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Annotation Guidelines for DDI Corpus

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22/11/2012

Annotation Guidelines for DDI Corpus

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1. Introduction

The aim of the DDI corpus is to provide a gold-standard annotation of drugs and drug-drug interactions in biomedical texts. This document includes a set of guidelines of how the annotation task should be carried out. The rules are given with examples clarifying their use and organized according to topic. This document is intended for annotators as well as any other users of the DDI corpus.

The DDI corpus consists of 233 MedLine abstracts selected from the query 'drug-drug interactions' as well as 785 documents describing drug interactions from the DrugBank¹ (Wishart et al., 2006) database.

Texts were first pre-processed to detect sentence boundaries and identify drug named entities substances using the MetaMap² tool (Aronson & Lang, 2010). This automated annotation aims at facilitating manual annotation by reducing time and effort of manual annotators. Then texts were reviewed and annotated by two annotators using XML Notepad³. The task of annotators consists in annotating named entities of pharmacological substances as well as annotating interactions between these entities.

2. Drug Information Resources

The concept of pharmacological substance may be more complex than previously thought. To determine whether a candidate name can refer a drug (and also assign the appropriate type to it) or whether there is an interaction between a given pair of drugs, annotators should use some of the following drug information resources that were selected by pharmacists and health professionals with expertise in pharmacovigilance:

- **WHO ATC:** *Anatomical Therapeutic Chemical (ATC) classification system.*

This system classifies active substances (chemical compounds that are responsible of the activity of a medication) according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. The system only provides information on generic International Nonproprietary Names (INN) of active substances approved for human use.

http://www.whocc.no/atc_ddd_index/

- **Drug@FDA:** *FDA Approved Drug Products.*

This resource is a searchable catalog of generic and brand drugs approved for human use by FDA (Food and Drug Administration) in USA.

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>

¹<http://www.drugbank.ca>

²<http://metamap.nlm.nih.gov/>

³<http://www.microsoft.com/en-us/download/details.aspx?id=7973>

- **EMA: European Medicines Agency.**

This web offers a search tool where users can look for information on human and veterinary medicines approved in Europe. Pharmacological substances can be found by their generic names as well as their brand names.

http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp&mid=WCOb01ac058001d124

- **CIMA: AEMPS Medicines Online Information Center – CIMA**

This resource is a searchable catalog of generic and brand drugs approved for human use in Spain.

<https://sinaem4.agemed.es/consaem/fichasTecnicas.do?metodo=detalleForm&version=n ew>

- **PubChem:**

This database contains information on chemical structures of small organic molecules and on their biological activities. It may be useful to find the chemical name of a drug.

<http://pubchem.ncbi.nlm.nih.gov/>

- **MeSH:**

MeSH (Medical Subject Headings) is the NLM controlled vocabulary thesaurus used for indexing articles for PubMed. It may be useful to find synonyms of drugs, chemical drugs, and groups of drugs.

<http://www.ncbi.nlm.nih.gov/pubmed/>

- **WHO ATCvet:**

It is the system for classification of veterinary medicines. It is based on the same principles as the ATC system.

<http://www.whocc.no/atcvet/>

- **DrugBank:**

DrugBank is a free and online database with about 4800 drug entries. Each entry contains more than 100 data fields that gather detailed chemical and pharmacological information (type, category, brand names, chemical formula, drug interactions, etc). This database contains information on FDA-approved drugs as well as on experimental drugs.

<http://www.drugbank.ca/>

- **Drugs.com:**

This website has a checker that helps you establish whether a given pair of drugs interacts. For each interaction, the tool contains information on its mechanism, its level of significance (major, moderate or minor), and sometimes, can also provide advices to avoid or lessen its side effects.

<http://www.drugs.com/>

3. Entities

A drug is a substance that is used in the treatment, cure, prevention or diagnosis of diseases. We distinguish different types of drugs such as generic drugs, brand drugs, group of drugs and other substances not approved for human use. These substances will be referred to as entities. Each entity has a text binding and a type. The text binding identifies the part of the sentence text that specifies the entity. Annotation of the largest-span of text is preferred. For example, in the case of “monoamine oxidase (MAO) inhibitors”, only “monoamine oxidase (MAO) inhibitors” is annotated and not “monoamine oxidase inhibitors” and/or “MAO inhibitors”. This means that nested entities -one entity is (textually and conceptually) contained within another- will not be annotated. The exact boundaries of the entity are specified. The type is one of the above types.

This section details the rules guiding the annotation of entities and provides examples clarifying their use. Entities refer to pharmacological substances. Established names of generic and brand drugs, drug substances not approved for human use, as well as established names of families or groups of these types are annotated as entities. Other types of entities (e.g. cells, proteins, genes, food, drunk, etc) are out of the scope of this corpus.

To determine whether a candidate name should be considered a pharmacological substance, typical use in literature and resources listed above should be followed.

The following table describes the DDI entities. For each entity type, an informal description and an example are given:

Entity type	Description	Example
drug	Any chemical agent used in the treatment, cure, prevention or diagnosis of disease that has been approved for human use. It is denominated by a generic or chemical name, and not by a trade name or brand name.	<i>Probenecid</i>
brand	Any chemical agent used in the treatment, cure, prevention or diagnosis of disease that has been approved for human use. It is denominated by a trade or brand name.	<i>Kineret®</i>
drug_n	Any chemical agent that affects living organisms. It's an active substance, but it is not approved to be used in humans with a medical purpose.	<i>MPTP</i>
group	A term in the text that describe different drugs into groups according to the organ or system on which they act or according to their chemical, pharmacological or therapeutic properties.	<i>Monoamine oxidase (MAO) inhibitors</i>

All mentions of an entity are annotated. Regardless of the type of entity, the span of the annotation should restrict to just the name of the pharmacological substance. When these names act as modifiers (for example, cyclosporine therapy, or levonorgestrel AUC), only the

pharmacological substances should be annotated. In the same way, information on dosage or other properties should not be annotated.

The following subsections describe, for each of the entity types, which spans of text should be annotated and how some special cases should be handled.

3.1 drug entity

Before a drug can be used in humans, this must be approved by the national medicine agencies of those countries where the drug will be marketed. American (FDA) and European (EMA) Medication Agencies are currently the two most important organizations for the evaluation of medicinal products. However not all drugs are approved in all countries. Indeed, drugs can be approved in other countries but not approved by the U.S. FDA. For example dipyrone, a non-steroidal anti-inflammatory agent, was withdrawn from several countries (such as USA, Sweden and Canada), however it is still approved by the Spanish Agency for Medicines and Healthcare Products (AEMPS).

In general, any mention of a pharmacological substance should be labeled with the category 'drug' when it is approved for human use and is neither a brand drug nor a group of drugs. Drugs that were approved in some country but withdrawn in others should be annotated with the type 'drug'. These issues are discussed in more detail below.

To know what pharmacological substances are approved at international level, the ATC system should be used as the main reference source. The ATC system normally provides the INN (International NonproprietaryName) of the substances. Additionally, the databases of the main medicines agencies (FDA, EMA, AEMPS, etc) can be consulted in order to find a given drug whose name is not an INN. For example *acetaminophen* is not found in the ATC system, since it is the name provided for USAN council. However, its synonym *paracetamol* (which is the INN), can be found in the ATC/DDD Index. DrugBank can be a valuable resource to manage the high degree of synonymy of drug names. Similarly, MeSH also provides a list of synonyms.

Any drug that is not included in some of the above resources, should be considered as a drug not approved for human use, and thereby, should be annotated as drug_n entity.

3.1.1 Generic names

A pharmacological substance should be labeled with the category 'drug' when it is approved for human use and appears in the text with its chemical or generic name. Each drug has a generic or nonproprietary name, which identifies a unique active ingredient. The generic name of a drug is also known as its International Nonproprietary Name (INN), which is assigned by WHO.

```

- <sentence id="DrugDDI.d378.s1" text="In vivo interaction studies in humans have demonstrated that digoxin and warfarin do not affect the PK properties of anagrelide, nor does anagrelide affect the PK properties of digoxin or warfarin.">
  <entity id="DrugDDI.d378.s1.e0" charOffset="61-67" type="drug" text="digoxin"/>
  <entity id="DrugDDI.d378.s1.e1" charOffset="73-80" type="drug" text="warfarin"/>
  <entity id="DrugDDI.d378.s1.e2" charOffset="117-126" type="drug" text="anagrelide"/>
  <entity id="DrugDDI.d378.s1.e3" charOffset="138-147" type="drug" text="anagrelide"/>
  <entity id="DrugDDI.d378.s1.e4" charOffset="177-183" type="drug" text="digoxin"/>
  <entity id="DrugDDI.d378.s1.e5" charOffset="188-195" type="drug" text="warfarin"/>
</sentence>
```

Figure 1 Annotation of drugs generic names

In some cases, names of substances may appear separated by signs such as “/” or “-”. Each of these substances should be annotated as a unique entity.

- *morphine/warfarin*; $[m\text{or}phine]_{\text{drug1}}/[w\text{ar}f\text{ar}in]_{\text{drug2}}$.
- *morphine-warfarin*; $[m\text{or}phine]_{\text{drug1}}-[w\text{ar}f\text{ar}in]_{\text{drug2}}$

Similarly, annotators should not include in the annotation those words linked to the name of a drug by some sign like ‘-’.

```

- <sentence id="DrugDDI.d23.s5" text="Digitalis glycosides: amphotericin B-induced hypokalemia may potentiate digitalis toxicity.">
  <entity id="DrugDDI.d23.s5.e0" charOffset="0-19" type="group" text="Digitalis glycosides"/>
  <entity id="DrugDDI.d23.s5.e1" charOffset="22-35" type="drug" text="amphotericin B"/>
  <entity id="DrugDDI.d23.s5.e2" charOffset="72-80" type="group" text="digitalis"/>
  <ddi id="DrugDDI.d23.s5.d0" e1="DrugDDI.d23.s5.e1" e2="DrugDDI.d23.s5.e2" type="effect"/>
</sentence>
```

Figure 2The term ‘-induced’ is not included in the annotation of the entity DrugDDI.d23.s5.e1 (second entity).

3.1.2 Chemical names

IUPAC and IUPAC-like chemical names of a pharmacological substance approved for human use should be annotated with the category ‘drug’. For example, the chemical name of **oxitriptan** is **5-hydroxy-L-tryptophan**:

- *In rats, 5-hydroxy-L-tryptophan decreased the initial absorption rate and increased AUC of gaboxadol.*

```

- <sentence id="DrugDDI.d1139.s0" text="Neurochemical and functional consequences following 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) and methamphetamine. ">
  <entity id="DrugDDI.d1139.s0.e0" charOffset="52-95" type="drug_n" text="1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine"/>
  <entity id="DrugDDI.d1139.s0.e1" charOffset="98-101" type="drug_n" text="MPTP"/>
  <entity id="DrugDDI.d1139.s0.e2" charOffset="108-122" type="drug" text="methamphetamine"/>
</sentence>
```

Figure 3The chemical name of an active substance should be annotated.

However, the chemical formula of an active substance should not be annotated.

```
- <sentence id="DrugDDI.d1189.s1" text="Palytoxin (PTX), C129H223N3O54, isolated from marine  
coelenterates of Palythoa tuberculosa, caused a first rapid contraction followed by the slow phasic  
contraction of guinea-pig vas deferens. ">  
    <entity id="DrugDDI.d1189.s1.e0" charOffset="0-8" type="drug_n" text="Palytoxin"/>  
    <entity id="DrugDDI.d1189.s1.e1" charOffset="11-13" type="drug_n" text="PTX"/>  
</sentence>
```

Figure 4 The chemical formula of a drug should not be annotated

3.1.3 Abbreviations

The **abbreviations** or **acronyms** of generic drugs are considered as entities of the type drug. For example, **5-HTP** is the abbreviation of **5-hydroxy-L-tryptophan**, and **MTX** is **Methotrexate**.

```
- <sentence id="DrugDDI.d529.s0" text="Methotrexate: HUMIRA has been studied in rheumatoid  
arthritis patients taking concomitant MTX.">  
    <entity id="DrugDDI.d529.s0.e0" charOffset="0-11" type="drug" text="Methotrexate"/>  
    <entity id="DrugDDI.d529.s0.e1" charOffset="14-19" type="brand" text="HUMIRA"/>  
    <entity id="DrugDDI.d529.s0.e2" charOffset="90-92" type="drug" text="MTX"/>  
</sentence>
```

Figure 5 Abbreviations of drug names should be annotated as drug entity

3.1.4 Synonyms

In some cases, a generic drug name may have one or more **synonyms** because the drug is approved in different countries with different names. For example, *Rifampicin* is the generic name (INN) designated by the World Health Organization (WHO) while *Rifampin* is the name assigned by the USAN (United States Adopted Names) council.

```
- <sentence id="DrugDDI.d145.s2" text="Pre-treatment with the CYP3A4 inducer rifampicin decreased  
erlotinib AUC by about 2/3.">  
    <entity id="DrugDDI.d145.s2.e0" charOffset="38-47" type="drug" text="rifampicin"/>  
    <entity id="DrugDDI.d145.s2.e1" charOffset="59-67" type="drug" text="erlotinib"/>  
    <ddi id="DrugDDI.d145.s2.d0" e1="DrugDDI.d145.s2.e0" e2="DrugDDI.d145.s2.e1"  
    type="mechanism"/>  
</sentence>  
  
- <sentence id="DrugDDI.d1246.s11" text="Amprenavir plus rifampin was well tolerated. ">  
    <entity id="DrugDDI.d1246.s11.e0" charOffset="0-9" type="drug" text="Amprenavir"/>  
    <entity id="DrugDDI.d1246.s11.e1" charOffset="16-23" type="drug" text="rifampin"/>  
</sentence>
```

Figure 6 Both synonyms should be annotated as entity type drug.

DrugBank or PubChem databases or Mesh thesaurus can be valuable resources to find synonyms of drug names.

3.1.5 Salts

Some drugs are formulated as their water-soluble forms (also called ionic compounds or **salts**) in order to increase their solubility and thereby improve their pharmacokinetic properties. A drug may be formulated as different salts (e.g. *atorvastatin calcium* or *atorvastatin magnesium*). As a generic (INN) name is usually designated for the active part of the molecule

only, the WHO decided to create a modified INNM (International Nonproprietary Name Modified) to name salts, esters, etc. These modified names usually start with the name of the drug followed by the name of the ion (e.g. *mepyramine maleate*).

```
- <sentence id="DrugDDI.d1124.s0" text="The CNS depressant effects of oxycodone hydrochloride may be additive with that of other CNS depressants..">
  <entity id="DrugDDI.d1124.s0.e0" charOffset="30-52" type="drug" text="oxycodone hydrochloride"/>
  <entity id="DrugDDI.d1124.s0.e1" charOffset="89-103" type="group" text="CNS depressants"/>
  <ddi id="DrugDDI.d1124.s0.d0" e1="DrugDDI.d1124.s0.e0" e2="DrugDDI.d1124.s0.e1" type="effect"/>
</sentence>
```

Figure 7 Annotation of salts

In some cases, the salts mentioned in text do not follow the above rule. Two possibilities have been identified:

- a) Text refers to a salt or salts of a drug generically, without specifying which type it is (e.g., *quinidine salts*). In this case, the annotators annotated the name of the active part of the molecule only.
 - *This time to peak levels is identical to the time measured when quinidine salts are administered orally.*
 - *The risk of severe hypermagnesemia is a major concern when magnesium salts are administered to hemodialysis patients*
- b) The type of salt is specified in brackets.

```
- <sentence id="DrugDDI.d21795430.s10" text="In conclusion, we demonstrated an isolated effect of calcium (as chloride) on absorption of 5 mg of iron provided as nonheme (as sulfate) and heme (as CRBC) iron. ">
  <entity id="DrugDDI.d21795430.s10.e0" charOffset="53-59" type="drug" text="calcium"/>
  <entity id="DrugDDI.d21795430.s10.e1" charOffset="117-123;157-160" type="drug" text="nonheme iron"/>
  <entity id="DrugDDI.d21795430.s10.e2" charOffset="142-145;157-160" type="drug" text="heme iron"/>
  <ddi id="DrugDDI.d21795430.s10.d0" e1="DrugDDI.d21795430.s10.e0"
  e2="DrugDDI.d21795430.s10.e1" type="mechanism"/>
  <ddi id="DrugDDI.d21795430.s10.d1" e1="DrugDDI.d21795430.s10.e0"
  e2="DrugDDI.d21795430.s10.e2" type="mechanism"/>
</sentence>
```

Figure 8 When the type of salt that is specified in brackets, this should not be included in the annotation

In both cases, the annotators annotated the name of the active part of the molecule only.

