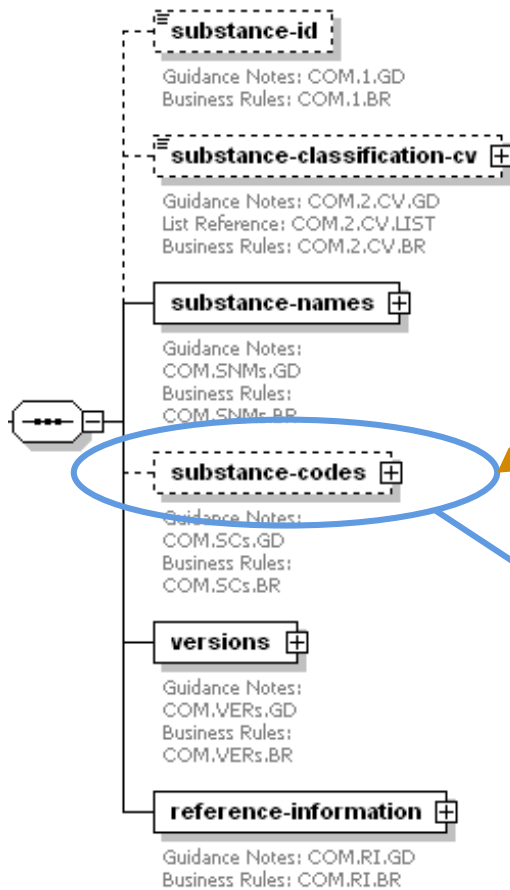
Envelope –
contains all
the
substances

Substance –
one instance for each
published substance

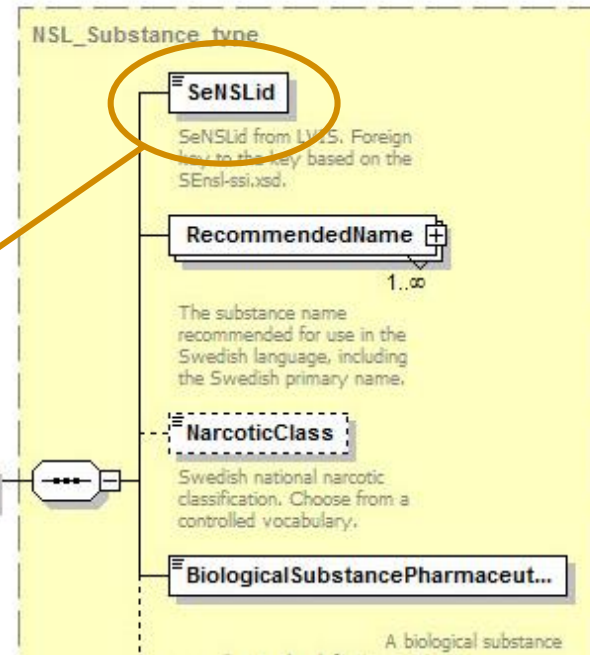


Coupling between the files

SEnsl-ssi.xsd



SEnsl-other.xsd



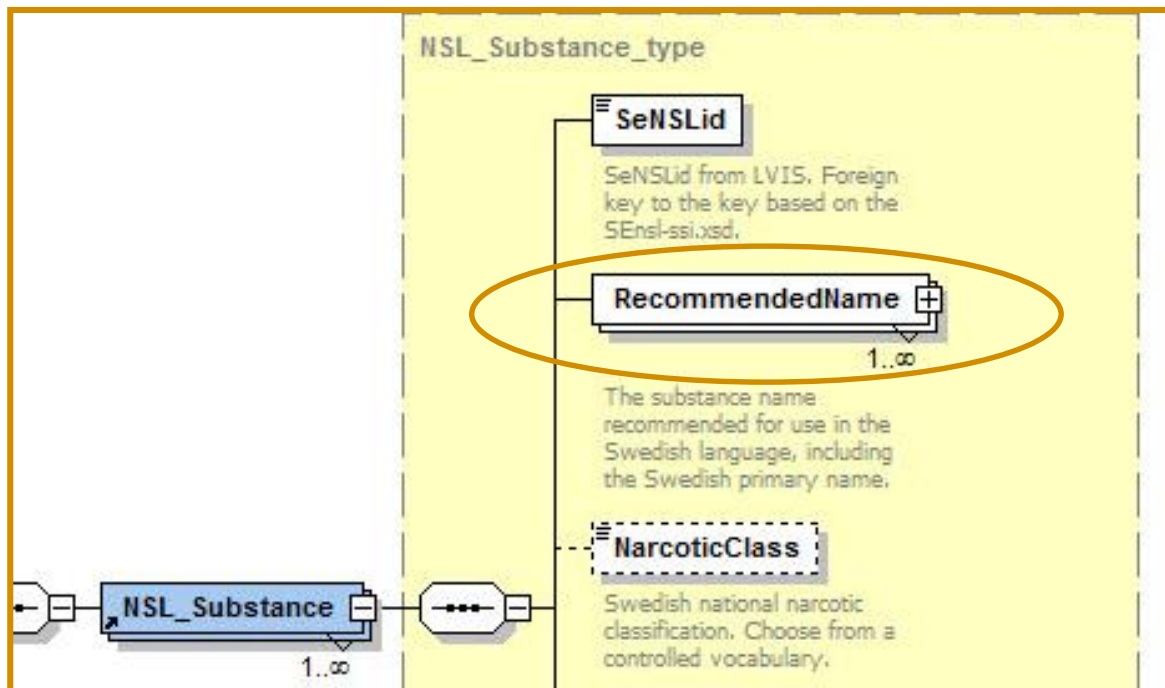
- **SeNSLid** – shall be coupled to this substance-code
- **NOT** substance-id

Coupling between the files, cont'd

- **SeNSLid** that is used here is the **SAME** ID that has always been used in NPL