3.1.6 Discontinuous names

Sometimes the names of pharmacological substances can appear as **discontinuous names** in texts. Discontinuous names usually arise from coordinators. The sentence below contains a coordinate structure (*aluminum and magnesium hydroxides*) with two different pharmacological substances (*aluminum hydroxide, magnesium hydroxide*). The first entity (*aluminum hydroxide* (DrugDDI.d460.s7.e1)) presents a discontinuous name. Note that its charOffset attribute contains the start and end positions of the two parts of the mention (separated by semicolon).

```

- <sentence id="DrugDDI.d460.s7" text="Antacids: Concomitant administration of aluminum and magnesium hydroxides does not interfere with absorption of meclofenamate sodium.">
  <entity id="DrugDDI.d460.s7.e0" charOffset="0-7" type="group" text="Antacids"/>
  <entity id="DrugDDI.d460.s7.e1" charOffset="39-46;62-70" type="drug" text="aluminum hydroxide"/>
  <entity id="DrugDDI.d460.s7.e2" charOffset="53-71" type="drug" text="magnesium hydroxide"/>
  <entity id="DrugDDI.d460.s7.e3" charOffset="112-131" type="drug" text="meclofenamate sodium"/>
</sentence>
```

Figure 9 Discontinuous names ('aluminum and magnesium hydroxide'). The `charOffset` attribute (see entity `DrugDDI.d460.s7.e1`) contains the start and end positions of the two parts of the mention (*aluminum hydroxide*) separated by semicolon.

3.1.7 Illegal drugs

Illegal drugs approved for a given indication in human should be annotated with the category 'drug'. For example, the illegal drug *cocaine* is still approved in some countries (under certain conditions of use) for introduction of local anesthesia in humans, so it appears in the ATC code.

```

- <sentence id="DrugDDI.d1256.s0" text="Behavioral responses to repeated cocaine exposure in mice selectively bred for differential sensitivity to pentobarbital. ">
  <entity id="DrugDDI.d1256.s0.e0" charOffset="33-39" type="drug" text="cocaine"/>
  <entity id="DrugDDI.d1256.s0.e1" charOffset="107-119" type="drug" text="pentobarbital"/>
</sentence>
```

Figure 10 Annotation of illegal drugs when these are approved for human use

However, if an illegal drug is not authorized for any medical purpose nowadays, it should not be annotated as drug, but as drug_n.

```

- <sentence id="DrugDDI.d1024.s5" text="Twelve strains of Staphylococcus aureus (a frequent cause of infection in heroin, but not in pentazocine and tripeleannamine, addicts) were completely inhibited by the drug combination. ">
  <entity id="DrugDDI.d1024.s5.e0" charOffset="74-79" type="drug_n" text="heroin"/>
  <entity id="DrugDDI.d1024.s5.e1" charOffset="93-103" type="drug" text="pentazocine"/>
  <entity id="DrugDDI.d1024.s5.e2" charOffset="109-122" type="drug" text="tripeleannamine"/>
  <ddi id="DrugDDI.d1024.s5.d0" e1="DrugDDI.d1024.s5.e1" e2="DrugDDI.d1024.s5.e2" type="effect"/>
</sentence>
```

Figure 11 The illegal drug 'heroin' should be annotated as drug_n

Please, use standard resources such as WHO ATC classification system to find which substances are approved for human use.

3.1.8 Alcohol

Names of specific drinks should not be annotated, however **ethanol**(also called **alcohol**), the chemical substance of basis contained in all alcoholic beverages, is annotated with the category 'drug'.

Ethanol is used therapeutically with different purposes: antiseptic and disinfectant (ATC code D08AX08), antidote (ATC code V03AB16) or nerve depressant (ATC code V03AZ01). *Ethanol* is known to cause a number of drug interactions, many of which may be harmful (*ethanol* and *barbiturates* may cause severe central nervous system depression) while others are used with

a therapeutic use (for example its combination with *disulfiram*)⁴. Several drug information resources usually contain information on drug-ethanol interactions because they are very prominent.

```
- <sentence id="DrugDDI.d27.s0" text="The concomitant intake of alcohol and Acamprosate does not affect the pharmacokinetics of either alcohol or acamprosate.">
    <entity id="DrugDDI.d27.s0.e0" charOffset="26-32" type="drug" text="alcohol"/>
    <entity id="DrugDDI.d27.s0.e1" charOffset="38-48" type="drug" text="Acamprosate"/>
    <entity id="DrugDDI.d27.s0.e2" charOffset="97-103" type="drug" text="alcohol"/>
    <entity id="DrugDDI.d27.s0.e3" charOffset="108-118" type="drug" text="acamprosate"/>
</sentence>
```

Figure 12 Annotation of *alcohol*

```
- <sentence id="DrugDDI.d1225.s3" text="In addition to this pharmacological interaction, this report describes a novel chemical reaction between temazepam (a benzodiazepine) and ethanol under acidic conditions similar to those found in vivo, resulting in a 3-ethoxylated product.">
    <entity id="DrugDDI.d1225.s3.e0" charOffset="105-113" type="drug" text="temazepam"/>
    <entity id="DrugDDI.d1225.s3.e1" charOffset="118-131" type="group" text="benzodiazepine"/>
    <entity id="DrugDDI.d1225.s3.e2" charOffset="138-144" type="drug" text="ethanol"/>
    <ddi id="DrugDDI.d1225.s3.d0" e1="DrugDDI.d1225.s3.e0" e2="DrugDDI.d1225.s3.e2"
        type="mechanism"/>
</sentence>
```

Figure 13 Annotation of *ethanol*

While *ethanol* should always be annotated as drug entity, annotators should establish the type for the term *alcohol* based on the following criteria:

- If *alcohol* is used synonymously with *ethanol* (that is, it refers to alcoholic beverages) should be annotated as type drug.
- If *alcohol* refers to the group of alkyl compounds containing a hydroxyl group, will not be labeled.
- If *alcohol* refers to a specific compound that does not have a therapeutic use (for example *methanol*) should be annotated as type *drug_n*.

```
- <sentence id="DrugDDI.d21794966.s1" text="An increase in serum osmolality and serum osmolal gap with or without high-anion-gap metabolic acidosis is an important clue to exposure to one of the toxic alcohols, which include methanol, ethylene glycol, diethylene glycol, propylene glycol, or isopropanol.">
    <entity id="DrugDDI.d21794966.s1.e0" charOffset="181-188" type="drug_n" text="methanol"/>
    <entity id="DrugDDI.d21794966.s1.e1" charOffset="191-205" type="drug_n" text="ethylene glycol"/>
    <entity id="DrugDDI.d21794966.s1.e2" charOffset="208-224" type="drug_n" text="diethylene glycol"/>
    <entity id="DrugDDI.d21794966.s1.e3" charOffset="227-242" type="drug_n" text="propylene glycol"/>
    <entity id="DrugDDI.d21794966.s1.e4" charOffset="248-258" type="drug" text="isopropanol"/>
</sentence>
```

Figure 14 Alcohols without a therapeutic use should be annotated as *drug_n* entity. Notice that the term 'alcohols' in this sentence is not annotated, since it refers to the group of alkyl compounds described next

3.1.9 Stereoisomers

Some chemical compounds, called *isomers*, are formed by the same type and number of atoms (and thereby they have the same molecular formula), but their molecular structure is different. A special kind of *isomers* are denominated *stereoisomers*, which have the same type and number of atoms and show an identical arrangement of bonds connecting them, yet the

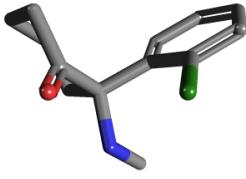
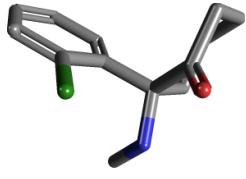
⁴Disulfiram Package Insert from <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=9355>

relative orientation of their atoms in space differs (Nau & Strichartz, 2002). *Stereoisomers* are classified into two groups: *enantiomers* and *diastereoisomers*. *Enantiomers* are pair of compounds that are mirror images of each other. Such compounds present identical physicochemical properties (as such as dielectric constant, melting point or boiling point) and cannot be separated. However they can present different pharmacology activity. A typical example is the drug *thalidomide*. The *racemic mixture* (that is, a mixture of *enantiomers*) of this drug was used for its sedative effects. It was found that *thalidomide* produced severe malformations of human babies. Although both *enantiomers* had the desired therapeutic effect, only one of them was responsible of the teratogen effect (*(S)-thalidomide*).

Diastereoisomers are compounds with identical compositions but with different physical properties and they are not images related. These, unlike *enantiomers*, can be chemically separated by different methods. For all these reason, *diastereomers* are often named as individual compounds⁵, although they can also receive a nomenclature following the rules described below.

Enantiomers are indentified with different prefixes preceding the name of the compound. It is not the purpose of this guide to deepen the meaning of each of them. However, they are listed for easy identification by annotators. The simplest naming system for *enantiomers* uses the prefixes: (d), dextro- (from *dextrorotatory*), (l)-, levo- (from *levorotatory*) in function of their optical properties. In some cases, these can be replaced by symbols (+) or (-), respectively. Another nomenclature system, based in the Cahn-Ingold-Prelog convention, uses the labels (R) or (S)(Lin, Li, & Chan, 2001). Limited for some substances, the Fischer convention descriptors L- and D- are rarely used nowadays to describe the configuration of *enantiomers*.

Sometimes these prefixes appear combined, so it is possible find denominations such as R(+) or R(-). Other complex cases (those molecules with more than one chiral center) may require the use of several of these labels, thereby we can find complicated denominations such as "(1'S, 6R, 7R)-Cefuroxime axetil". A more detailed study of the nature and nomenclature of *stereoisomers* can be found in (Fisher & Arnold, 2012), (Huang, 2007). As an example, the names of the *enantiomers* of the drug *ketamine* are described below⁶.

(R)-Ketamine or R-ketamine	(S)-ketamine or S-ketamine
(+)-Ketamine	(-)-Ketamine
(R)-(+)-Ketamine or R(+)-ketamine	(S)-()-Ketamine or S(-)-ketamine
(d)-Ketamine or d-ketamine	l-Ketamine or (l)-ketamine
	

⁵<http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/geometric-isomerism-chirality-the-usan-perspective.page>

⁶Figures taken from PubChem Compound Database

Notice that this annotation rule is referred only to those names that describe a specific *stereoisomer*. In those cases where reference is made generically (e.g. '*the enantiomers of ketamine*') only the name of the drug should be annotated.

```
- <sentence id="DrugDDI.d21716267.s0" text="Exposure to oral S-ketamine is unaffected by itraconazole but greatly increased by ticlopidine.">
    <entity id="DrugDDI.d21716267.s0.e0" charOffset="17-26" type="drug" text="S-ketamine"/>
    <entity id="DrugDDI.d21716267.s0.e1" charOffset="45-56" type="drug" text="itraconazole"/>
    <entity id="DrugDDI.d21716267.s0.e2" charOffset="83-93" type="drug" text="ticlopidine"/>
    <ddi id="DrugDDI.d21716267.s0.d0" e1="DrugDDI.d21716267.s0.e0" e2="DrugDDI.d21716267.s0.e2" type="effect"/>
</sentence>
```

Figure 15 Annotation of an enantiomer as type drug.

3.2 brand entity

A pharmacological substance should be labeled with the category 'brand' when it is a brand name of a drug, that is, is a product marketed by a specific pharmaceutical company.

Drugs with the same composition or active substance may be produced by different companies in different countries and with different brand names. For example, there are more than 160 brand names for the analgesic drug *paracetamol* (whose United States Adopted Name (USAN) is *acetaminophen*).

Brand names are usually capitalized while generic names are not.

In scientific texts drugs are usually mentioned by their generic names. However, texts from databases such as DrugBank or the DailyMed usually contain brand drug names. This may be due primarily to these drug information sources include information from the product labels of drugs developed by pharmaceutical companies.

Brand Name	Generic Name	Resource
Abilify	<i>Aripiprazol</i>	AEMPS
Aspirin	<i>Acetylsalicylic acid</i>	FDA
Innovar	<i>Droperidol</i>	DrugBank

Table 1 Brand and generic drugs.

Some examples of brand names in corpus sentences appear below:

```
- <sentence id="DrugDDI.d457.s4" text="Other 5-HT1B/1D Agonists Concomitant use of other 5-HT1B/1D agonists within 24 hours of treatment with AXERT is contraindicated.">
    <entity id="DrugDDI.d457.s4.e0" charOffset="6-23" type="group" text="5-HT1B/1D Agonists"/>
    <entity id="DrugDDI.d457.s4.e1" charOffset="50-67" type="group" text="5-HT1B/1D agonists"/>
    <entity id="DrugDDI.d457.s4.e2" charOffset="103-107" type="brand" text="AXERT"/>
    <ddi id="DrugDDI.d457.s4.d0" e1="DrugDDI.d457.s4.e1" e2="DrugDDI.d457.s4.e2" type="advise"/>
</sentence>
```

Figure 16 Example of annotation of brand drugs (AXERT)

Notice that, if the generic and the brand name of a drug appear in the same sentence, both terms should be annotated as unique entities and with their respective label.

```
- <sentence id="DrugDDI.d21897348.s1" text="The FDA has approved ticagrelor (Brilinta-AstraZeneca), an oral antiplatelet drug, for use with low-dose aspirin to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS). ">
  <entity id="DrugDDI.d21897348.s1.e0" charOffset="21-30" type="drug" text="ticagrelor"/>
  <entity id="DrugDDI.d21897348.s1.e1" charOffset="33-40" type="brand" text="Brilinta"/>
  <entity id="DrugDDI.d21897348.s1.e2" charOffset="64-80" type="group" text="antiplatelet drug"/>
  <entity id="DrugDDI.d21897348.s1.e3" charOffset="105-111" type="brand" text="aspirin"/>
  <ddi id="DrugDDI.d21897348.s1.d0" e1="DrugDDI.d21897348.s1.e0" e2="DrugDDI.d21897348.s1.e3" type="effect"/>
  <ddi id="DrugDDI.d21897348.s1.d1" e1="DrugDDI.d21897348.s1.e1" e2="DrugDDI.d21897348.s1.e3" type="effect"/>
</sentence>
```

Figure 17 Both the generic name (ticagrelor) and the brand name (Bilinta) should be annotated as entities. (AstraZeneca is the marketed company name and it should not be annotated).

3.3 drug_n entity

A drug interaction occurs when the activity of a drug is altered by the concomitant use of another substance such as a drug, a food, a drink or environmental chemicals. In fact, drug interactions involving substances not approved for human use are very common in scientific texts. Although these substances cannot be considered as drugs, we decided to include them in the annotation due to the large number of interactions involving these substances that are presented in the texts of the corpus. Therefore, any active substance susceptible to interaction and not approved for human use should be annotated as drug_n entity. The following table contains some example. Also, below subsections describe, in more detail, the rules for annotating these substances.

Substance/ Sentence	Is drug_n?	Cause	Resource
Beta-endorphin <i>"Intraventricular injection of beta-endorphin and morphine produced an inhibition of the tail-flick response to the heat stimulus in rats"</i>	Yes	Beta-endorphin is an endogenous substance. It should be annotated because it is administered (injection).	MeSH
Endoxifen <i>"It is extensively transformed into its active metabolites by the cytochrome P450 enzyme system, especially into endoxifen by isoenzyme CYP</i>	Yes	Endoxifen is a metabolite.	MeSH

2D6"			
N-demethylated metabolite y metabolite I <i>"The interaction of intramuscularly injected ketamine and its N-demethylated metabolite (metabolite I) with halothane was evaluated in rats."</i>	No No	N-demethylated metabolite refers to the metabolite resulting from the chemical transformation of ketamine, but it is not denominated by a specific name. Metabolite I is a common name used by the author.	-
Fenofibric acid <i>"Fenofibrate is a prodrug that is rapidly and completely hydrolyzed to fenofibric acid, the active moiety."</i>	Yes	The metabolic reaction of fenofibrate results in fenofibric acid.	Fenofibric acid is considered as a metabolite by DrugBank. (see Absorption in http://www.drugbank.ca/drugs/DB01039)
Fenofibric acid <i>"A new orally administered agent, fenofibric acid, was developed as an alternative to fenofibrate."</i>	No	In this case, fenofibric acid should be annotated as entity type 'drug' because the sentence points out that it is a drug (orally administered agent).	In DrugBank, 'fenofibric acid' and 'fenofibrate' are synonyms. Therefore, annotators should disambiguate the term before assigning a type.
CH12 <i>To investigate the effect of a monoclonal antibody (CH12), targeted against epidermal growth factor receptor type III variant (EGFRvIII), on human ovarian cancer cells when administered in combination with cisplatin chemotherapy"</i>	Yes	It is an experimental drug.	-
Flavonoids, flavonols, flavones, flavanonols and catechins <i>"The effect of a series of flavonoids, including flavonols, flavones, isoflavone, flavanone, flavanonols and catechins, on the elimination of luteolin and apigenin was studied"</i>	Yes.	These terms are groups of active substances but not group of drugs.	MeSH

Calcium "Thiazides are known to induce hypercalcemia by the reduction of calcium excretion in urine.	No	The text refers to calcium as a substance produced by the organism.	-
---	----	---	---

3.3.1 Experimental drugs

An experimental drug is a pharmacologically active substance that has been tested in a laboratory or clinical trials but has not been approved for human use. Some experimental drugs were approved in the past, but currently they have been withdrawn from the market because of risks to the patients. However, they can be useful tools for research and can be used in vitro studies, in vivo studies, and ex vivo studies. These substances should be annotated as drug_n entity.

```
- <sentence id="DrugDDI.d21753255.s6" text="Male rats demonstrated sensitization to amphetamine, although this was muted compared with female rats, and were unaffected by neonatal quinpirole. ">
  <entity id="DrugDDI.d21753255.s6.e0" charOffset="40-50" type="drug" text="amphetamine"/>
  <entity id="DrugDDI.d21753255.s6.e1" charOffset="136-145" type="drug_n" text="quinpirole"/>
</sentence>
```

Figure 18 Annotation of an experimental drug

When a drug is approved it is then given a generic name and one or various trade names. Those active substances that are pending for approval can be named by a pharmaceutical compound number (for example, E2020) and should be annotated as drug_n entity.

- [E2020]_{drug_n1} is marketed as [Aricept]_{brand1}.

3.3.2 Veterinary drugs

A veterinary or animal drug is any active substance that is used with a therapeutical purpose in animals. In some cases, there are active substances that are approved for both human and animal use (for example, the anti-inflammatory drug *meloxicam*). These substances should always be annotated as drug entity, while those substances approved for animal use only should be annotated as drug_n entity.

```
- <sentence id="DrugDDI.d46730.s1" text="Interactions between treatments with coumaphos, bishydroxycoumarin (an anticoagulant), trichlorfon (an organophosphorous compound), and phenobarbital sodium (an inducer of microsomal enzymes) were investigated in sheep. ">
  <entity id="DrugDDI.d46730.s1.e0" charOffset="37-45" type="drug_n" text="coumaphos"/>
  <entity id="DrugDDI.d46730.s1.e1" charOffset="48-65" type="drug" text="bishydroxycoumarin"/>
  <entity id="DrugDDI.d46730.s1.e2" charOffset="71-83" type="group" text="anticoagulant"/>
  <entity id="DrugDDI.d46730.s1.e3" charOffset="87-97" type="drug_n" text="trichlorfon"/>
  <entity id="DrugDDI.d46730.s1.e4" charOffset="103-128" type="group" text="organophosphorous compound"/>
  <entity id="DrugDDI.d46730.s1.e5" charOffset="136-155" type="drug" text="phenobarbital sodium"/>
</sentence>
```

Figure 19 Veterinary drugs should be annotated as drug_n entity.

Resources such as the publicly available drug databases on the FDA and EMA websites or the ATCvet system can be valuable tools to identify veterinary drugs.

3.3.3 Endogenous substances

An endogenous substance is a substance developed or originated within the organism. This definition can be extended to include those substances not synthetized in the body but present in the organism and involved in physiological and biochemical processes (Marzo & Rescigno, 1993).

Vitamin D and *insulin* are examples of endogenous substances. *Vitamin D* is produced by the organism and is also naturally present in some foods. Since some individuals may have deficiency of *vitamin D*, several drug therapies have been developed to include *vitamin D* as active substance. *Insulin* is a hormone produced by the pancreas. Also, *insulin* can be synthesized in the laboratory and used as drug to control insulin-dependent diabetes mellitus.

Annotators should determine whether text describes a natural process in which the substance is produced in the organism or, on the contrary describes a process in which the substance is being used with a particular purpose. Only those substances that are administered as exogenous drugs should be annotated as drug_n entity. That is, the endogenous substances that are patients' own body substances should not be included in the annotation.

- <sentence id="DrugDDI.d1062.s3" text="In adult diabetic patients under treatment with either sulfonylureas or insulin there is no change in the clinical effects of either TOLECTIN or the hypoglycemic agents. ">
 <entity id="DrugDDI.d1062.s3.e0" charOffset="55-67" type="group" text="sulfonylureas"/>
 <entity id="DrugDDI.d1062.s3.e1" charOffset="72-78" type="drug" text="insulin"/>
 <entity id="DrugDDI.d1062.s3.e2" charOffset="133-140" type="brand" text="TOLECTIN"/>
 <entity id="DrugDDI.d1062.s3.e3" charOffset="149-167" type="group" text="hypoglycemic agents"/>
</sentence>
- <sentence id="DrugDDI.d1157.s3" text="Intraventricular injection of beta-endorphin and morphine produced an inhibition of the tail-flick response to the heat stimulus in rats. ">
 <entity id="DrugDDI.d1157.s3.e0" charOffset="30-43" type="drug_n" text="beta-endorphin"/>
 <entity id="DrugDDI.d1157.s3.e1" charOffset="49-56" type="drug" text="morphine"/>
</sentence>

Figure 20 In these sentences, both 'insulin' and 'beta-endorphin' are exogenous substances.

In the following sentence, calcium is not annotated because it refers to an endogenous substance:

- <sentence id="DrugDDI.d113.s4" text="Thiazides: Thiazides are known to induce hypercalcemia by the reduction of calcium excretion in urine.">
 <entity id="DrugDDI.d113.s4.e0" charOffset="0-8" type="group" text="Thiazides"/>
 <entity id="DrugDDI.d113.s4.e1" charOffset="11-19" type="group" text="Thiazides"/>
</sentence>

Figure 21 'calcium' is not annotated because it is an endogenous substance produced by the organism

3.3.4 Toxins

Toxins are substances chemicals, usually proteins, that are produced by microbes, plants or animals and which are poisonous to other organisms. Toxins are not used for therapeutical use, but they are often used in research for new drugs. Toxins should be annotated as drug_n entity.

```

- <sentence id="DrugDDI.d21809690.s2" text="and/or antibiotic drug doxycycline (100 mg/kg, p. o.), as well as that of neurotoxin 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP) (4 x 20 mg/kg, i. p.)">
  <entity id="DrugDDI.d21809690.s2.e0" charOffset="7-21" type="group" text="antibiotic drug"/>
  <entity id="DrugDDI.d21809690.s2.e1" charOffset="23-33" type="drug" text="doxycycline"/>
  <entity id="DrugDDI.d21809690.s2.e2" charOffset="85-128" type="drug_n" text="1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine"/>
  <entity id="DrugDDI.d21809690.s2.e3" charOffset="131-134" type="drug_n" text="MPTP"/>
</sentence>
```

Figure 22 ‘1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine’ and its acronym (MPTP) should be annotated as drug_n entity

However, only the terms referring to specific toxins should be annotated. Common words such as ‘toxins’ or ‘neurotoxin’ should not be annotated.

3.3.5 Excipients

An excipient is a pharmacologically inactive ingredient that is used as a vehicle for administering an active substance. Excipients should be annotated as drug_n entity, but water and saline should not be included in the annotation.

```

- <sentence id="DrugDDI.d21753875.s4" text="The colchicine nanoemulsion was prepared with isopropyl myristate, eugenol, Tween80, ethanol and water, and eugenol was used as an oil phase in the formulation; ">
  <entity id="DrugDDI.d21753875.s4.e0" charOffset="4-13" type="drug" text="colchicine"/>
  <entity id="DrugDDI.d21753875.s4.e1" charOffset="46-64" type="drug_n" text="isopropyl myristate"/>
  <entity id="DrugDDI.d21753875.s4.e2" charOffset="67-73" type="drug" text="eugenol"/>
  <entity id="DrugDDI.d21753875.s4.e3" charOffset="76-82" type="drug_n" text="Tween80"/>
  <entity id="DrugDDI.d21753875.s4.e4" charOffset="85-91" type="drug" text="ethanol"/>
  <entity id="DrugDDI.d21753875.s4.e5" charOffset="108-114" type="drug" text="eugenol"/>
</sentence>
```

Figure 23 Annotation of excipients (Tween80, isopropyl myristate)

3.3.6 Metabolites

A metabolite is any chemical compound produced as a result of metabolism or a metabolic reaction. Many drugs (called prodrugs) must be metabolized to intermediates before they become active, thus some metabolites have pharmacological activity. For example, the active substance *azathioprine* must be metabolized to its metabolite *mercaptopurine* in order to result its immunosuppressive effect.

Metabolites can be named in different ways: chemical name (*6,7-dihydro-3H-purine-6-thione*) and generic name (*mercaptopurine*).

```

- <sentence id="DrugDDI.d258.s4" text="The threohydrobupropion metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes.">
  <entity id="DrugDDI.d258.s4.e0" charOffset="4-22" type="drug_n" text="threohydrobupropion"/>
  <entity id="DrugDDI.d258.s4.e1" charOffset="38-46" type="drug" text="bupropion"/>
</sentence>
```

Figure 24 Annotation of a metabolite with generic name (threohydrobupropion)

```

- <sentence id="DrugDDI.d236.s1" text="There was a small increase in plasma concentrations of
  capecitabine and one metabolite (5-DFCR);">
  <entity id="DrugDDI.d236.s1.e0" charOffset="55-66" type="drug" text="capecitabine"/>
  <entity id="DrugDDI.d236.s1.e1" charOffset="88-93" type="drug_n" text="5-DFCR"/>
</sentence>
```

Figure 25 Annotation of a metabolite with chemical name (5-DFCR)

However, when the metabolite is named by a common name (**N-demethylated metabolite**, it should not be included in the annotation. The name of metabolite (*metabolite I*, see below example) named by the author should not be annotated yet.

```

- <sentence id="DrugDDI.d1032.s1" text="The interaction of intramuscularly injected ketamine and
  its N-demethylated metabolite (metabolite I) with halothane was evaluated in rats. ">
  <entity id="DrugDDI.d1032.s1.e0" charOffset="44-51" type="drug" text="ketamine"/>
  <entity id="DrugDDI.d1032.s1.e1" charOffset="107-115" type="drug" text="halothane"/>
</sentence>
```

Figure 26 Common names of a metabolite should not be annotated as drug_n.

3.3.7 Group of active substances

As occurs with drugs, an active substance considered in this corpus as an entity type drug_n can be classified and defined within groups. However, there is not a specific type for those terms. So, a term that defines a group of active substances (considered individually such as entities type drug_n) should also be annotated as type drug_n.

```

- <sentence id="DrugDDI.d21901983.s7" text="The effect of a series of flavonoids, including
  flavonols, flavones, isoflavone, flavanone, flavanonols and catechins, on the elimination of luteolin
  and apigenin was studied. ">
  <entity id="DrugDDI.d21901983.s7.e0" charOffset="26-35" type="drug_n" text="flavonoids"/>
  <entity id="DrugDDI.d21901983.s7.e1" charOffset="48-56" type="drug_n" text="flavonols"/>
  <entity id="DrugDDI.d21901983.s7.e2" charOffset="59-66" type="drug_n" text="flavones"/>
  <entity id="DrugDDI.d21901983.s7.e3" charOffset="69-78" type="drug_n" text="isoflavone"/>
  <entity id="DrugDDI.d21901983.s7.e4" charOffset="81-89" type="drug_n" text="flavanone"/>
  <entity id="DrugDDI.d21901983.s7.e5" charOffset="92-102" type="drug_n"
  text="flavanonols"/>
  <entity id="DrugDDI.d21901983.s7.e6" charOffset="108-116" type="drug_n" text="catechins"/>
  <entity id="DrugDDI.d21901983.s7.e7" charOffset="141-148" type="drug_n" text="luteolin"/>
  <entity id="DrugDDI.d21901983.s7.e8" charOffset="154-161" type="drug_n" text="apigenin"/>
</sentence>
```

Figure 27 Flavonoids is a group of active substances, however it should be annotated as drug_n entity.

3.3.8 Chemical names

When an active substance not approved for human use is described by its chemical name, this term should be also annotated with the type drug_n (see Figure 22).

3.3.9 Abbreviations

If an active substance no approved for human use is named by an abbreviation, this term should be also annotated as type drug_n (see Figure 22).

3.3.10 Synonyms

A drug no approved for human use can be named with several synonyms. These synonyms should be also annotated as drug_n entity.

3.3.11 Discontinuous names

In some cases, these substances can appear as discontinuous names in text, and they should be annotated as drug_n entity.

3.3.12 Salts

Salts of drugs no approved for human use should be annotated as type drug_n following the rules explained in subsection 3.1.5

3.3.13 Stereoisomers

Stereoisomers of drugs no approved for human use should be annotated as type drug_n following the criteria explained in subsection 3.1.9.

3.4 group entity

Those terms in the text that describe different drugs into groups according to the organ or system on which they act or according to their chemical, pharmacological or therapeutic properties should be annotated as group entity.

Drug Interaction resources normally provide information on drug interactions involving groups due to the similarities of the drugs within the same group may help to prevent this drug interaction for each member of the group. For example, the interaction between amantidine and the thiazide group is usually collected by the most of drug interaction resources.

Pharmacological substances can be classified in many ways: according to their chemical structure, according to their mode of action, according to their effects, according to the body system on which they act, etc. For example, pregabalin is classified as an antiepileptic by the ATC classification system; however it is classified as an anticonvulsant by other classification systems. Both classifications are right: the first one is assigned according to its therapeutic use while the second one refers to its pharmacological action.

3.4.1 Groups collected from ATC system.

The wide range of classification criteria for drugs may be a problem for the annotation process. Below, some resources are recommended to help annotators to distinguish those substances that should be annotated as group entity.

The main resource is the ATC system that classifies active substances according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Drugs are classified into groups at 5 different levels: the first level indicates the anatomical main group, the second level indicates the therapeutic main group, the third level indicates the therapeutic/pharmacological subgroup, the fourth level indicates the chemical/therapeutic/pharmacological subgroup, and finally, the fifth one refers to the chemical substance. The second, third and fourth levels identify pharmacological subgroups. Therefore, those terms from these three ATC levels should be annotated as group entity.

```
- <sentence id="DrugDDI.d1444.s0" text="Sulfoxone may increase the effects of barbiturates, tolbutamide, and uricosurics.">
    <entity id="DrugDDI.d1444.s0.e0" charOffset="0-8" type="drug" text="Sulfoxone"/>
    <entity id="DrugDDI.d1444.s0.e1" charOffset="38-49" type="group" text="barbiturates"/>
    <entity id="DrugDDI.d1444.s0.e2" charOffset="52-62" type="drug" text="tolbutamide"/>
    <entity id="DrugDDI.d1444.s0.e3" charOffset="69-79" type="group" text="uricosurics"/>
    <ddi id="DrugDDI.d1444.s0.d0" e1="DrugDDI.d1444.s0.e0" e2="DrugDDI.d1444.s0.e1" type="effect"/>
    <ddi id="DrugDDI.d1444.s0.d1" e1="DrugDDI.d1444.s0.e0" e2="DrugDDI.d1444.s0.e2" type="effect"/>
    <ddi id="DrugDDI.d1444.s0.d2" e1="DrugDDI.d1444.s0.e0" e2="DrugDDI.d1444.s0.e3" type="effect"/>
</sentence>
```

Figure 28 Annotation of a group found in the ATC system (barbiturates) and another found in MeSH (uricosurics)

3.4.2 Groups collected from MeSH thesaurus.

Unfortunately many terms referring to drug groups are not collected by the ATC system (for example, Central Nervous System depressants). The MeSH (Medical Subject Headings) thesaurus can help to recognize those groups not identified by the ATC system. Its category '*Chemicals and Drugs Category*' collects all names of drug groups as well as their individual drugs in a hierarchical way. Thus the descendants of the category '[*Chemicals and Drugs Category*](#)' should be annotated as group entity when they meet the requirements to be a group of drugs (that is, including substances that are considered drug entities)

```
- <sentence id="DrugDDI.d297.s3" text="Antidepressants (tricyclic), atropine or other anticholinergic agents, or digitalis glycosides: concurrent use with arbutamine may produce additive inotropic and/or chronotropic effects.">
    <entity id="DrugDDI.d297.s3.e0" charOffset="0-14" type="group" text="Antidepressants"/>
    <entity id="DrugDDI.d297.s3.e1" charOffset="17-25" type="group" text="tricyclic"/>
    <entity id="DrugDDI.d297.s3.e2" charOffset="29-36" type="drug" text="atropine"/>
    <entity id="DrugDDI.d297.s3.e3" charOffset="47-68" type="group" text="anticholinergic agents"/>
    <entity id="DrugDDI.d297.s3.e4" charOffset="74-93" type="group" text="digitalis glycosides"/>
    <entity id="DrugDDI.d297.s3.e5" charOffset="116-125" type="drug" text="arbutamine"/>
</sentence>
```

Figure 29 Annotation of groups found in Mesh and ATC classification (Antidepressants, tricyclic)

```
- <sentence id="DrugDDI.d21706316.s0" text="Effect of ketoconazole-mediated CYP3A4 inhibition on clinical pharmacokinetics of panobinostat (LBH589), an orally active histone deacetylase inhibitor.">
    <entity id="DrugDDI.d21706316.s0.e0" charOffset="10-21" type="drug" text="ketoconazole"/>
    <entity id="DrugDDI.d21706316.s0.e1" charOffset="82-93" type="drug" text="panobinostat"/>
    <entity id="DrugDDI.d21706316.s0.e2" charOffset="96-101" type="drug" text="LBH589"/>
    <entity id="DrugDDI.d21706316.s0.e3" charOffset="122-150" type="group" text="histone deacetylase inhibitor"/>
</sentence>
```

Figure 30 Annotation of groups found in Mesh (histone deacetylase inhibitor)

3.4.3 Variations and Synonyms

Given combinations or variations of the names of groups collected from Mesh or ATC should also be annotated as group entity. For example, annotators should annotate the term '*erection-supporting medication*' as group entity because this is clearly a synonym for the term '*Drug used in erectile dysfunction*'(ATC code G04BE). Similarly '*Type 1C antiarrhythmics*' and '*Antiarrhythmics class 1c*' (ATC code C01BC) can be considered synonyms (see Figure 32).