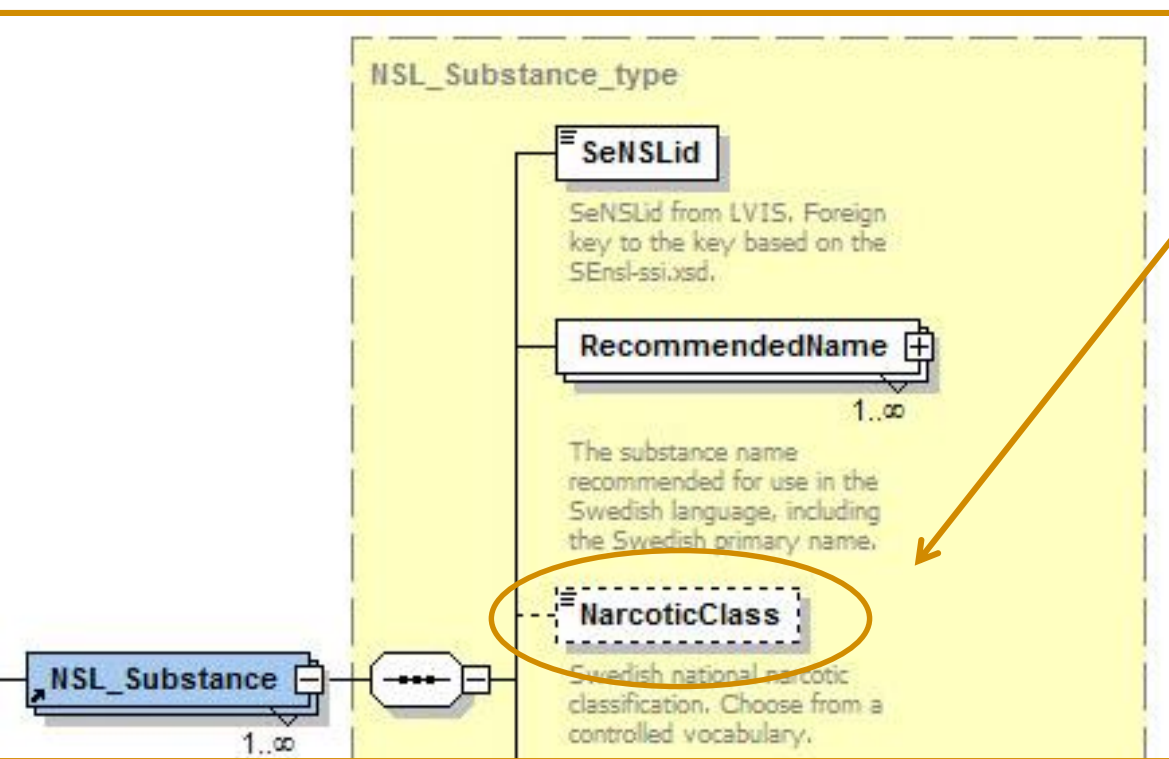
SEnsl-other.xsd – Recommended name



- **One recommended name in Swedish**
- **Zero to many alternative* recommended Swedish names**
- **One English selected name in Sweden**

*Alternative recommended name to be used in e.g. text.

SEnsl-other.xsd – narcotic classification



NarcoticClass – same values as in NPL

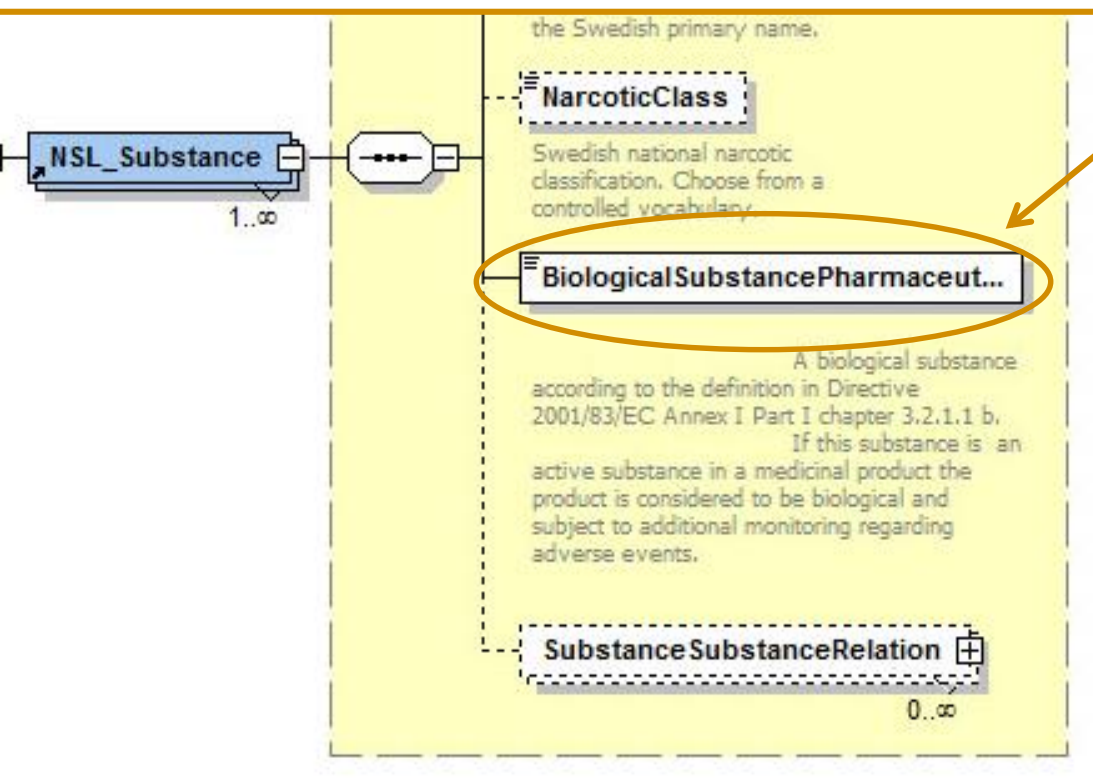
Values:

- Not classified as a narcotic
- I
- II
- III
- IV
- V

Definitions: narcotic classifications

- **Not classified as a narcotic**
- **I - Narcotics that do not occur in medicinal products.**
- **II - Narcotic. Substances with greater abuse potential and limited therapeutic use.**
- **III - Narcotic. Preparations exempted from certain provisions are listed in the Annex to LVFS 2011:9**
- **IV - Narcotic. Substances with lower abuse potential and broad therapeutic use.**
- **V - Narcotic under Swedish law only.**