MeSH provides several synonyms (such as "Agents, Antineoplastic", "Antitumor Drugs", "Drugs, Antitumor", "Antitumor Agents", "Agents, Antitumor", "Antineoplastic Drugs", "Drugs, Antineoplastic", "Antineoplastics") for the term 'Antineoplastic agents'. Synonyms should also be annotated as group entity.

```
- <sentence id="DrugDDI.d1194.s1" text="Since the arrival of oral erection-supporting medication, patients want to know how safe sexual activity is in cardiovascular disease in general and during use of erection-supporting medication in particular.">
    <entity id="DrugDDI.d1194.s1.e0" charOffset="26-55" type="group" text="erection-supporting medication"/>
    <entity id="DrugDDI.d1194.s1.e1" charOffset="163-192" type="group" text="erection-supporting medication"/>
</sentence>
```

Figure 31 'erection-supporting medication' should be annotated since it is a variation of the group 'Drug used in erectile dysfunction' (ATC code G04BE).

```

- <sentence id="DrugDDI.d124.s16" text="Therefore, co-administration of tricyclic antidepressants with other drugs that are metabolized by this isoenzyme, including other antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics (eg, propafenone, flecainide, and encainide), or that inhibit this enzyme (eg, quinidine), should be approached with caution.">
  <entity id="DrugDDI.d124.s16.e0" charOffset="32-56" type="group" text="tricyclic antidepressants"/>
  <entity id="DrugDDI.d124.s16.e1" charOffset="131-145" type="group" text="antidepressants"/>
  <entity id="DrugDDI.d124.s16.e2" charOffset="148-161" type="group" text="phenothiazines"/>
  <entity id="DrugDDI.d124.s16.e3" charOffset="164-176" type="drug" text="carbamazepine"/>
  <entity id="DrugDDI.d124.s16.e4" charOffset="183-205" type="group" text="Type 1C antiarrhythmics"/>
  <entity id="DrugDDI.d124.s16.e5" charOffset="212-222" type="drug" text="propafenone"/>
  <entity id="DrugDDI.d124.s16.e6" charOffset="225-234" type="drug" text="flecainide"/>
  <entity id="DrugDDI.d124.s16.e7" charOffset="241-249" type="drug" text="encainide"/>
  <entity id="DrugDDI.d124.s16.e8" charOffset="286-294" type="drug" text="quinidine"/>
  <ddi id="DrugDDI.d124.s16.d0" e1="DrugDDI.d124.s16.e0" e2="DrugDDI.d124.s16.e1" type="advise"/>
  <ddi id="DrugDDI.d124.s16.d1" e1="DrugDDI.d124.s16.e0" e2="DrugDDI.d124.s16.e2" type="advise"/>
  <ddi id="DrugDDI.d124.s16.d2" e1="DrugDDI.d124.s16.e0" e2="DrugDDI.d124.s16.e3" type="advise"/>
  <ddi id="DrugDDI.d124.s16.d3" e1="DrugDDI.d124.s16.e0" e2="DrugDDI.d124.s16.e4" type="advise"/>
  <ddi id="DrugDDI.d124.s16.d4" e1="DrugDDI.d124.s16.e0" e2="DrugDDI.d124.s16.e5" type="advise"/>
  <ddi id="DrugDDI.d124.s16.d5" e1="DrugDDI.d124.s16.e0" e2="DrugDDI.d124.s16.e6" type="advise"/>
  <ddi id="DrugDDI.d124.s16.d6" e1="DrugDDI.d124.s16.e0" e2="DrugDDI.d124.s16.e7" type="advise"/>
  <ddi id="DrugDDI.d124.s16.d7" e1="DrugDDI.d124.s16.e0" e2="DrugDDI.d124.s16.e8" type="advise"/>
</sentence>

```

Figure 32 ‘Type 1C antiarrhythmics’ should be annotated since it is a variation of the term ‘Antiarrhythmics class 1c’ (ATC code C01BC)

```

- <sentence id="DrugDDI.d1200.s0" text="Determinants of cellular sensitivity to topoisomerase-targeting antitumor drugs.">
  <entity id="DrugDDI.d1200.s0.e0" charOffset="40-78" type="group" text="topoisomerase-targeting antitumor drugs"/>
</sentence>

```

Figure 33 The term ‘antitumor drugs’ should be annotated since it is a synonym of ‘Antineoplastic agents’.

3.4.4 Nested named entities

It is not unusual that group names are formed by other group names. For example, the group name “thiazide diuretics” is formed by two different groups “thiazide” and “diuretics”. In these cases, both terms should be annotated as a unique entity, since it is considered that the first one (more specific) acts as a modifier for the last one (more general).

```

- <sentence id="DrugDDI.d1013.s6" text="Concomitantly given thiazide diuretics did not interfere with the absorption of a tablet of digoxin. ">
  <entity id="DrugDDI.d1013.s6.e0" charOffset="20-37" type="group" text="thiazide diuretics"/>
  <entity id="DrugDDI.d1013.s6.e1" charOffset="92-98" type="drug" text="digoxin"/>
</sentence>

```

Figure 34 When entities are nested, both terms should be annotated as the same group.

3.4.5 Adjectives modifying drug groups

Adjectives that modify the name of a drug group should be included as part of the name of the group when they specify a category within the group. For example, although the term ‘short-acting nitrates’ is not found in either ATC system nor MeSH thesaurus, the modifier ‘short-acting’ should be included in the annotation since it allows to identify a subgroup within the group of nitrates.

These modifiers can describe different characteristics of the group, such as: chemical structure (e.g. ‘thieno-benzodiazepine derivative’), molecular mechanism (e.g. ‘kappa-selective opioids’), origin (e.g. synthetic or natural estrogens), development within the group (first or second

generation; typical or atypical antipsychotics), pharmacokinetic properties (short or long acting analgesics), etc.

As it is explained in section 7.5.1, modifiers referring to the administration route should not be included in the annotation.

Note that these expressions are different from the nested named entities in one aspect: while nested named entities (e.g. ‘macrolide antibiotics’) are those entities that appear within other longer entities and may appear by themselves in texts, adjectives modifying drug groups have no complete sense without its modified name.

```
- <sentence id="DrugDDI.d1001.s1" text="Quetiapine fumarate ('Seroquel') is a newly introduced atypical antipsychotic with demonstrated efficacy in the treatment of positive and negative symptoms of schizophrenia.">
    <entity id="DrugDDI.d1001.s1.e0" charOffset="0-18" type="drug" text="Quetiapine fumarate"/>
    <entity id="DrugDDI.d1001.s1.e1" charOffset="22-29" type="brand" text="Seroquel"/>
    <entity id="DrugDDI.d1001.s1.e2" charOffset="55-76" type="group" text="atypical antipsychotic"/>
</sentence>
```

Figure 35 The modifier ‘atypical’ should be included in the annotation text.

```
- <sentence id="DrugDDI.d1210.s3" text="Advantages offered by this class of antibiotics include optimal pharmacokinetics, effectiveness against multidrug-resistant organisms, and oral administration even when parenteral antibiotics are generally used.">
    <entity id="DrugDDI.d1210.s3.e0" charOffset="36-46" type="group" text="antibiotics"/>
    <entity id="DrugDDI.d1210.s3.e1" charOffset="180-190" type="drug" text="antibiotics"/>
</sentence>
```

Figure 36 The term ‘parenteral’ refers to the route of administration. Therefore, it should not be included in the annotation text.

3.4.6 Abbreviations

The **abbreviations** or **acronyms** of names of groups are considered as entities of the type group. For example **SSRIs** is the abbreviation of **Selective Serotonin Reuptake Inhibitors**.

```
- <sentence id="DrugDDI.d91.s16" text="While all the selective serotonin reuptake inhibitors (SSRIs), e.g. fluoxetine, sertraline, paroxetine, and fluvoxamine, inhibit P450 2D6, they may vary in the extent of inhibition.">
    <entity id="DrugDDI.d91.s16.e0" charOffset="14-52" type="group" text="selective serotonin reuptake inhibitors"/>
    <entity id="DrugDDI.d91.s16.e1" charOffset="55-59" type="group" text="SSRIs"/>
    <entity id="DrugDDI.d91.s16.e2" charOffset="69-78" type="drug" text="fluoxetine"/>
    <entity id="DrugDDI.d91.s16.e3" charOffset="81-90" type="drug" text="sertraline"/>
    <entity id="DrugDDI.d91.s16.e4" charOffset="93-102" type="drug" text="paroxetine"/>
    <entity id="DrugDDI.d91.s16.e5" charOffset="109-119" type="drug" text="fluvoxamine"/>
</sentence>
```

Figure 37 Annotation of abbreviation of groups

When the acronym occurs in the middle of the name of the group, this should be annotated as a unique entity (see Figure 38, monoamine oxidase (MAO) inhibitors).

```

- <sentence id="DrugDDI.d223.s0" text="The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.">
  <entity id="DrugDDI.d223.s0.e0" charOffset="19-28" type="drug" text="butalbital"/>
  <entity id="DrugDDI.d223.s0.e1" charOffset="49-82" type="group" text="monoamine oxidase (MAO) inhibitors"/>
  <ddi id="DrugDDI.d223.s0.d0" e1="DrugDDI.d223.s0.e0" e2="DrugDDI.d223.s0.e1" type="effect"/>
</sentence>
```

Figure 38 Example of annotation of a group name containing its acronym

However, if the acronym (or abbreviation) occurs just after of a drug name then it is considered as a different entity.

```

- <sentence id="DrugDDI.d21878085.s1" text="Nonsteroidal anti-inflammatory drugs (NSAIDs) represent class of medicines which is wide concerning chemical structure and mechanism of action.">
  <entity id="DrugDDI.d21878085.s1.e0" charOffset="0-35" type="group" text="Nonsteroidal anti-inflammatory drugs"/>
  <entity id="DrugDDI.d21878085.s1.e1" charOffset="38-43" type="group" text="NSAIDs"/>
</sentence>
```

Figure 39 Abbreviations just after an entity should be annotated as a new entity

3.4.7 Discontinuous names

Sometimes the name of groups can appear as discontinuous text because they occur in a coordinate structure. In the below sentence the text ‘loop or thiazide diuretics’ refers to two different groups (loop diuretics and thiazide diuretics), and annotators should indicate the start and end positions of both groups.

```

- <sentence id="DrugDDI.d433.s4" text="The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded.">
  <entity id="DrugDDI.d433.s4.e0" charOffset="78-108" type="group" text="non-potassium sparing diuretics"/>
  <entity id="DrugDDI.d433.s4.e1" charOffset="119-122;136-144" type="group" text="loop diuretics"/>
  <entity id="DrugDDI.d433.s4.e2" charOffset="127-144" type="group" text="thiazide diuretics"/>
  <entity id="DrugDDI.d433.s4.e3" charOffset="174-186" type="group" text="beta-agonists"/>
  <entity id="DrugDDI.d433.s4.e4" charOffset="233-244" type="group" text="beta-agonist"/>
  <ddi id="DrugDDI.d433.s4.d0" e1="DrugDDI.d433.s4.e0" e2="DrugDDI.d433.s4.e3" type="effect"/>
  <ddi id="DrugDDI.d433.s4.d1" e1="DrugDDI.d433.s4.e1" e2="DrugDDI.d433.s4.e3" type="effect"/>
  <ddi id="DrugDDI.d433.s4.d2" e1="DrugDDI.d433.s4.e2" e2="DrugDDI.d433.s4.e3" type="effect"/>
</sentence>
```

Figure 40 Annotation of discontinuous names of groups (loop and thiazide diuretics)

3.4.8 Some terms to identify group names

Terms such as “drugs”, “medicines”, “agents”, “supplements”, “medications”, “products”, “preparations”, “agonists”, “adjuvants”, “antagonists”, “blockers” or “inhibitors” can be considered as useful clues to identify drug groups.

```

- <sentence id="DrugDDI.d82.s23" text="When used concomitantly, anesthetics and calcium channel blockers should be titrated carefully.">
  <entity id="DrugDDI.d82.s23.e0" charOffset="25-35" type="group" text="anesthetics"/>
  <entity id="DrugDDI.d82.s23.e1" charOffset="41-64" type="group" text="calcium channel blockers"/>
  <ddi id="DrugDDI.d82.s23.d0" e1="DrugDDI.d82.s23.e0" e2="DrugDDI.d82.s23.e1" type="advise"/>
</sentence>
```

Figure 41 ‘calcium channel blockers’ is a group

Sometimes a group may appear without being accompanied by any of the above common nouns (see Figure 42).

```

- <sentence id="DrugDDI.d467.s3" text="Narcotic analgesics may potentiate the hypotensive effects of clonidine.">
  <entity id="DrugDDI.d467.s3.e0" charOffset="0-18" type="group" text="Narcotic analgesics"/>
  <entity id="DrugDDI.d467.s3.e1" charOffset="62-70" type="drug" text="clonidine"/>
  <ddi id="DrugDDI.d467.s3.d0" e1="DrugDDI.d467.s3.e0" e2="DrugDDI.d467.s3.e1" type="effect"/>
</sentence>
```

Figure 42 The mention ‘Narcotic analgesics’ occurs without any of the above common nouns referring to groups.

However, if the group name appears accompanied by any of the above common nouns that refer to groups, the compound name should be annotated. That is, these common nouns should always be included in the annotation of the group. Figure 43 contains a sentence with three mentions of groups. The first mention ‘antihistaminics’ appears without any of the common nouns referring to groups. The other two mentions (‘analgesic agents’ and ‘analgesic adjuvants’) are formed by an adjective determining the group followed by a common name referring to a group.

```

- <sentence id="DrugDDI.d1239.s1" text="The literature provides considerable evidence indicating that several, but not all antihistaminics, are indeed analgesic agents and some are analgesic adjuvants as well.">
  <entity id="DrugDDI.d1239.s1.e0" charOffset="83-97" type="group" text="antihistaminics"/>
  <entity id="DrugDDI.d1239.s1.e1" charOffset="111-126" type="group" text="analgesic agents"/>
  <entity id="DrugDDI.d1239.s1.e2" charOffset="141-159" type="group" text="analgesic adjuvants"/>
</sentence>
```

Figure 43 ‘antihistaminics’, ‘analgesic agents’ and ‘analgesic adjuvants’ are annotated as group entity

3.4.9 What is not a group entity?

3.4.9.1 Effects or activities

Expressions describing the pharmacological effect or activity of a group of drugs are very common in the texts of the corpus. These expressions (formed by a group name followed by ‘effect(s)’ or ‘activity(-ies)’) usually refer to the effect or activity of the group.

In these cases, the name of group acts as an adjective. Annotators should not annotate those group names preceding the word ‘effect’ or ‘activity’ when they are used as an adjective.