SEnsl-other.xsd – Biological substance

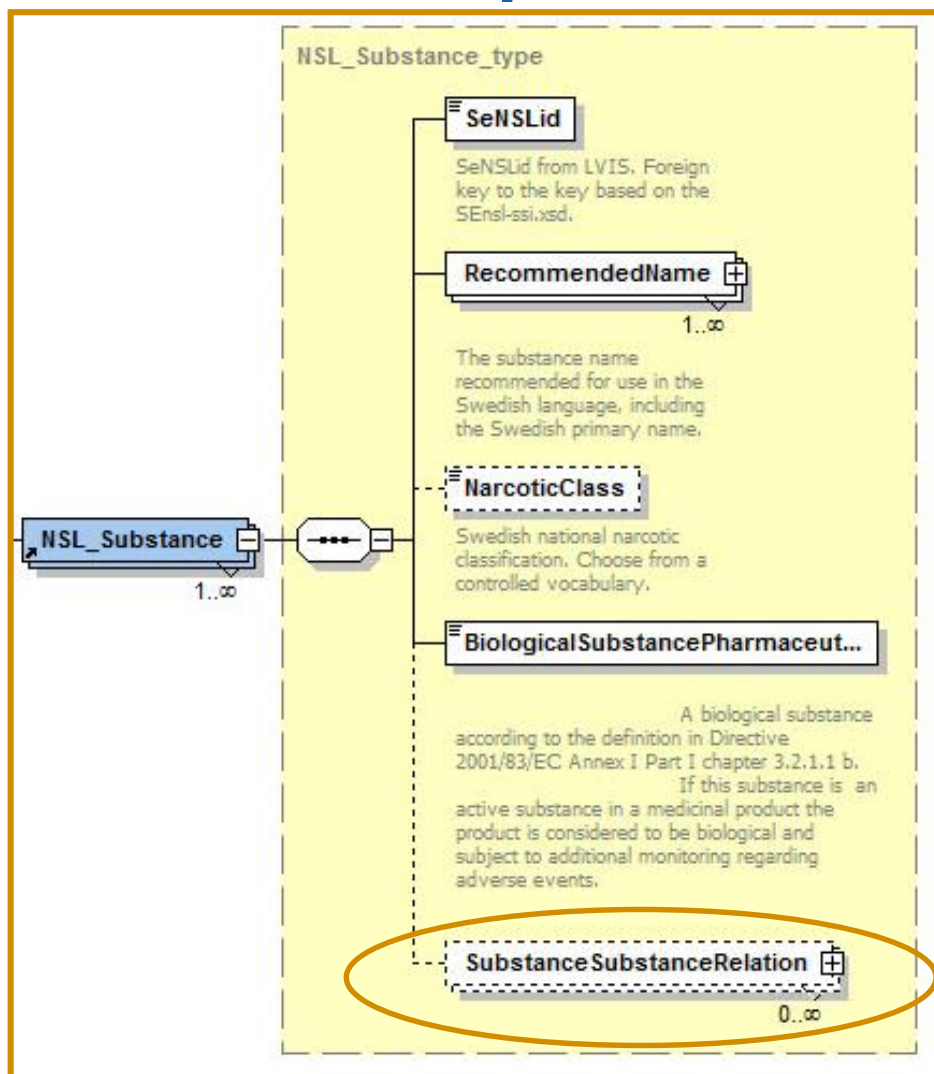


Biological Substance Pharmaceutical Legislation – Yes or No

A biological substance according to the definition in Directive 2001/83/EC Annex I Part I chapter 3.2.1.1 b.

If this substance is an active substance in a medicinal product the product is considered to be biological and subject to additional monitoring regarding adverse events.

SEnsl-other.xsd – parent–child



- A parent can have several children
- A child can have several parents

Dictionary values:

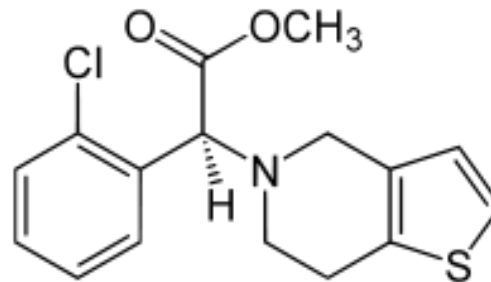
- Has child
- Has parent

SEnsl-other.xsd – parent-child

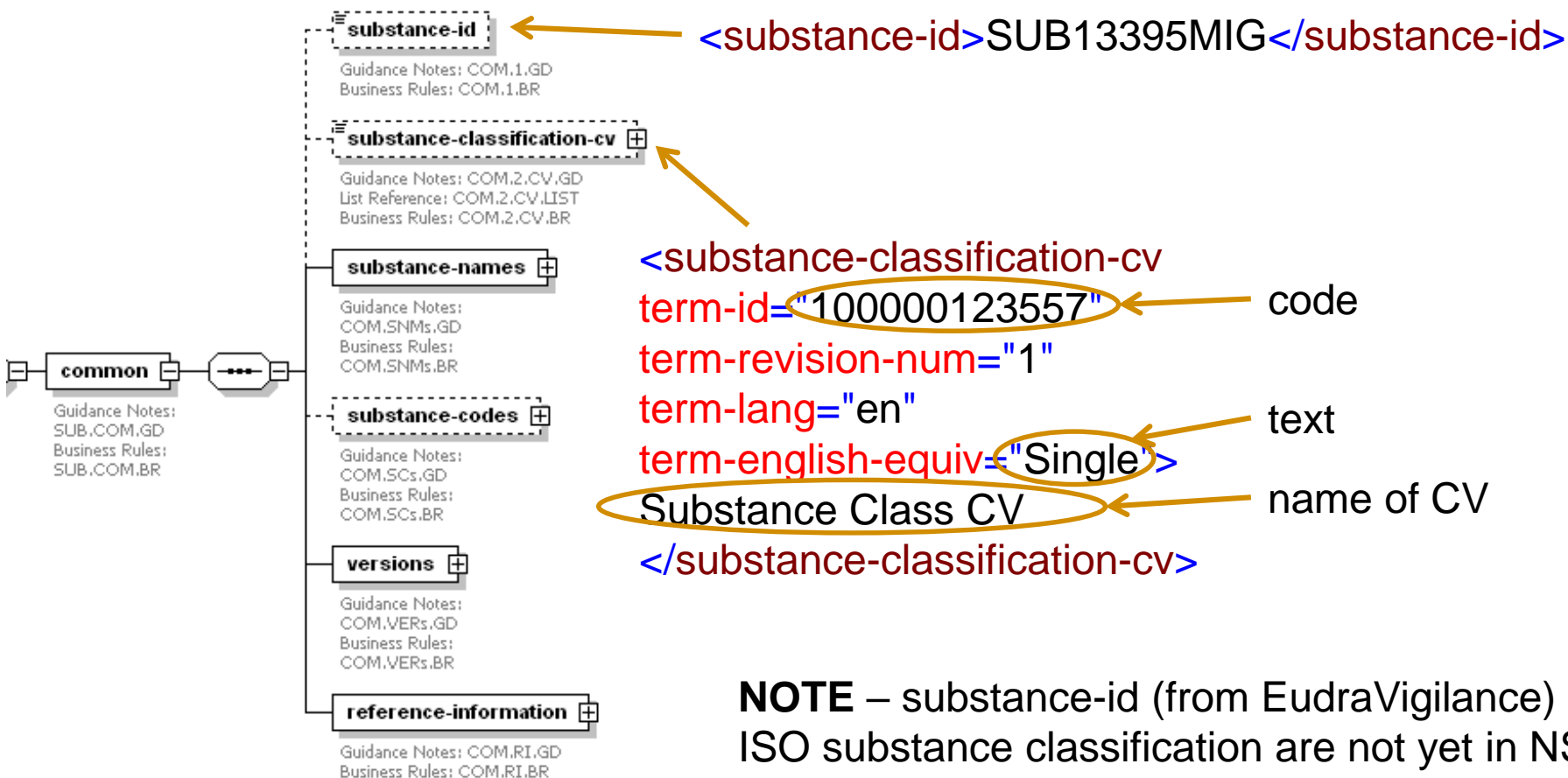
- Salts of substances will be children.
- Hydrates/solvates will be children.
- Hydrated/solvated salts of substances are also children (not grandchildren).
- Salts of two active substances will received two parents.
 - Very rare
 - physostigmine salicylate: has both physostigmine and salicylic acid as parents
- Inorganic salts will not be given children, e.g. calcium will not be given calcium carbonate as a child substance.