In the example below appear different groups of drugs. Notice that, the same term ‘CNS depressant(s)’ and ‘anticholinergic(s)’ can be used to describe a group of drugs as well as a determine effect or activity. The first occurrence of ‘CNS depressants’ refers to a group and it is annotated (see entity DrugDDI.d368.s0.e1), while its second occurrence (‘the CNS

depressant effects of ... ') refers to the effect of the CNS depressant group and antihistamines on central nervous system (CNS). Similarly, the first occurrence of 'anticholinergics' refers to a group and it is annotated (see entity DrugDDI.d368.s0.e2), while the following occurrence ('anticholinergic effects may be...') refers to the blocking of the neurotransmitter acetylcholine in the central and the peripheral nervous system. The expression 'anticholinergic effects' cannot be replaced by 'the effects of anticholinergic agents', and thereby, 'anticholinergic' should not be annotated as group entity.

```
- <sentence id="DrugDDI.d368.s0" text="This drug may interact with alcohol or other CNS depressants (may potentiate the CNS depressant effects of either these medications or antihistamines), anticholinergics or other medications with anticholinergic activity (anticholinergic effects may be potentiated when these medications are used concurrently with antihistamines), and monoamine oxidase (MAO) inhibitors (concurrent use with antihistamines may prolong and intensify the anticholinergic and CNS depressant effects of antihistamines).">
  <entity id="DrugDDI.d368.s0.e0" charOffset="28-34" type="drug" text="alcohol"/>
  <entity id="DrugDDI.d368.s0.e1" charOffset="45-59" type="group" text="CNS depressants"/>
  <entity id="DrugDDI.d368.s0.e2" charOffset="135-148" type="group" text="antihistamines"/>
  <entity id="DrugDDI.d368.s0.e3" charOffset="152-167" type="group" text="anticholinergics"/>
  <entity id="DrugDDI.d368.s0.e4" charOffset="314-327" type="group" text="antihistamines"/>
  <entity id="DrugDDI.d368.s0.e5" charOffset="335-368" type="group" text="monoamine oxidase (MAO) inhibitors"/>
  <entity id="DrugDDI.d368.s0.e6" charOffset="391-404" type="group" text="antihistamines"/>
  <entity id="DrugDDI.d368.s0.e7" charOffset="482-495" type="group" text="antihistamines"/>
</sentence>
```

Figure 44 Expressions that describe the effects or the activity of a group of drugs should not be annotated.

```
- <sentence id="DrugDDI.d564.s2" text="Particular caution is necessary when using ROMAZICON in cases of mixed drug overdosage since the toxic effects (such as convulsions and cardiac dysrhythmias) of other drugs taken in overdose (especially cyclic antidepressants) may emerge with the reversal of the benzodiazepine effect by flumazenil.">
  <entity id="DrugDDI.d564.s2.e0" charOffset="43-51" type="brand" text="ROMAZICON"/>
  <entity id="DrugDDI.d564.s2.e1" charOffset="203-224" type="group" text="cyclic antidepressants"/>
  <entity id="DrugDDI.d564.s2.e2" charOffset="263-276" type="group" text="benzodiazepine"/>
  <entity id="DrugDDI.d564.s2.e3" charOffset="288-297" type="drug" text="flumazenil"/>
  <ddi id="DrugDDI.d564.s2.d0" e1="DrugDDI.d564.s2.e0" e2="DrugDDI.d564.s2.e1" type="effect"/>
</sentence>
```

Figure 45 'benzodiazepine effect' and 'effect of benzodiazepine' share the same meaning

```
- <sentence id="DrugDDI.d1124.s0" text="The CNS depressant effects of oxycodone hydrochloride may be additive with that of other CNS depressants..">
  <entity id="DrugDDI.d1124.s0.e0" charOffset="30-52" type="drug" text="oxycodone hydrochloride"/>
  <entity id="DrugDDI.d1124.s0.e1" charOffset="89-103" type="group" text="CNS depressants"/>
  <ddi id="DrugDDI.d1124.s0.d0" e1="DrugDDI.d1124.s0.e0" e2="DrugDDI.d1124.s0.e1" type="effect"/>
</sentence>
```

Figure 46 'CNS depressant' should not be annotated because it refers to an effect.

- <sentence id="DrugDDI.d1444.s1" text="It may also interact with thiazides (increased thrombocytopenia), cyclosporine (increased nephrotoxicity), sulfonylurea agents (increased hypoglycemic response), warfarin (increased anticoagulant effect), methotrexate (decreased renal excretion of methotrexate), phenytoin (decreased hepatic clearance of phenytoin).">
 <entity id="DrugDDI.d1444.s1.e0" charOffset="26-34" type="group" text="thiazides"/>
 <entity id="DrugDDI.d1444.s1.e1" charOffset="66-77" type="drug" text="cyclosporine"/>
 <entity id="DrugDDI.d1444.s1.e2" charOffset="107-125" type="group" text="sulfonylurea agents"/>
 <entity id="DrugDDI.d1444.s1.e3" charOffset="162-169" type="drug" text="warfarin"/>
 <entity id="DrugDDI.d1444.s1.e4" charOffset="205-216" type="drug" text="methotrexate"/>
 <entity id="DrugDDI.d1444.s1.e5" charOffset="248-259" type="drug" text="methotrexate"/>
 <entity id="DrugDDI.d1444.s1.e6" charOffset="263-271" type="drug" text="phenytoin"/>
 <entity id="DrugDDI.d1444.s1.e7" charOffset="305-313" type="drug" text="phenytoin"/>
 </sentence>

Figure 47 ‘anticoagulant effect’ or ‘hypoglycemic response’ should not be annotated.

This is not a general rule for all those group names preceding the words ‘effect’, ‘activity’, etc. For example, in Figure 48 ‘benzodiazepine effect’ may be replaced by ‘effect of benzodiazepine’: the group ‘benzodiazepine’ does not act as an adjective, and thereby, this group should be annotated. In the following sentence, ‘Adenosine’ is annotated though it is followed by the term ‘effects’.

- <sentence id="DrugDDI.d131.s6" text="Adenosine effects are potentiated by dipyridamole.">
 <entity id="DrugDDI.d131.s6.e0" charOffset="0-8" type="drug" text="Adenosine"/>
 <entity id="DrugDDI.d131.s6.e1" charOffset="37-48" type="drug" text="dipyridamole"/>
 <ddi id="DrugDDI.d131.s6.d0" e1="DrugDDI.d131.s6.e0" e2="DrugDDI.d131.s6.e1" type="effect"/>
 </sentence>

Figure 49 Name of drugs should always be annotated (though they are followed by terms such as effects or activity)

- <sentence id="DrugDDI.d1253.s8" text="Indomethacin was also ineffective in altering resveratrol activity in arteries from both lean and dietary-obese rats. ">
 <entity id="DrugDDI.d1253.s8.e0" charOffset="0-11" type="drug" text="Indomethacin"/>
 <entity id="DrugDDI.d1253.s8.e1" charOffset="46-56" type="drug_n" text="resveratrol"/>
 </sentence>

Figure 50 Resveratrol is not approved for human use. It is annotated though it is followed by the term ‘activity’

3.4.9.2 Therapy and chemotherapy

Those compound names that consist of a group name followed by the term ‘therapy’ (or ‘chemotherapy’) should be annotated, because it will be considered that a term such as ‘anticoagulant therapy’ can be expressed like ‘therapy with anticoagulant drugs’.

- <sentence id="DrugDDI.d260.s0" text="Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.">
 <entity id="DrugDDI.d260.s0.e0" charOffset="8-20" type="group" text="tetracyclines"/>
 <entity id="DrugDDI.d260.s0.e1" charOffset="98-110" type="group" text="anticoagulant"/>
 <entity id="DrugDDI.d260.s0.e2" charOffset="161-173" type="group" text="anticoagulant"/>
 <ddi id="DrugDDI.d260.s0.d0" e1="DrugDDI.d260.s0.e0" e2="DrugDDI.d260.s0.e1" type="advise"/>
 </sentence>

Figure 51 ‘anticoagulant’ preceding the term ‘therapy’ should be annotated

```

- <sentence id="DrugDDI.d63.s13" text="Monitoring for amiodarone toxicity and serial measurement of amiodarone serum concentration during concomitant protease inhibitor therapy should be considered.">
    <entity id="DrugDDI.d63.s13.e0" charOffset="15-24" type="drug" text="amiodarone"/>
    <entity id="DrugDDI.d63.s13.e1" charOffset="61-70" type="drug" text="amiodarone"/>
    <entity id="DrugDDI.d63.s13.e2" charOffset="111-128" type="group" text="protease inhibitor"/>
    <ddi id="DrugDDI.d63.s13.d0" e1="DrugDDI.d63.s13.e1" e2="DrugDDI.d63.s13.e2" type="advise"/>
</sentence>
```

Figure 52 The term ‘protease inhibitor’ should be annotated as a group.

Similarly, this rule applies to the other type of entities (drug, brand, drug_n). Hence, when the term ‘therapy’ is preceded by the name of a specific substance, it should be annotated.

```

- <sentence id="DrugDDI.d341.s3" text="FACTIVE had no significant effect on the anticoagulant effect of warfarin in healthy subjects on stable warfarin therapy.">
    <entity id="DrugDDI.d341.s3.e0" charOffset="0-6" type="brand" text="FACTIVE"/>
    <entity id="DrugDDI.d341.s3.e1" charOffset="65-72" type="drug" text="warfarin"/>
    <entity id="DrugDDI.d341.s3.e2" charOffset="104-111" type="drug" text="warfarin"/>
</sentence>
```

Figure 53 ‘warfarin’ is annotated though it is followed by the term ‘therapy’

The term “*chemotherapeutic*” should be annotated as group entity when it refers to an agent used in chemotherapy.

```

- <sentence id="DrugDDI.d1237.s4" text="No cross-resistance with other chemotherapeutic agents, radiotherapy or steroids has been demonstrated.">
    <entity id="DrugDDI.d1237.s4.e0" charOffset="31-53" type="group"
text="chemotherapeutic agents"/>
    <entity id="DrugDDI.d1237.s4.e1" charOffset="72-79" type="group" text="steroids"/>
</sentence>
```

Figure 54 “chemotherapeutic” should be annotated as group entity

3.4.9.3 Terms not found in any classification system

Those terms that may refer to groups but are not collected in some of above resources should not be included in the annotation.

```

- <sentence id="DrugDDI.d23.s10" text="Other nephrotoxic medications: agents such as aminoglycosides, cyclosporine, and pentamidine may enhance the potential for drug-induced renal toxicity, and should be used concomitantly only with great caution.">
    <entity id="DrugDDI.d23.s10.e0" charOffset="46-60" type="group" text="aminoglycosides"/>
    <entity id="DrugDDI.d23.s10.e1" charOffset="63-74" type="drug" text="cyclosporine"/>
    <entity id="DrugDDI.d23.s10.e2" charOffset="81-91" type="drug" text="pentamidine"/>
</sentence>
```

Figure 55 ‘nephrotoxic’ is not annotated since it is not found neither in ATC nor in MeSH.

3.5 What is not a pharmacological substance?

3.5.1 Dose and dosage form

The dose is the amount of drug taken at any one time. The dosage form is the physical form of a dose of drug such as tablets, capsules, creams, ointments, aerosols and patches. The amount

of drug in the dosage form is called strength. The dose can be expressed as the weight of drug, volume of drug solution or the number of dosage forms. Neither the dose nor the dosage form should be included in the annotation.

```
- <sentence id="DrugDDI.d1021.s1" text="Prostatic epithelium proliferates in a defined medium consisting of basal medium RPMI1640 containing transferrin (1 microgram/ml), EGF (10 ng/ml), and insulin (3.7 micrograms/ml or 0.1 IU/ml). ">
  <entity id="DrugDDI.d1021.s1.e0" charOffset="101-111" type="drug_n" text="transferrin"/>
  <entity id="DrugDDI.d1021.s1.e1" charOffset="131-133" type="drug_n" text="EGF"/>
  <entity id="DrugDDI.d1021.s1.e2" charOffset="151-157" type="drug" text="insulin"/>
</sentence>
```

Figure 56 Doses should not be included in the annotation

However, in some rare cases or exceptions we should include the dosage form in the annotation to annotate the full name of the entity, generally when the term is describing a group.

```
- <sentence id="DrugDDI.d1247.s0" text="Other short-acting beta adrenergic aerosol bronchodilators should not be used concomitantly with MAXAIR AUTOHALER because they may have additive effects.">
  <entity id="DrugDDI.d1247.s0.e0" charOffset="6-57" type="group" text="short-acting beta adrenergic aerosol bronchodilators"/>
  <entity id="DrugDDI.d1247.s0.e1" charOffset="97-112" type="brand" text="MAXAIR AUTOHALER"/>
  <ddi id="DrugDDI.d1247.s0.d0" e1="DrugDDI.d1247.s0.e0" e2="DrugDDI.d1247.s0.e1" type="advise"/>
</sentence>
```

Figure 57The mention of the group 'beta adrenergic aerosol bronchodilators' contains its dosage form. In this case, we should include this dosage form in the annotation of the entity.

Remember that you should include the dosage form in the annotation only if it is not possible to exclude it from the annotation text.

```
- <sentence id="DrugDDI.d98.s3" text="For example, since cholestyramine may reduce the gastrointestinal absorption of both the oral anticoagulants and vitamin K, the net effects are unpredictable.">
  <entity id="DrugDDI.d98.s3.e0" charOffset="19-32" type="drug" text="cholestyramine"/>
  <entity id="DrugDDI.d98.s3.e1" charOffset="94-107" type="group" text="anticoagulants"/>
  <entity id="DrugDDI.d98.s3.e2" charOffset="113-121" type="group" text="vitamin K"/>
  <ddi id="DrugDDI.d98.s3.d0" e1="DrugDDI.d98.s3.e0" e2="DrugDDI.d98.s3.e1" type="mechanism"/>
  <ddi id="DrugDDI.d98.s3.d1" e1="DrugDDI.d98.s3.e0" e2="DrugDDI.d98.s3.e2" type="mechanism"/>
</sentence>
```

Figure 58In this sentence it is possible to annotate the entity type group excluding the mention of the route of administration, so it should be annotated just the word 'anticoagulants'.

3.5.2 Dosage regimen and duration

The dosage regimen is the frequency at which the drug doses are given. This information, as well as the duration of the treatment (how long the drug is to be administered) should not be included in the annotation.

```
- <sentence id="DrugDDI.d168.s0" text="Warfarin: Concomitant administration of daptomycin (6 mg/kg once every 24 hours for 5 days) and warfarin (25 mg single oral dose) had no significant effect on the pharmacokinetics of either drug, and the INR was not significantly altered.">
  <entity id="DrugDDI.d168.s0.e0" charOffset="0-7" type="drug" text="Warfarin"/>
  <entity id="DrugDDI.d168.s0.e1" charOffset="40-49" type="drug" text="daptomycin"/>
  <entity id="DrugDDI.d168.s0.e2" charOffset="96-103" type="drug" text="warfarin"/>
</sentence>
```

Figure 59 Dosage regimen and duration should not be included in the annotation (24 hours for 5 days)

3.5.3 Route of administration

The route of administration is the path by which a drug is introduced into the body, that is, the way the dosage form is given. The common routes of administration are as follows: oral, sublingual, rectal, topical, parental, local, general, etc. These terms should not be included in the annotation.

```
- <sentence id="DrugDDI.d21897348.s1" text="The FDA has approved ticagrelor (Brilinta-AstraZeneca), an  
oral antiplatelet drug, for use with low-dose aspirin to reduce the rate of thrombotic cardiovascular events in  
patients with acute coronary syndrome (ACS). ">  
    <entity id="DrugDDI.d21897348.s1.e0" charOffset="21-30" type="drug" text="ticagrelor"/>  
    <entity id="DrugDDI.d21897348.s1.e1" charOffset="33-40" type="brand" text="Brilinta"/>  
    <entity id="DrugDDI.d21897348.s1.e2" charOffset="64-80" type="group" text="antiplatelet drug"/>  
    <entity id="DrugDDI.d21897348.s1.e3" charOffset="105-111" type="brand" text="aspirin"/>  
    <ddi id="DrugDDI.d21897348.s1.d0" e1="DrugDDI.d21897348.s1.e0" e2="DrugDDI.d21897348.s1.e3"  
        type="effect"/>  
    <ddi id="DrugDDI.d21897348.s1.d1" e1="DrugDDI.d21897348.s1.e1" e2="DrugDDI.d21897348.s1.e3"  
        type="effect"/>  
</sentence>
```

Figure 60 Routes of administration should not be included in the annotation. The term ‘oral’ should not be included in the annotation of the group ‘antiplatelet drug’.

```
- <sentence id="DrugDDI.d100.s1" text="When other potent parental antihypertensive drugs, such as diazoxide,  
are used in combination with hydralazine, patients should be continuously observed for any  
excessive fall in blood pressure.">  
    <entity id="DrugDDI.d100.s1.e0" charOffset="27-48" type="group" text="antihypertensive drugs"/>  
    <entity id="DrugDDI.d100.s1.e1" charOffset="59-67" type="drug" text="diazoxide"/>  
    <entity id="DrugDDI.d100.s1.e2" charOffset="99-109" type="drug" text="hydralazine"/>  
    <ddi id="DrugDDI.d100.s1.d0" e1="DrugDDI.d100.s1.e0" e2="DrugDDI.d100.s1.e1" type="effect"/>  
    <ddi id="DrugDDI.d100.s1.d1" e1="DrugDDI.d100.s1.e0" e2="DrugDDI.d100.s1.e2" type="effect"/>  
</sentence>
```

Figure 61 Routes of administration should not be included in the annotation. The term ‘parental’ should not be included in the annotation of the group ‘antihypertensive drugs’.

```
- <sentence id="DrugDDI.d320.s1" text="Concurrent use with general anesthetics may result in arrhythmias.">  
    <entity id="DrugDDI.d320.s1.e0" charOffset="28-38" type="group" text="anesthetics"/>  
</sentence>
```

Figure 62 Routes of administration should not be included in the annotation. The term ‘general’ should not be included in the annotation of the group ‘anesthetics’.

Although there are terms (such as ‘oral contraceptives’ or ‘general anesthetics’) in the MeSH index or in the ATC system, the route of administration should not be included in the annotation.

```
- <sentence id="DrugDDI.d35.s5" text="In common with other broad-spectrum antibiotics, AUGMENTIN XR  
may reduce the efficacy of oral contraceptives">  
    <entity id="DrugDDI.d35.s5.e0" charOffset="21-46" type="group" text="broad-spectrum antibiotics"/>  
    <entity id="DrugDDI.d35.s5.e1" charOffset="49-60" type="brand" text="AUGMENTIN XR"/>  
    <entity id="DrugDDI.d35.s5.e2" charOffset="94-107" type="group" text="contraceptives"/>  
    <ddi id="DrugDDI.d35.s5.d0" e1="DrugDDI.d35.s5.e0" e2="DrugDDI.d35.s5.e2" type="effect"/>  
    <ddi id="DrugDDI.d35.s5.d1" e1="DrugDDI.d35.s5.e1" e2="DrugDDI.d35.s5.e2" type="effect"/>  
</sentence>
```

Figure 63 ‘Oral contraceptives’ can be found in the Mesh index, however its route should not be included in the annotation.

3.5.4 Enzymes inhibitors, inducers or substrates

One particular characteristics of drugs that is frequently described in drug interaction texts is its relation with an enzyme or group of enzymes, so the drug can be described as an ‘inhibitor’ an ‘inducer’ or a ‘substrate’ of a determined enzyme. These terms should not be annotated as entities because the extraction of such terms is not an aim of this corpus. These drug-enzyme relationships can be expressed in several ways, being the most common the examples described below.

```
- <sentence id="DrugDDI.d253.s13" text="The interaction is a consequence of blocking hepatic metabolism of vardenafil by ritonavir, a highly potent CYP3A4 inhibitor, which also inhibits CYP2C9.">
  <entity id="DrugDDI.d253.s13.e0" charOffset="67-76" type="drug" text="vardenafil"/>
  <entity id="DrugDDI.d253.s13.e1" charOffset="81-89" type="drug" text="ritonavir"/>
  <ddi id="DrugDDI.d253.s13.d0" e1="DrugDDI.d253.s13.e0" e2="DrugDDI.d253.s13.e1" type="mechanism"/>
</sentence>
```

Figure 64 Ritonavir is a drug that inhibits the activity of the isoenzymes CYP3A4 and CYP2c9. These isoenzymes should not be annotated as entities.

```
- <sentence id="DrugDDI.d65.s0" text="Digoxin: Coadministration of digoxin, a P-glycoprotein substrate, with oral conivaptan resulted in a reduction in clearance and an increase in digoxin Cmax and AUC values.">
  <entity id="DrugDDI.d65.s0.e0" charOffset="0-6" type="drug" text="Digoxin"/>
  <entity id="DrugDDI.d65.s0.e1" charOffset="29-35" type="drug" text="digoxin"/>
  <entity id="DrugDDI.d65.s0.e2" charOffset="76-85" type="drug" text="conivaptan"/>
  <entity id="DrugDDI.d65.s0.e3" charOffset="143-149" type="drug" text="digoxin"/>
  <ddi id="DrugDDI.d65.s0.d0" e1="DrugDDI.d65.s0.e1" e2="DrugDDI.d65.s0.e2" type="mechanism"/>
</sentence>
```

Figure 65 Digoxin is a substrate of the multidrug transporter P-glycoprotein, which should not be annotated as entity.

Figure 66 Rifampin is a potent inducer of the isoenzyme CYP3A4, which should not be annotated as entity.

3.5.5 Interacting substances out of scope of our study

A drug interaction may occur between a drug and a substance such as food (e.g. cheese or chocolate), drinks (different fruit juices such as grapefruit juice), alcoholic beverages, herbal medicines (e.g. *Hypericum perforatum*, also called St. John’s Wort) or environmental chemicals (such as pesticides). The purpose of this corpus is not to recognize those kinds of drug interactions, so any food, drink, herbal medicine, etc., described in the text should not be annotated as an entity. Some examples of these terms in sentences within the corpus are described below.

```
- <sentence id="DrugDDI.d432.s3" text="Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. Johns Wort.">
  <entity id="DrugDDI.d432.s3.e0" charOffset="43-74" type="group" text="combined hormonal contraceptives"/>
</sentence>
```

Figure 67 St. Johns Wort is an herbal medicine that has been described to interact with a variety of drugs. However, you should not annotate it since this kind of medicinal products are out of the scope of our annotation.

```

- <sentence id="DrugDDI.d133.s2" text="On the basis of the metabolism of bexarotene by cytochrome P450 3A4, ketoconazole, itraconazole, erythromycin, gemfibrozil, grapefruit juice, and other inhibitors of cytochrome P450 3A4 would be expected to lead to an increase in plasma bexarotene concentrations.">
    <entity id="DrugDDI.d133.s2.e0" charOffset="34-43" type="drug" text="bexarotene"/>
    <entity id="DrugDDI.d133.s2.e1" charOffset="69-80" type="drug" text="ketoconazole"/>
    <entity id="DrugDDI.d133.s2.e2" charOffset="83-94" type="drug" text="itraconazole"/>
    <entity id="DrugDDI.d133.s2.e3" charOffset="97-108" type="drug" text="erythromycin"/>
    <entity id="DrugDDI.d133.s2.e4" charOffset="111-121" type="drug" text="gemfibrozil"/>
    <entity id="DrugDDI.d133.s2.e5" charOffset="237-246" type="drug" text="bexarotene"/>
    <ddi id="DrugDDI.d133.s2.d0" e1="DrugDDI.d133.s2.e1" e2="DrugDDI.d133.s2.e5" type="mechanism"/>
    <ddi id="DrugDDI.d133.s2.d1" e1="DrugDDI.d133.s2.e2" e2="DrugDDI.d133.s2.e5" type="mechanism"/>
    <ddi id="DrugDDI.d133.s2.d2" e1="DrugDDI.d133.s2.e3" e2="DrugDDI.d133.s2.e5" type="mechanism"/>
    <ddi id="DrugDDI.d133.s2.d3" e1="DrugDDI.d133.s2.e4" e2="DrugDDI.d133.s2.e5" type="mechanism"/>
</sentence>
```

Figure 68 Althoug the ingestion of grapefruit juice and bexarotene may lead to an interaction, this drunk should not be annotated.

```

- <sentence id="DrugDDI.d160.s0" text="Milk, milk products, and calcium-rich foods or drugs may impair the absorption of EMCYT.">
    <entity id="DrugDDI.d160.s0.e0" charOffset="25-31" type="drug" text="calcium"/>
    <entity id="DrugDDI.d160.s0.e1" charOffset="82-86" type="brand" text="EMCYT"/>
    <ddi id="DrugDDI.d160.s0.d0" e1="DrugDDI.d160.s0.e0" e2="DrugDDI.d160.s0.e1" type="mechanism"/>
</sentence>
```

Figure 69 A specific foods such as milk should not be annotated. ‘Calcium’, however, is a substance present in a variety of foods. This specific substance should be annotated.

There is a unique exception for this rule, for the active substance alcohol. More information can be found in subsection 3.1.8.

4 Relationships

The guidelines in this section describe how to add the interactions between pharmacological substances that occur in texts of the corpus.

The definition of drug-drug interaction (DDI) is broadly described as a change in the effects of one drug by the presence of another drug. These relationships are annotated by identifying its arguments (interacting entities) and its type. A drug interaction may be classified according to several different criteria such as its mechanism (pharmacodynamic or pharmacokinetic), its consequence, its severity, its clinical relevance, the probability that the interaction occurs or its level of documentation, among others.

In our corpus, drug interactions are classified depending on the type of information that their descriptions include. Basing on the study of our texts, we realized that most sentences describing a drug-drug interaction also included information on its **effect**, its **mechanism** or the **advice** to prevent or lessen its adverse effects. These aspects are crucial for clinicians to recognize and manage properly a given drug-drug interaction. Additionally, most drug interaction compendiums (Stockley⁷, DRUG-REAX SYSTEM, etc) usually show information on drug interactions with emphasis on the above aspects. Our classification proposed for drug interactions information is described in more detail below:

⁷ <http://www.pharmpress.com/product/9780853699149/stockley>

1. **Advice:** this category is assigned to those drug-drug interactions in which a recommendation or advice regarding the concomitant use of two drugs involved in them is described. Some examples of this type of drug-drug interactions are:
 - Interactions may be expected, and **UROXATRAL** should NOT be used in combination with other **alpha-blockers**.
 - Literature reports suggest that oral **calcium antagonists** may be used in combination with **beta-adrenergic blocking agents** when heart function is normal, but should be avoided in patients with impaired cardiac function.
 - Because of **foscarnets** tendency to cause renal impairment, the use of **FOSCAVIR** should be avoided in combination with potentially nephrotoxic drugs such as **aminoglycosides**, **amphotericin B** and intravenous **pentamidine** unless the potential benefits outweigh the risks to the patient.
2. **Effect:** this type is assigned when the effect of the drug-drug interaction is described. The effect can be a pharmacological effect, a clinical finding, signs or symptoms, an unspecific modification of the effect or action of one of the drugs, an increased of the toxicity or a protective effect, or therapeutic failure. Likewise, this type is assigned when the sentence describes a pharmacodynamic mechanism or effect of interaction (see appendix). The detection of the effect is not required in this task. Some examples are shown below:
 - Some **quinolones**, including **ciprofloxacin**, have been associated with transient elevations in serum creatinine in patients receiving **cyclosporine** concomitantly.
 - The concomitant administration of **ciprofloxacin** with the **sulfonylurea glyburide** has, on rare occasions, resulted in severe hypoglycemia.
 - In uninfected volunteers, 46% developed rash while receiving **SUSTIVA** and **clarithromycin**.
 - **Quinolones** may enhance the effects of the oral anticoagulant, **warfarin**, or its derivatives.
 - Use of **Cerubidine** in a patient who has previously received **doxorubicin** increases the risk of cardiotoxicity.
 - **Methionine** may protect against the ototoxic effects of **gentamicin**.
 - **Chlorthalidone** may add to or potentiate the action of other **antihypertensive drugs**.
 - Antagonism has been demonstrated between **clindamycin** and **erythromycin** in vitro.
3. **mechanism:** The mechanism of interaction can be **pharmacodynamic** (the effects of one drug are changed by the presence of another drug at its site of action, for example, '*alcohol potentiates the depressor effect of barbiturates*') or **pharmacokinetic** (the processes by which drugs are absorbed, distributed, metabolized and excreted are affected, for example, '*induced the metabolism of*', '*increased the clearance of*') (Baxter & Stockely, 2010). In this corpus, however, the type mechanism is assigned when a pharmacokinetic mechanism is described, including changes in levels or concentration of the entities (see appendix). As already noted, a pharmacodynamic relationship

between entities must be considered type effect. Some examples of type mechanism ddi are shown below:

- **Grepafloxacin**, like other **quinolones**, may inhibit the metabolism of **caffeine** and **theobromine**.
 - **Grepafloxacin** is a competitive inhibitor of the metabolism of **theophylline**.
 - Blood levels of **hydromorphone** increased 24% when **dolasetron** was coadministered with **cimetidine** (nonselective inhibitor of cytochrome P-450) for 7 days, and decreased 28% with coadministration of **rifampin** (potent inducer of cytochrome P-450) for 7 days.
 - Elevated plasma levels of **theophylline** have been reported with concomitant **quinolone** use.
4. **int**: this type is assigned when the sentence simply states that an interaction occurs and does not provide any information about the interaction, so none of the other types can be assigned
- The interaction of **omeprazole** and **ketoconazole** has been established.

All the annotations will be based on XML since it is easier for the machine to process it and is human readable. In the corpus DDI, a *ddi* relationship describes an interaction between two any entities, independently of their types. Each<ddi>element has the following attributes:

- **id** – A unique id that is composed by the name of the corpus (DDI-DrugBank or DDI-MedLine), the id of the document (d505), the id of the sentence, and an id beginning with ‘d’ and followed by the index of the ddi in the sentence (the first ddi of the sentence should have the index 0).
- **e1**- stores the id of the first interacting entity.
- **e2**- stores the id of the second interacting entity
- **type** – stores the type of the drug-drug interaction (ddi, advice, effect, mechanism).

Interactions should be annotated at sentence level only. That is, those interactions spanning several sentences are not included in the annotation.

4.1 effect ddi

This type should be assigned to those ddi relationships that describe the effect of a drug-drug interaction. The effect may be described like a pharmacological effect, a clinical finding, an unexpected effect of some of the drugs, an increase in toxicity or a protective effect, treatment failure, etc. Moreover, this type is assigned to those ddi relationships that describe a pharmacodynamic relationship between entities.

4.1.1 Interactions that describe a pharmacological effect

```
- <sentence id="DrugDDI.d307.s7" text="Butyrophенones (such as haloperidol) and phenothiazines can suppress the dopaminergic renal and mesenteric vasodilation induced with low dose dopamine infusion.">
  <entity id="DrugDDI.d307.s7.e0" charOffset="0-13" type="group" text="Butyrophенones"/>
  <entity id="DrugDDI.d307.s7.e1" charOffset="24-34" type="drug" text="haloperidol"/>
  <entity id="DrugDDI.d307.s7.e2" charOffset="41-54" type="group" text="phenothiazines"/>
  <entity id="DrugDDI.d307.s7.e3" charOffset="73-80" type="drug" text="dopamine"/>
  <ddi id="DrugDDI.d307.s7.d0" e1="DrugDDI.d307.s7.e0" e2="DrugDDI.d307.s7.e3" type="effect"/>
  <ddi id="DrugDDI.d307.s7.d1" e1="DrugDDI.d307.s7.e1" e2="DrugDDI.d307.s7.e3" type="effect"/>
  <ddi id="DrugDDI.d307.s7.d2" e1="DrugDDI.d307.s7.e2" e2="DrugDDI.d307.s7.e3" type="effect"/>
</sentence>
```

Figure 70 Example of interactions describing a pharmacological effect

The following sentence contains six interactions whose effect is ‘severe, prolonged hypertension’

```
- <sentence id="DrugDDI.d261.s0" text="The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors, tricyclic antidepressants or phenothiazines may produce severe, prolonged hypotension or hypertension.">
  <entity id="DrugDDI.d261.s0.e0" charOffset="28-47" type="group" text="anesthetic solutions"/>
  <entity id="DrugDDI.d261.s0.e1" charOffset="60-70" type="drug" text="epinephrine"/>
  <entity id="DrugDDI.d261.s0.e2" charOffset="75-88" type="drug" text="norepinephrine"/>
  <entity id="DrugDDI.d261.s0.e3" charOffset="112-139" type="group" text="monoamine oxidase inhibitors"/>
  <entity id="DrugDDI.d261.s0.e4" charOffset="142-166" type="group" text="tricyclic antidepressants"/>
  <entity id="DrugDDI.d261.s0.e5" charOffset="171-184" type="group" text="phenothiazines"/>
  <ddi id="DrugDDI.d261.s0.d0" e1="DrugDDI.d261.s0.e0" e2="DrugDDI.d261.s0.e4" type="effect"/>
  <ddi id="DrugDDI.d261.s0.d1" e1="DrugDDI.d261.s0.e0" e2="DrugDDI.d261.s0.e5" type="effect"/>
  <ddi id="DrugDDI.d261.s0.d2" e1="DrugDDI.d261.s0.e1" e2="DrugDDI.d261.s0.e3" type="effect"/>
  <ddi id="DrugDDI.d261.s0.d3" e1="DrugDDI.d261.s0.e1" e2="DrugDDI.d261.s0.e4" type="effect"/>
  <ddi id="DrugDDI.d261.s0.d4" e1="DrugDDI.d261.s0.e1" e2="DrugDDI.d261.s0.e5" type="effect"/>
  <ddi id="DrugDDI.d261.s0.d5" e1="DrugDDI.d261.s0.e2" e2="DrugDDI.d261.s0.e3" type="effect"/>
  <ddi id="DrugDDI.d261.s0.d6" e1="DrugDDI.d261.s0.e2" e2="DrugDDI.d261.s0.e4" type="effect"/>
  <ddi id="DrugDDI.d261.s0.d7" e1="DrugDDI.d261.s0.e2" e2="DrugDDI.d261.s0.e5" type="effect"/>
</sentence>
```

Figure 71 Interactions that describe a pharmacological effect

4.1.2 Interactions that describe the change of one drug’s effect

In the following cases, the interaction involves the change in an effect of some of the drugs:

```
- <sentence id="DrugDDI.d71.s8" text="Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine.">
  <entity id="DrugDDI.d71.s8.e0" charOffset="0-13" type="drug" text="Chlorthalidone"/>
  <entity id="DrugDDI.d71.s8.e1" charOffset="73-86" type="drug" text="norepinephrine"/>
  <ddi id="DrugDDI.d71.s8.d0" e1="DrugDDI.d71.s8.e0" e2="DrugDDI.d71.s8.e1" type="effect"/>
</sentence>
```