Example - Clopidogrel

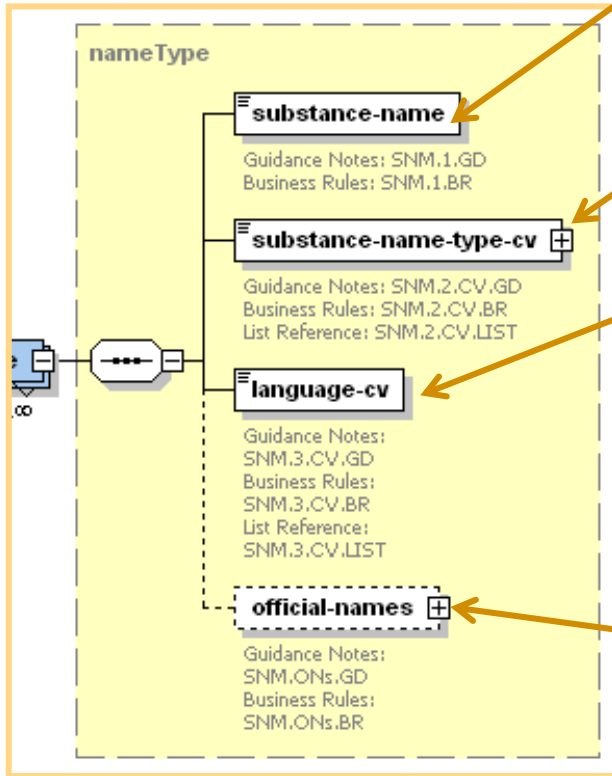
- **Two files**
 - **SEnsl-ssi.xml** based on **SEnsl-ssi.xsd**
 - **SEnsl-other.xml** based on **SEnsl-other.xsd**



Clopidogrel in SEnsl-ssi.xml



Clopidogrel in SEnsl-ssi.xml – substance-name



<substance-name>

```
<substance-name>clopidogrel</substance-name>
```

```
<substance-name-type-cv
```

```
  term-id="100000123558"
```

```
  term-revision-num="1"
```

```
  term-lang="en"
```

```
  term-english-equiv="Official Name">
```

```
    Substance Name Type CV
```

```
</substance-name-type-cv>
```

```
<language-cv>eng</language-cv>
```

```
<official-names>
```

```
<official-name>
```

```
<official-name-type-cv
```

```
  term-id="100000075715"
```

```
  term-revision-num="1"
```

```
  term-lang="en"
```

```
  term-english-equiv="International Non-proprietary
```

```
    Name">Source CV
```

```
</official-name-type-cv>
```

```
<official-name-status-cv
```

```
  term-id="100000123543"
```

```
  term-revision-num="1"
```

```
  term-lang="en"
```

```
  term-english-equiv="Current">Source CV
```

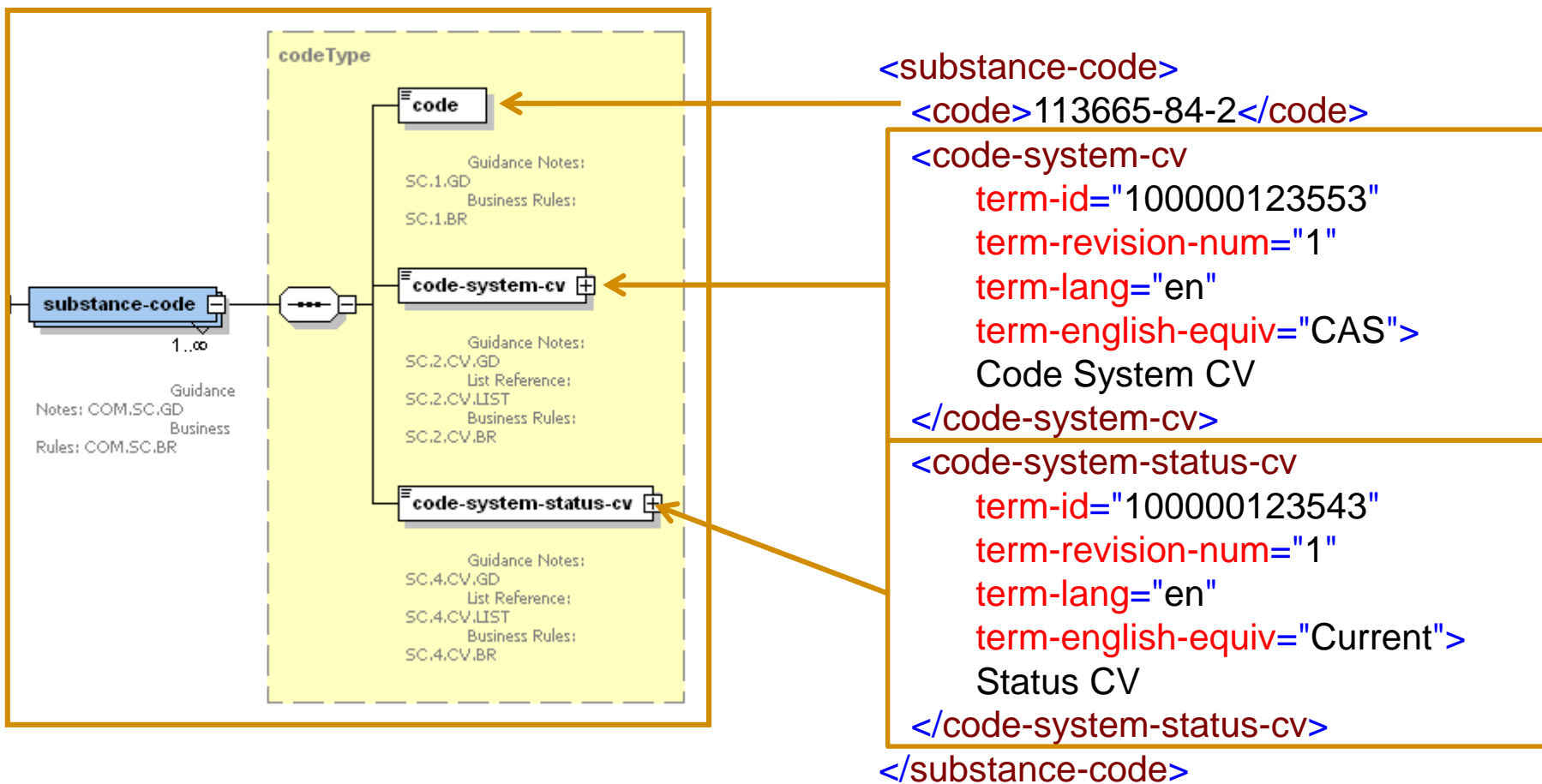
```
</official-name-status-cv>
```

```
</official-name>
```

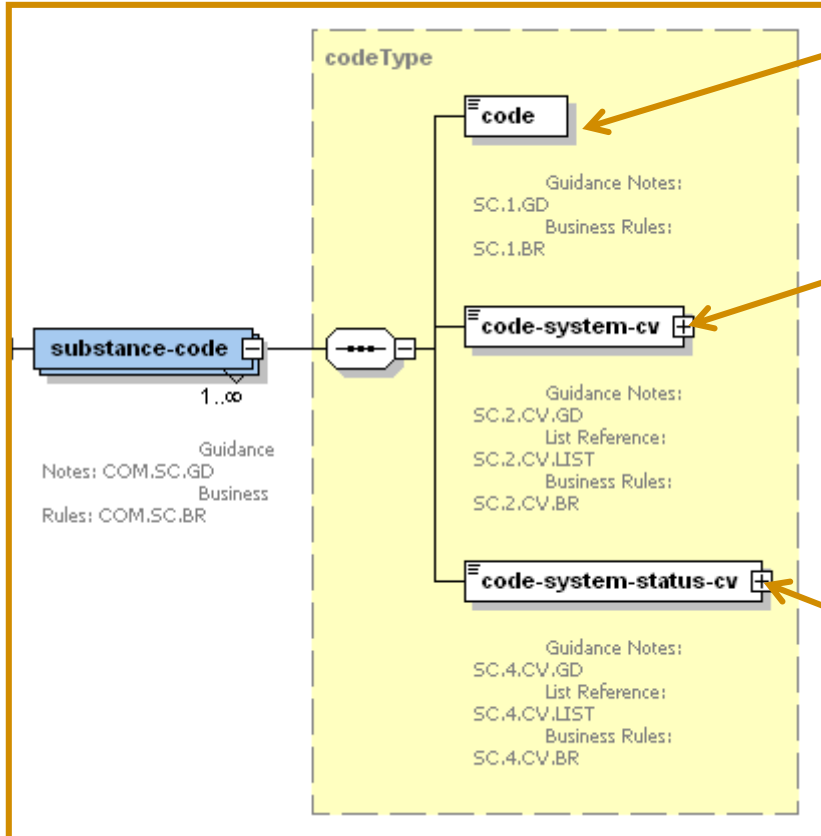
```
</official-names>
```

```
</substance-name>
```

Clopidogrel in SEnsl-ssi.xml – substance-code



Clopidogrel in SEnsl-ssi.xml – substance-code - SeNSLId



`<substance-code>`
`<code>IDE4POFLUB372VERT1</code>`

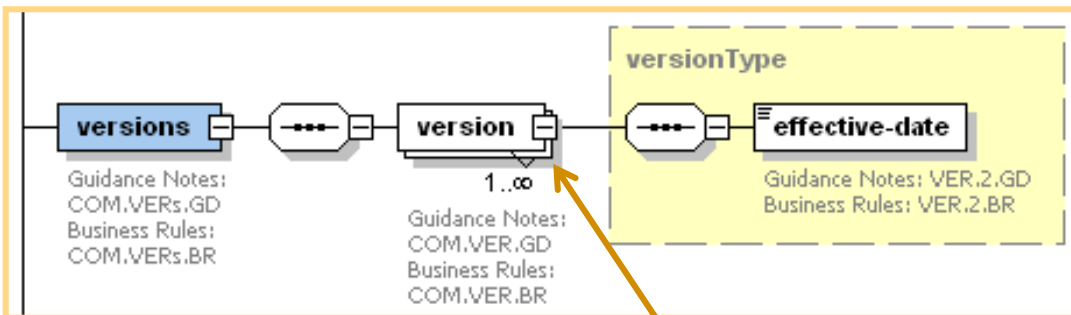
```
<code-system-cv  
  term-id="SENSLIDSENSL"  
  term-revision-num="1"  
  term-lang="en"  
  term-english-equiv="Swedish National Drug  
    Substance Registry ID">  
  Code System CV  
</code-system-cv>
```

```
<code-system-status-cv  
  term-id="100000123543"  
  term-revision-num="1"  
  term-lang="en"  
  term-english-equiv="Current">  
  Status CV  
</code-system-status-cv>
```