Figure 72 The arterial responsiveness to norepinephrine is decreased in presence of chlorthalidone.

```

- <sentence id="DrugDDI.d397.s3" text="Anticholinergics: Concurrent administration of certain anticholinergic compounds, such as belladonna alkaloids and dicyclomine, would be expected to compromise the beneficial effects of cisapride.">
  <entity id="DrugDDI.d397.s3.e0" charOffset="0-15" type="group" text="Anticholinergics"/>
  <entity id="DrugDDI.d397.s3.e1" charOffset="55-79" type="group" text="anticholinergic compounds"/>
  <entity id="DrugDDI.d397.s3.e2" charOffset="90-109" type="group" text="belladonna alkaloids"/>
  <entity id="DrugDDI.d397.s3.e3" charOffset="115-125" type="drug" text="dicyclomine"/>
  <entity id="DrugDDI.d397.s3.e4" charOffset="186-194" type="drug" text="cisapride"/>
  <ddi id="DrugDDI.d397.s3.d0" e1="DrugDDI.d397.s3.e1" e2="DrugDDI.d397.s3.e4" type="effect"/>
  <ddi id="DrugDDI.d397.s3.d1" e1="DrugDDI.d397.s3.e2" e2="DrugDDI.d397.s3.e4" type="effect"/>
  <ddi id="DrugDDI.d397.s3.d2" e1="DrugDDI.d397.s3.e3" e2="DrugDDI.d397.s3.e4" type="effect"/>
</sentence>
```

Figure 73The beneficial effects of cisapride may be dissipated

4.1.3 Interactions that describe a clinical finding, a sing or a symptom.

Following sentences show interactions that describe clinical findings, signs or symptoms as possible effects.

```

- <sentence id="DrugDDI.d462.s10" origId="s10" text="Seizures have been reported in patients taking another quinolone class antimicrobial and the nonsteroidal anti-inflammatory drug fenbufen concurrently.">
  <entity id="DrugDDI.d462.s10.e0" origId="s10.p118" charOffset="55-83" type="group" text="quinolone class antimicrobial"/>
  <entity id="DrugDDI.d462.s10.e1" origId="s10.p120" charOffset="93-127" type="group" text="nonsteroidal anti-inflammatory drug"/>
  <entity id="DrugDDI.d462.s10.e2" origId="" charOffset="129-136" type="drug" text="fenbufen"/>
  <ddi id="DrugDDI.d462.s10.d0" e1="DrugDDI.d462.s10.e0" e2="DrugDDI.d462.s10.e1" type="effect"/>
  <ddi id="DrugDDI.d462.s10.d1" e1="DrugDDI.d462.s10.e0" e2="DrugDDI.d462.s10.e2" type="effect"/>
</sentence>
```

Figure 74The concomitant administration of quinolone class antimicrobial and NSAIDs may cause seizures

```

- <sentence id="DrugDDI.d444.s2" origId="s2" text="Some quinolones, including ciprofloxacin, have been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.">
  <entity id="DrugDDI.d444.s2.e0" origId="s2.p19" charOffset="5-14" type="group" text="quinolones"/>
  <entity id="DrugDDI.d444.s2.e1" origId="s2.p21" charOffset="27-39" type="drug" text="ciprofloxacin"/>
  <entity id="DrugDDI.d444.s2.e2" origId="s2.p29" charOffset="131-142" type="drug" text="cyclosporine"/>
  <ddi id="DrugDDI.d444.s2.d0" e1="DrugDDI.d444.s2.e0" e2="DrugDDI.d444.s2.e1" type="effect"/>
  <ddi id="DrugDDI.d444.s2.d1" e1="DrugDDI.d444.s2.e0" e2="DrugDDI.d444.s2.e2" type="effect"/>
</sentence>
```

Figure 75 ‘Transient elevations in serum creatinine’ may describe the effect of the interaction between quinolones and cyclosporine

```

- <sentence id="DrugDDI.d162.s8" origId="s8" text="Data suggest that coadministration of oral ketoconazole and cisapride can result in prolongation of the QT interval on the ECG.">
  <entity id="DrugDDI.d162.s8.e0" origId="s8.p94" charOffset="43-54" type="drug" text="ketoconazole"/>
  <entity id="DrugDDI.d162.s8.e1" origId="s8.p96" charOffset="60-68" type="drug" text="cisapride"/>
  <ddi id="DrugDDI.d162.s8.d0" e1="DrugDDI.d162.s8.e0" e2="DrugDDI.d162.s8.e1" type="effect"/>
</sentence>
```

Figure 76This interactions causes the prolongation of the QT interval on the ECG

4.1.4 Pharmacodynamic interactions

Pharmacodynamic interactions are those in which the effects of one drug are changed by the presence of another drug at the site of action. These interactions can occur through complex mechanism. Generally, literature describes synergistic interactions (additive or potentiated effects) or antagonistic interactions (see appendix).

```

- <sentence id="DrugDDI.d40.s2" origId="s2" text="Antagonism has been demonstrated between clindamycin and erythromycin in vitro.">
  <entity id="DrugDDI.d40.s2.e0" origId="s2.p25" charOffset="41-51" type="drug" text="clindamycin"/>
  <entity id="DrugDDI.d40.s2.e1" origId="s2.p27" charOffset="57-68" type="drug" text="erythromycin"/>
  <ddi id="DrugDDI.d40.s2.d0" e1="DrugDDI.d40.s2.e0" e2="DrugDDI.d40.s2.e1" type="effect"/>
</sentence>
```

Figure 77‘Antagonism’ indicates that two drugs have activities that are opposed to each other.

```

- <sentence id="DrugDDI.d71.s0" origId="s0" text="Chlorthalidone may add to or potentiate the action of other antihypertensive drugs.">
  <entity id="DrugDDI.d71.s0.e0" origId="s0.p0" charOffset="0-13" type="drug" text="Chlorthalidone"/>
  <entity id="DrugDDI.d71.s0.e1" origId="s0.p7" charOffset="60-81" type="group" text="antihypertensive drugs"/>
  <ddi id="DrugDDI.d71.s0.d0" e1="DrugDDI.d71.s0.e0" e2="DrugDDI.d71.s0.e1" type="effect"/>
</sentence>
```

Figure 78'may add to or potentiate the action of' indicates a synergistic interaction in which both drugs have the same pharmacological effect, so it could be observed a greater response than it was expected.

Since pharmacodynamic interactions involve changes in the effect of a drug, often the information on the pharmacodynamic mechanism and the result of interaction are described in the same sentence or it is used a similar vocabulary.

```

- <sentence id="DrugDDI.d357.s0" origId="s0" text="Additive CNS depression may occur when antihistamines are administered concomitantly with other CNS depressants including barbiturates, tranquilizers, and alcohol.">
  <entity id="DrugDDI.d357.s0.e0" origId="s0.p4" charOffset="39-52" type="group" text="antihistamines"/>
  <entity id="DrugDDI.d357.s0.e1" origId="s0.p8" charOffset="96-110" type="group" text="CNS depressants"/>
  <entity id="DrugDDI.d357.s0.e2" origId="s0.p10" charOffset="122-133" type="group" text="barbiturates"/>
  <entity id="DrugDDI.d357.s0.e3" origId="s0.p11" charOffset="136-148" type="group" text="tranquilizers"/>
  <entity id="DrugDDI.d357.s0.e4" origId="s0.p13" charOffset="155-161" type="drug" text="alcohol"/>
  <ddi id="DrugDDI.d357.s0.d0" e1="DrugDDI.d357.s0.e0" e2="DrugDDI.d357.s0.e1" type="effect"/>
  <ddi id="DrugDDI.d357.s0.d1" e1="DrugDDI.d357.s0.e0" e2="DrugDDI.d357.s0.e2" type="effect"/>
  <ddi id="DrugDDI.d357.s0.d2" e1="DrugDDI.d357.s0.e0" e2="DrugDDI.d357.s0.e3" type="effect"/>
  <ddi id="DrugDDI.d357.s0.d3" e1="DrugDDI.d357.s0.e0" e2="DrugDDI.d357.s0.e4" type="effect"/>
</sentence>
```

Figure 79'CNS depression' describes the effect of the interaction, and the term 'Additive' refers to the pharmacodynamic mechanism.

An additive effect can occur with an undesirable effect, so we can found sentences describing the potentiation or the increase of a side effect or of the toxicity of the drugs.

```

- <sentence id="DrugDDI.d166.s2" text="EDECRIN may increase the ototoxic potential of other drugs such as aminoglycoside and some cephalosporin antibiotics.">
  <entity id="DrugDDI.d166.s2.e0" charOffset="0-6" type="brand" text="EDECRIN"/>
  <entity id="DrugDDI.d166.s2.e1" charOffset="67-80" type="group" text="aminoglycoside"/>
  <entity id="DrugDDI.d166.s2.e2" charOffset="91-115" type="group" text="cephalosporin antibiotics"/>
  <ddi id="DrugDDI.d166.s2.d0" e1="DrugDDI.d166.s2.e0" e2="DrugDDI.d166.s2.e1" type="effect"/>
  <ddi id="DrugDDI.d166.s2.d1" e1="DrugDDI.d166.s2.e0" e2="DrugDDI.d166.s2.e2" type="effect"/>
</sentence>
```

Figure 80 Example of side effect

Likewise, antagonism pharmacodynamic interaction can have a protective effect for the patient.

```

- <sentence id="DrugDDI.d25.s2" text="Gentamicin - Methionine may protect against the ototoxic effects of gentamicin.">
  <entity id="DrugDDI.d25.s2.e0" charOffset="0-9" type="drug" text="Gentamicin"/>
  <entity id="DrugDDI.d25.s2.e1" charOffset="13-23" type="drug" text="Methionine "/>
  <entity id="DrugDDI.d25.s2.e2" charOffset="68-77" type="drug" text="gentamicin"/>
  <ddi id="DrugDDI.d25.s2.d0" e1="DrugDDI.d25.s2.e1" e2="DrugDDI.d25.s2.e2" type="effect"/>
</sentence>
```

Figure 81The protective action of gentamicin should be considered a type effect ddi

4.2 mechanism ddi

This type should be assigned to those ddi relationships that describe how a pharmacokinetic interaction occurs. These sentences would be described by a change in a pharmacokinetic process, a change in a pharmacokinetic parameter or a change in the levels or concentrations of the drugs.

- Co-administration with **efavirenz** or **fluconazole** had a modest effect on the pharmacokinetics of **azithromycin**.
- These studies indicate that **ketoconazole** or **erythromycin** co-administration enhances **fexofenadine** gastrointestinal absorption.
- Based on total **ertapenem** concentrations, **probenecid** increased the AUC by 25% and reduced the plasma and renal clearances by 20% and 35%, respectively.
- Elevated serum levels of cyclosporine have been reported with concomitant use of **cyclosporine** with other members of the **quinolone class**.

Pharmacokinetic interactions are those in which one drug increases or decreases the concentration of another drug. In these interactions the processes by which a drug is absorbed, distributed, metabolized and excreted are altered. Moreover, a pharmacokinetic study can explain describing the change in several pharmacokinetic parameters, such as volume of distribution, bioavailability of a drug, peak level, clearance and half-life (see Appendix). All the information regarding these processes should be annotated as type mechanism, since it is related with a pharmacokinetic mechanism of a drug interaction.

Some useful examples of this type of ddi information are described below.

4.2.1 Altering a pharmacokinetic process

```
-<sentence id="DrugDDI.d1166.s3" text="Drugs that impair intestinal absorption of fat-soluble vitamins, such as cholestyramine, may interfere with the absorption of Zemplar Capsules.">
  <entity id="DrugDDI.d1166.s3.e0" charOffset="43-62" type="group" text="fat-soluble vitamins"/>
  <entity id="DrugDDI.d1166.s3.e1" charOffset="73-86" type="drug" text="cholestyramine"/>
  <entity id="DrugDDI.d1166.s3.e2" charOffset="126-132" type="brand" text="Zemplar"/>
  <ddi id="DrugDDI.d1166.s3.d0" e1="DrugDDI.d1166.s3.e0" e2="DrugDDI.d1166.s3.e1" type="mechanism"/>
  <ddi id="DrugDDI.d1166.s3.d1" e1="DrugDDI.d1166.s3.e1" e2="DrugDDI.d1166.s3.e2" type="mechanism"/>
</sentence>
```

Figure 82The interaction describes a possible problem with the absorption of Zemplar.

```
-<sentence id="DrugDDI.d162.s22" text="Concomitant administration of ketoconazole tablets with phenytoin may alter the metabolism of one or both of the drugs.">
  <entity id="DrugDDI.d162.s22.e0" charOffset="30-41" type="drug" text="ketoconazole"/>
  <entity id="DrugDDI.d162.s22.e1" charOffset="56-64" type="drug" text="phenytoin"/>
  <ddi id="DrugDDI.d162.s22.d0" e1="DrugDDI.d162.s22.e0" e2="DrugDDI.d162.s22.e1" type="mechanism"/>
</sentence>
```

Figure 83The change in the metabolism describes pharmacokinetic mechanism

4.2.2 Changing of pharmacokinetic parameters and variation of levels

```
-<sentence id="DrugDDI.d1032.s5" origId="s5" text="The half-life of ketamine in plasma and brain was longer in the presence of halothane than when ketamine was given alone.">
  <entity id="DrugDDI.d1032.s5.e0" origId="s5.p64" charOffset="17-24" type="drug" text="ketamine"/>
  <entity id="DrugDDI.d1032.s5.e1" origId="s5.p71" charOffset="76-84" type="drug" text="halothane"/>
  <entity id="DrugDDI.d1032.s5.e2" origId="s5.p74" charOffset="96-103" type="drug" text="ketamine"/>
  <ddi id="DrugDDI.d1032.s5.d0" e1="DrugDDI.d1032.s5.e0" e2="DrugDDI.d1032.s5.e1" type="mechanism"/>
</sentence>
```

Figure 84The interaction may cause an increase in the half-life of ketamine.

```
-<sentence id="DrugDDI.d89.s5" origId="s5" text="There was a small decrease in the clearance of cetirizine caused by a 400-mg dose of theophylline;">
  <entity id="DrugDDI.d89.s5.e0" origId="s5.p58" charOffset="47-56" type="drug" text="cetirizine"/>
  <entity id="DrugDDI.d89.s5.e1" origId="s5.p61" charOffset="85-96" type="drug" text="theophylline"/>
  <ddi id="DrugDDI.d89.s5.d0" e1="DrugDDI.d89.s5.e0" e2="DrugDDI.d89.s5.e1" type="mechanism"/>
</sentence>
```

Figure 85The interaction may cause a decrease in the pharmacokinetic parameter clearance of cetirizine

```
-<sentence id="DrugDDI.d462.s7" origId="s7" text="Also, concomitant administration of quinolones with products containing iron, multivitamins containing zinc, or Videx (didanosine) chewable/buffered tablets or the pediatric powder for oral solution may result in low urine levels.">
  <entity id="DrugDDI.d462.s7.e0" origId="s7.p70" charOffset="36-45" type="group" text="quinolones"/>
  <entity id="DrugDDI.d462.s7.e1" origId="s7.p73" charOffset="72-75" type="drug" text="iron"/>
  <entity id="DrugDDI.d462.s7.e2" origId="s7.p74" charOffset="78-90" type="group" text="multivitamins"/>
  <entity id="DrugDDI.d462.s7.e3" origId="s7.p76" charOffset="103-106" type="drug" text="zinc"/>
  <entity id="DrugDDI.d462.s7.e4" origId="s7.p78" charOffset="112-116" type="brand" text="Videx"/>
  <entity id="DrugDDI.d462.s7.e5" origId="s7.p80" charOffset="119-128" type="drug" text="didanosine"/>
<ddi id="DrugDDI.d462.s7.d0" e1="DrugDDI.d462.s7.e0" e2="DrugDDI.d462.s7.e1" type="mechanism"/>
<ddi id="DrugDDI.d462.s7.d1" e1="DrugDDI.d462.s7.e0" e2="DrugDDI.d462.s7.e2" type="mechanism"/>
<ddi id="DrugDDI.d462.s7.d2" e1="DrugDDI.d462.s7.e0" e2="DrugDDI.d462.s7.e3" type="mechanism"/>
<ddi id="DrugDDI.d462.s7.d3" e1="DrugDDI.d462.s7.e0" e2="DrugDDI.d462.s7.e4" type="mechanism"/>
<ddi id="DrugDDI.d462.s7.d4" e1="DrugDDI.d462.s7.e0" e2="DrugDDI.d462.s7.e5" type="mechanism"/>
</sentence>
```

Figure 86Theseinteracnts may cause a reduction in the urine levels or concentrations.