`</substance-code>`

NOTE – neither SeNSLid or Snomed-CT are in the list of codes in the ISO code list from EMA – the MPA has defined the codes

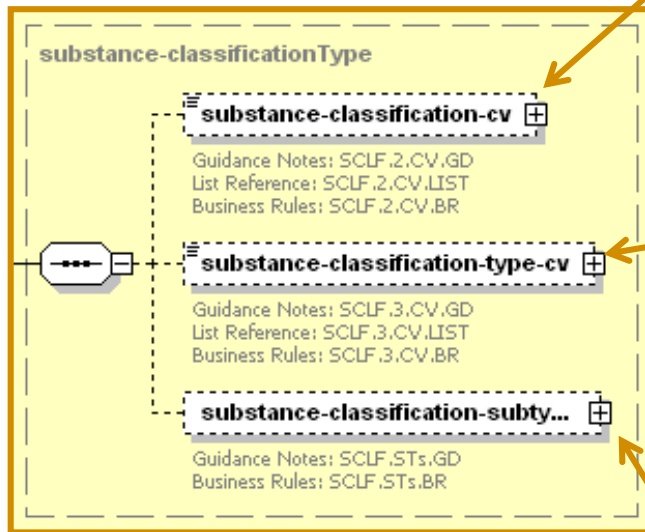
Clopidogrel in SEnsl-ssi.xml - version



```
<versions>  
<version>  
  <effective-date>2012-09-25</effective-date>  
</version>  
</versions>
```

Date when the substance information was last changed.
Applies for **all** the substance information

Clopidogrel in SEnsl-ssi.xml – substance-classification



```
<substance-classification>
```

```
<substance-classification-cv  
  term-id="100000123557"  
  term-revision-num="1"  
  term-lang="en"  
  term-english-equiv="Single">  
  Substance Class CV  
</substance-classification-cv>
```

```
<substance-classification-type-cv  
  term-id="100000075670"  
  term-revision-num="1"  
  term-lang="en"  
  term-english-equiv="Chemical ">  
  Substance Type CV  
</substance-classification-type-cv>
```

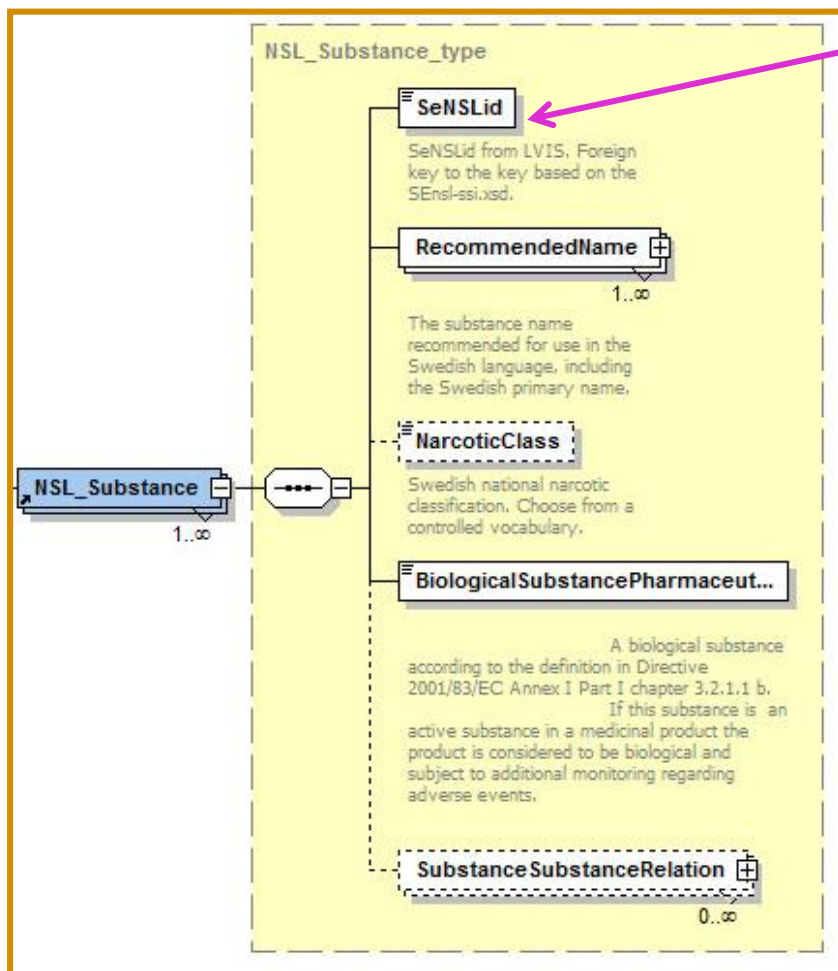
```
<substance-classification-subtypes>  
  <substance-classification-subtype>  
    <substance-classification-subtype-cv  
      term-id="missingxxxx"  
      term-revision-num="1"  
      term-lang="en"  
      term-english-equiv="Stoichiometric">  
      Substance subtype CV  
    </substance-classification-subtype-cv>  
  </substance-classification-subtype>  
</substance-classification-subtypes>
```

```
</substance-classification>
```

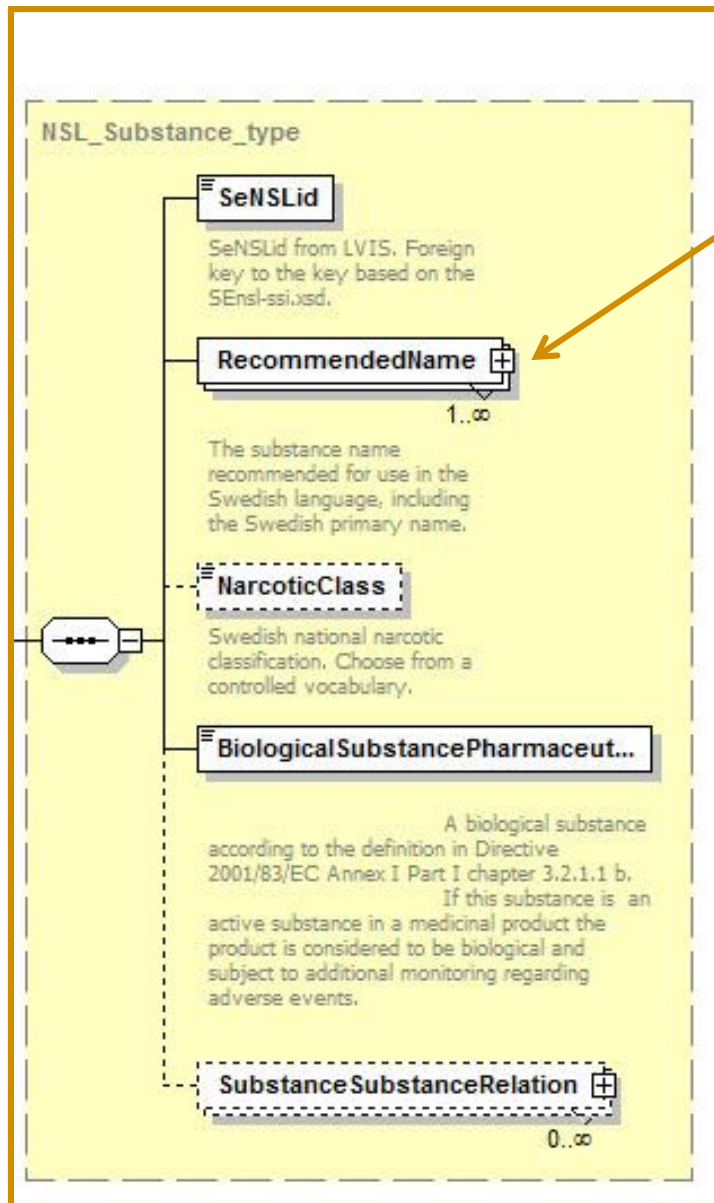
NOTE – ISO classification is not in NSL yet

Clopidogrel in SEnsl-other.xml - SeNSLid

<SeNSLid>IDE4POFLUB372VERT1</SeNSLid>



Clopidogrel in SEnsl-other.xml – RecommendedName



```
<RecommendedName>  
  <Name>klopidogrel</Name>  
<RecommendedNameClassLx>rec  
</RecommendedNameClassLx>  
</RecommendedName>
```

RecommendedNameClassLx:

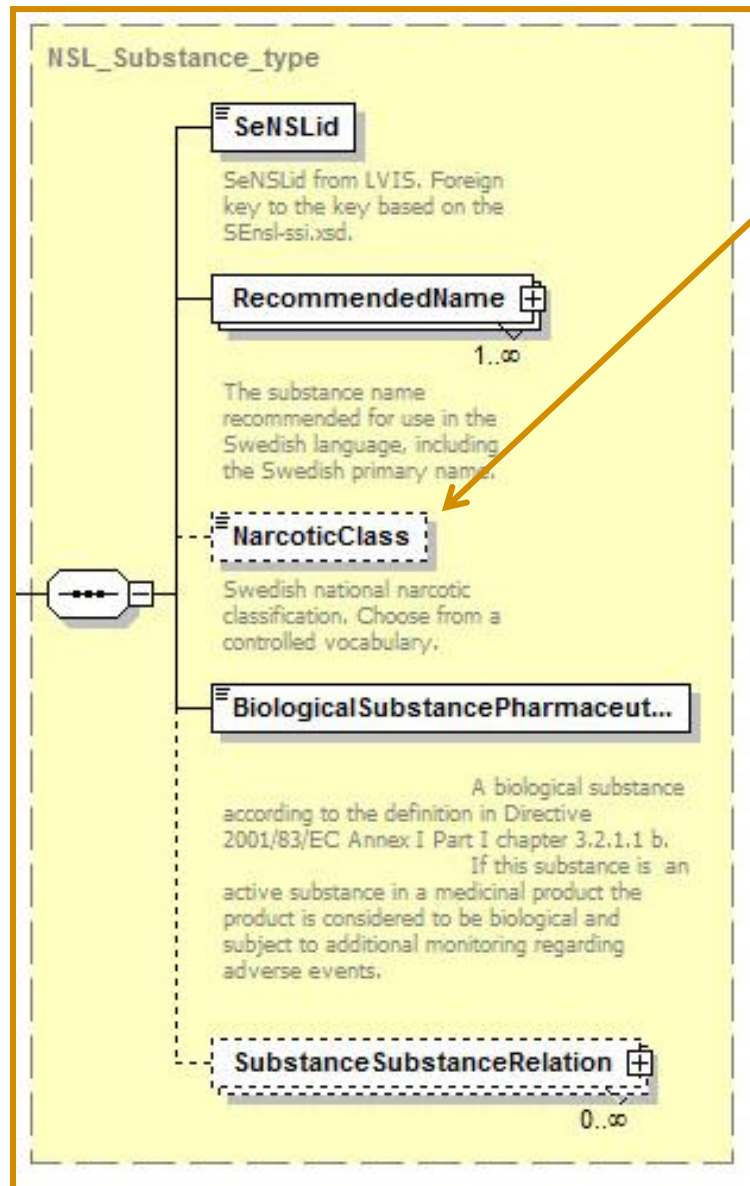
rec = Recommended Swedish name

altrec = Alternative recommended Swedish name

seleng = English selected name in Sweden

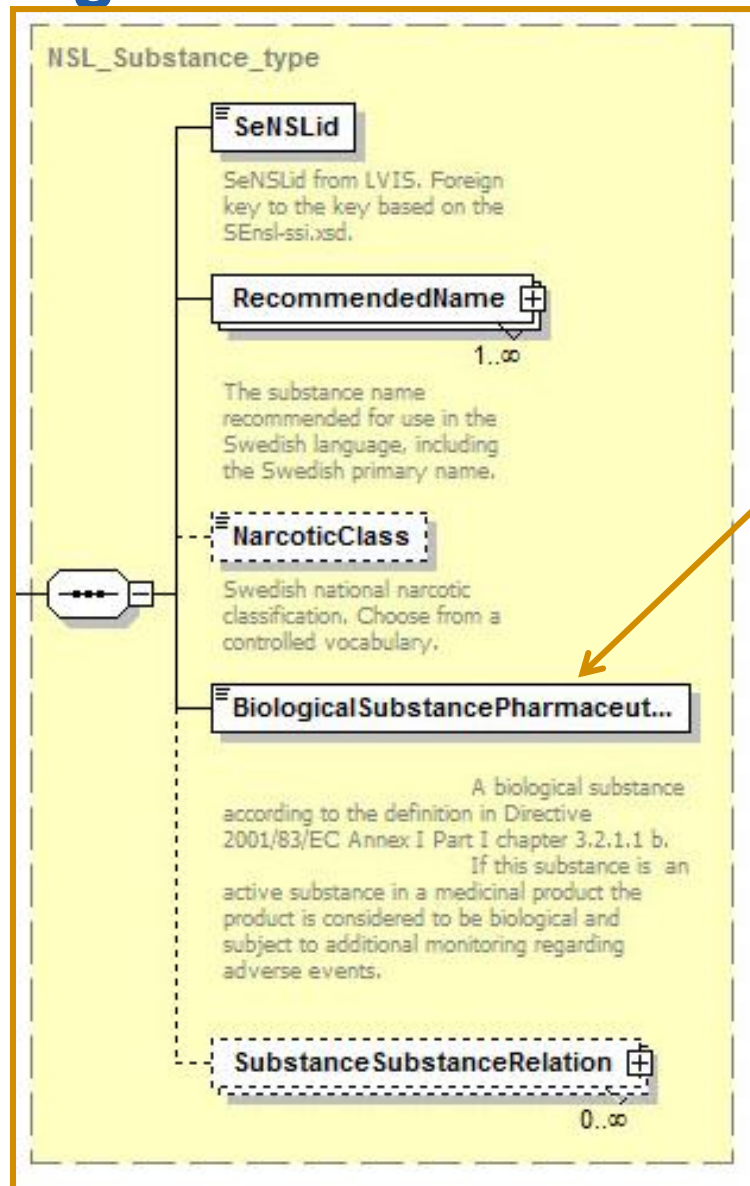
There will always be a recommended Swedish name and a selected English name.

Clopidogrel in SEnsl-other.xml – NarcoticClass



`<NarcoticClass>0</NarcoticClass>`

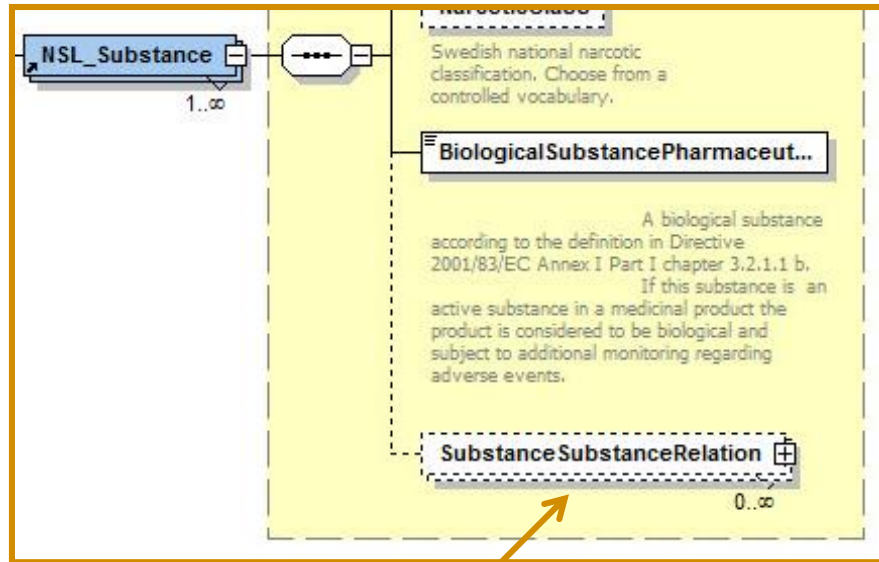
Clopidogrel in SEnsl-other.xml – BiologicalSubstancePharmaceuticalLegislation



`<BiologicalSubstancePharmaceutical
Legislation>N</BiologicalSubstance
PharmaceuticalLegislation >`

A biological substance according to the definition in Directive 2001/83/EC Annex I Part I chapter 3.2.1.1 b.

Clopidogrel in SEnsl-other.xml – SubstanceSubstanceRelation



SeNSLid that clopidogrel is related to, in this case clopidogrel hydrochloride

```

<SubstanceSubstanceRelation>
  <RelatedSeNSLid>IDSXARUW1AYQ2YQMSR</RelatedSeNSLid>
  <SubstSubstRelationLx>CHILD</SubstSubstRelationLx>
</SubstanceSubstanceRelation>
  
```

Clopidogrel has child clopidogrel hydrochloride

SubstanceSubstanceRelation in SEnsl-other.xml

Clopidogrel

```
<SeNSLid>
  IDE4POFLUB372VERT1
</SeNSLid>
<NarcoticClass>0</NarcoticClass>
<SubstanceSubstanceRelation>
  <RelatedSeNSLid>
    IDSXARUW1AYQ2YQMSR
  </RelatedSeNSLid>
  <SubstSubstRelationLx>
    CHILD
  </SubstSubstRelationLx>
</SubstanceSubstanceRelation>
```

Clopidogrel hydrochloride

```
<SeNSLid>
  IDSXARUW1AYQ2YQMSR
</SeNSLid>
<NarcoticClass>0</NarcoticClass>
<SubstanceSubstanceRelation>
  <RelatedSeNSLid>
    IDE4POFLUB372VERT1
  </RelatedSeNSLid>
  <SubstSubstRelationLx>
    PARENT
  </SubstSubstRelationLx>
</SubstanceSubstanceRelation>
```


References

Ref 1. Chapter 4: Structured substance information,

Detailed guidance on the electronic submission of information on medicinal products for human use by marketing authorisation holders to the European Medicines Agency in accordance with Article 57(2), second subparagraph of Regulation (EC) No. 726/2004 Version 2.0 (1 sep 2011)

Ref 2. Chapter 6: Definitions I Detailed guidance on the electronic submission of information on medicinal products for human use by marketing authorisation holders to the European Medicines Agency in accordance with Article 57(2), second subparagraph of Regulation (EC) No. 726/2004,