4.3 advise ddi

This type should be assigned to those drug-drug interactions in which a recommendation or advice regarding the concomitant use of two drugs involved in them is described. Some examples are shown below.

```
-<sentence id="DrugDDI.d383.s1" origId="s1" text="DISULFIRAM SHOULD BE USED WITH CAUTION IN THOSE PATIENTS RECEIVING PHENYTOIN AND ITS CONGENERS.">
  <entity id="DrugDDI.d383.s1.e0" origId="s1.p19" charOffset="0-9" type="drug" text="DISULFIRAM"/>
  <entity id="DrugDDI.d383.s1.e1" origId="s1.p24" charOffset="67-75" type="drug" text="PHENYTOIN"/>
  <ddi id="DrugDDI.d383.s1.d0" e1="DrugDDI.d383.s1.e0" e2="DrugDDI.d383.s1.e1" type="advise"/>
</sentence>

-<sentence id="DrugDDI.d383.s7" origId="s7" text="Patients taking isoniazid when disulfiram is given should be observed for the appearance of unsteady gait or marked changes in mental status;">
  <entity id="DrugDDI.d383.s7.e0" origId="s7.p75" charOffset="16-24" type="drug" text="isoniazid"/>
  <entity id="DrugDDI.d383.s7.e1" origId="s7.p77" charOffset="31-40" type="drug" text="disulfiram"/>
  <ddi id="DrugDDI.d383.s7.d0" e1="DrugDDI.d383.s7.e0" e2="DrugDDI.d383.s7.e1" type="advise"/>
</sentence>

-<sentence id="DrugDDI.d462.s10" origId="s10" text="therefore concomitant administration of Itraconazole with cisapride is contraindicated.">
  <entity id="DrugDDI.d462.s10.e0" origId="s10.p112" charOffset="40-51" type="drug" text="Itraconazole"/>
  <entity id="DrugDDI.d462.s10.e1" origId="s10.p113" charOffset="58-66" type="drug" text="cisapride"/>
  <ddi id="DrugDDI.d462.s10.d0" e1="DrugDDI.d462.s10.e0" e2="DrugDDI.d462.s10.e1" type="advise"/>
</sentence>

-<sentence id="DrugDDI.d462.s22" origId="s22" text="therefore, plasma concentrations of phenytoin should also be monitored when it is given concurrently with Itraconazole.">
  <entity id="DrugDDI.d462.s22.e0" origId="s22.p261" charOffset="36-44" type="drug" text="phenytoin"/>
  <entity id="DrugDDI.d462.s22.e1" origId="s22.p271" charOffset="106-117" type="drug" text="itraconazole"/>
  <ddi id="DrugDDI.d462.s22.d0" e1="DrugDDI.d462.s22.e0" e2="DrugDDI.d462.s22.e1" type="advise"/>
</sentence>

-<sentence id="DrugDDI.d1030.s5" origId="s5" text="Indinavir may be taken with a light meal 1 h following the administration of 400 mg of didanosine.">
  <entity id="DrugDDI.d1030.s5.e0" origId="s5.p67" charOffset="0-8" type="drug" text="Indinavir"/>
  <entity id="DrugDDI.d1030.s5.e1" origId="s5.p75" charOffset="87-96" type="drug" text="didanosine"/>
  <ddi id="DrugDDI.d1030.s5.d0" e1="DrugDDI.d1030.s5.e0" e2="DrugDDI.d1030.s5.e1" type="advise"/>
</sentence>

-<sentence id="DrugDDI.d496.s15" origId="s15" text="To avoid this interaction, delavirdine or indinavir should be given 1 hour prior to dosing with VIDEX.">
  <entity id="DrugDDI.d496.s15.e0" origId="s15.p269" charOffset="27-37" type="drug" text="delavirdine"/>
  <entity id="DrugDDI.d496.s15.e1" origId="s15.p271" charOffset="42-50" type="drug" text="indinavir"/>
  <entity id="DrugDDI.d496.s15.e2" origId="s15.p277" charOffset="96-100" type="brand" text="VIDEX"/>
  <ddi id="DrugDDI.d496.s15.d0" e1="DrugDDI.d496.s15.e0" e2="DrugDDI.d496.s15.e2" type="advise"/>
  <ddi id="DrugDDI.d496.s15.d1" e1="DrugDDI.d496.s15.e1" e2="DrugDDI.d496.s15.e2" type="advise"/>
</sentence>
```

Figure 87 Some examples of advice ddis.

4.4 int ddi

In some cases, a sentence may show that there is a drug-drug interaction without providing any additional information. Therefore, those drug-drug interactions that do not provide any information related to the above types (advice, effect, mechanism) should be annotated as 'int'ddi. They usually appear in the titles of abstracts.

```
- <sentence id="DrugDDI.d15.s1" text="Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents.">
  <entity id="DrugDDI.d15.s1.e0" charOffset="11-19" type="drug" text="linezolid"/>
  <entity id="DrugDDI.d15.s1.e1" charOffset="60-69" type="group" text="adrenergic"/>
  <entity id="DrugDDI.d15.s1.e2" charOffset="75-93" type="group" text="serotonergic agents"/>
  <ddi id="DrugDDI.d15.s1.d0" e1="DrugDDI.d15.s1.e0" e2="DrugDDI.d15.s1.e1" type="int"/>
  <ddi id="DrugDDI.d15.s1.d1" e1="DrugDDI.d15.s1.e0" e2="DrugDDI.d15.s1.e2" type="int"/>
</sentence>

- <sentence id="DrugDDI.d29.s9" origId="s9" text="Thus, the interaction observed between erythromycin and terfenadine is not expected for dirithromycin.">
  <entity id="DrugDDI.d29.s9.e0" origId="s9.p105" charOffset="39-50" type="drug" text="erythromycin"/>
  <entity id="DrugDDI.d29.s9.e1" origId="s9.p107" charOffset="56-66" type="drug" text="terfenadine"/>
  <entity id="DrugDDI.d29.s9.e2" origId="s9.p111" charOffset="88-100" type="drug" text="dirithromycin"/>
  <ddi id="DrugDDI.d29.s9.d0" e1="DrugDDI.d29.s9.e0" e2="DrugDDI.d29.s9.e1" type="int"/>
</sentence>

- <sentence id="DrugDDI.d105.s4" origId="s4" text="Beta-adrenergic blocking agents may also interact with sympathomimetics.">
  <entity id="DrugDDI.d105.s4.e0" origId="s4.p38" charOffset="0-30" type="group" text="Beta-adrenergic blocking agents"/>
  <entity id="DrugDDI.d105.s4.e1" origId="s4.p42" charOffset="55-70" type="group" text="sympathomimetics"/>
  <ddi id="DrugDDI.d105.s4.d0" e1="DrugDDI.d105.s4.e0" e2="DrugDDI.d105.s4.e1" type="int"/>
</sentence>

- <sentence id="DrugDDI.d320.s3" text="conversely, diethylpropion may interfere with antihypertensive drugs (i.e., guanethidine, a-methyldopa).">
  <entity id="DrugDDI.d320.s3.e0" charOffset="12-25" type="drug" text="diethylpropion"/>
  <entity id="DrugDDI.d320.s3.e1" charOffset="46-67" type="group" text="antihypertensive drugs"/>
  <entity id="DrugDDI.d320.s3.e2" charOffset="76-87" type="drug" text="guanethidine"/>
  <entity id="DrugDDI.d320.s3.e3" charOffset="90-101" type="drug" text="a-methyldopa"/>
  <ddi id="DrugDDI.d320.s3.d0" e1="DrugDDI.d320.s3.e0" e2="DrugDDI.d320.s3.e1" type="int"/>
  <ddi id="DrugDDI.d320.s3.d1" e1="DrugDDI.d320.s3.e0" e2="DrugDDI.d320.s3.e2" type="int"/>
  <ddi id="DrugDDI.d320.s3.d2" e1="DrugDDI.d320.s3.e0" e2="DrugDDI.d320.s3.e3" type="int"/>
</sentence>
```

Figure 88 Some examples of 'int' ddis

4.5 Special cases

4.5.1 Negated interactions

Although the negation of given drug-drug interactions may be a valuable information to physicians, negated interactions are not included in the annotation.

```
- <sentence id="DrugDDI.d59.s3" origId="s3" text="Clinical studies in healthy volunteers show that the pharmacokinetics of CANCIDAS are not altered by itraconazole, amphotericin B, mycophenolate, neffinavir, or tacrolimus.">
  <entity id="DrugDDI.d59.s3.e0" origId="s3.p31" charOffset="73-80" type="brand" text="CANCIDAS"/>
  <entity id="DrugDDI.d59.s3.e1" origId="s3.p35" charOffset="101-112" type="drug" text="itraconazole"/>
  <entity id="DrugDDI.d59.s3.e2" origId="s3.p36" charOffset="115-128" type="drug" text="amphotericin B"/>
  <entity id="DrugDDI.d59.s3.e3" origId="s3.p37" charOffset="131-143" type="drug" text="mycophenolate"/>
  <entity id="DrugDDI.d59.s3.e4" origId="s3.p38" charOffset="146-155" type="drug" text="neffinavir"/>
  <entity id="DrugDDI.d59.s3.e5" origId="s3.p40" charOffset="161-170" type="drug" text="tacrolimus"/>
</sentence>
```

Figure 89 Negated interactions are not annotated

4.5.2 Possible interactions

A drug interaction should be annotated regardless of the levels of certainty that are shown in the text.

```
-<sentence id="DrugDDI.d463.s9" origId="s9" text="Data from in vitro studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine.">
  <entity id="DrugDDI.d463.s9.e0" origId="s9.p172" charOffset="30-39" type="drug" text="alprazolam"/>
  <entity id="DrugDDI.d463.s9.e1" origId="s9.p175" charOffset="82-91" type="drug" text="alprazolam"/>
  <entity id="DrugDDI.d463.s9.e2" origId="s9.p178" charOffset="112-121" type="drug" text="sertraline"/>
  <entity id="DrugDDI.d463.s9.e3" origId="s9.p180" charOffset="127-136" type="drug" text="paroxetine"/>
  <ddi id="DrugDDI.d463.s9.d0" e1="DrugDDI.d463.s9.e1" e2="DrugDDI.d463.s9.e2" type="int"/>
  <ddi id="DrugDDI.d463.s9.d1" e1="DrugDDI.d463.s9.e1" e2="DrugDDI.d463.s9.e3" type="int"/>
</sentence>

-<sentence id="DrugDDI.d21795430.s2" text="However, the evidence for a calcium effect on iron absorption mainly comes from studies that did not isolate the effect of calcium from that of other dietary components, because it was detected in single-meal studies. ">
  <entity id="DrugDDI.d21795430.s2.e0" charOffset="28-34" type="drug" text="calcium"/>
  <entity id="DrugDDI.d21795430.s2.e1" charOffset="46-49" type="drug" text="iron"/>
  <entity id="DrugDDI.d21795430.s2.e2" charOffset="123-129" type="drug" text="calcium"/>
  <ddi id="DrugDDI.d21795430.s2.d0" e1="DrugDDI.d21795430.s2.e0" e2="DrugDDI.d21795430.s2.e1" type="mechanism"/>
</sentence>

-<sentence id="DrugDDI.d1441.s0" origId="s0" text="Some anticonvulsants may interact with Mephenytoin. ">
  <entity id="DrugDDI.d1441.s0.e0" origId="s0.p0" charOffset="5-19" type="group" text="anticonvulsants"/>
  <entity id="DrugDDI.d1441.s0.e1" origId="s0.p3" charOffset="39-49" type="drug" text="Mephenytoin"/>
  <ddi id="DrugDDI.d1441.s0.d0" e1="DrugDDI.d1441.s0.e0" e2="DrugDDI.d1441.s0.e1" type="int"/>
</sentence>
```

Figure 90 Examples of possible interactions

4.5.3 Beneficial and harmful interactions

A drug interaction should be annotated regardless of its effects are beneficial or harmful.

```
-<sentence id="DrugDDI.d21809690.s5" origId="s5" text="Acute administration of hemantane or doxycycline failed to influence locomotion in mice, while their combination normalized motor activity. ">
  <entity id="DrugDDI.d21809690.s5.e0" origId="" charOffset="24-32" type="drug_n" text="hemantane"/>
  <entity id="DrugDDI.d21809690.s5.e1" origId="s5.p55" charOffset="37-47" type="drug" text="doxycycline"/>
  <ddi id="DrugDDI.d21809690.s5.d0" e1="DrugDDI.d21809690.s5.e0" e2="DrugDDI.d21809690.s5.e1" type="effect"/>
</sentence>

-<sentence id="DrugDDI.d25.s2" origId="s2" text="Gentamicin - Methionine may protect against the ototoxic effects of gentamicin.">
  <entity id="DrugDDI.d25.s2.e0" origId="s2.p17" charOffset="0-9" type="drug" text="Gentamicin"/>
  <entity id="DrugDDI.d25.s2.e1" origId="" charOffset="13-23" type="drug" text="Methionine "/>
  <entity id="DrugDDI.d25.s2.e2" origId="s2.p21" charOffset="68-77" type="drug" text="gentamicin"/>
  <ddi id="DrugDDI.d25.s2.d0" e1="DrugDDI.d25.s2.e1" e2="DrugDDI.d25.s2.e2" type="effect"/>
</sentence>
```

Figure 91 Interactions with beneficial effects

```
-<sentence id="DrugDDI.d21897348.s1" text="The FDA has approved ticagrelor (Brilinta-AstraZeneca), an oral antiplatelet drug, for use with low-dose aspirin to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS). ">
  <entity id="DrugDDI.d21897348.s1.e0" charOffset="21-30" type="drug" text="ticagrelor"/>
  <entity id="DrugDDI.d21897348.s1.e1" charOffset="33-40" type="brand" text="Brilinta"/>
  <entity id="DrugDDI.d21897348.s1.e2" charOffset="64-80" type="group" text="antiplatelet drug"/>
  <entity id="DrugDDI.d21897348.s1.e3" charOffset="105-111" type="brand" text="aspirin"/>
  <ddi id="DrugDDI.d21897348.s1.d0" e1="DrugDDI.d21897348.s1.e0" e2="DrugDDI.d21897348.s1.e3" type="effect"/>
  <ddi id="DrugDDI.d21897348.s1.d1" e1="DrugDDI.d21897348.s1.e1" e2="DrugDDI.d21897348.s1.e3" type="effect"/>
</sentence>
```

Figure 92 Ticagrelor is coadministered with aspirin to reduce the risk of cardiovascular events

```

-<sentence id="DrugDDI.d523.s24" origId="s24" text="However, caution should be used when administering CELEBREX with warfarin since these patients are at increased risk of bleeding complications.">
  <entity id="DrugDDI.d523.s24.e0" origId="s24.p273" charOffset="51-58" type="brand" text="CELEBREX"/>
  <entity id="DrugDDI.d523.s24.e1" origId="s24.p274" charOffset="65-72" type="drug" text="warfarin"/>
  <ddi id="DrugDDI.d523.s24.d0" e1="DrugDDI.d523.s24.e0" e2="DrugDDI.d523.s24.e1" type="advise"/>
</sentence>

```

Figure 93 Interaction with a harmful effect

4.5.4 Contradictory information

In some cases, sentences may contain contradictory information about the same interaction. If the occurrence of an interaction is affirmed, this should be annotated regardless of it may also occur negated in the same sentence.

```

-<sentence id="DrugDDI.d462.s5" origId="s5" text="Although this interaction has not been reported with cinoxacin, caution should be exercised when cinoxacin is given concomitantly with caffeine-containing products.">
  <entity id="DrugDDI.d462.s5.e0" origId="s5.p49" charOffset="53-61" type="drug" text="cinoxacin"/>
  <entity id="DrugDDI.d462.s5.e1" origId="s5.p55" charOffset="97-105" type="drug" text="cinoxacin"/>
  <entity id="DrugDDI.d462.s5.e2" origId="s5.p59" charOffset="135-142" type="drug" text="caffeine"/>
  <ddi id="DrugDDI.d462.s5.d0" e1="DrugDDI.d462.s5.e1" e2="DrugDDI.d462.s5.e2" type="advise"/>
</sentence>

```

Figure 94 There is no previous study that identified this interaction, however caution is recommended.

```

-<sentence id="DrugDDI.d21868520.s8" origId="s8" text="Imexon and dacarbazine show additive effects in vitro but not in vivo in human A375 melanoma cells.">
  <entity id="DrugDDI.d21868520.s8.e0" origId="s8.p84" charOffset="0-5" type="drug" text="Imexon"/>
  <entity id="DrugDDI.d21868520.s8.e1" origId="s8.p86" charOffset="11-21" type="drug" text="dacarbazine"/>
  <ddi id="DrugDDI.d21868520.s8.d0" e1="DrugDDI.d21868520.s8.e0" e2="DrugDDI.d21868520.s8.e1" type="effect"/>
</sentence>

```

Figure 95 This interaction does not have additive effects in vivo. It may not have clinical relevance, but it should be annotated as a ddi

4.5.5 Studies on interactions

A drug-interaction should only be annotated when it occurs in the text. The following sentences show some studies about given interactions were performed, however these sentences do not provide any confirmation. Therefore, these possible interactions should not be annotated.

```

-<sentence id="DrugDDI.d1107.s1" origId="s1" text="The interaction of prostaglandin F2alpha and synthetic oxytocin on placental vessels was studied in vitro. ">
  <entity id="DrugDDI.d1107.s1.e0" origId="s1.p6" charOffset="19-39" type="drug" text="prostaglandin F2alpha"/>
  <entity id="DrugDDI.d1107.s1.e1" origId="s1.p8" charOffset="55-62" type="drug" text="oxytocin"/>
</sentence>

```

Figure 96 Althoug the drug interaction has been study, this sentence do not provide any information about if it really occurs, so it should not be annotated.

4.5.6 Drug incompatibility

Drug incompatibility can be defined as an undesirable reaction that occurs between the drug and the solution, container or another drug. The main difference between drug interaction and drug incompatibility is that the interaction occurs inside the body and cannot be seen, while the drug incompatibility is usually visible. An example is the chemical precipitation of *midazolam* as a result of an unfavorable pH medium. These reactions are not considered as interactions, and thereby, they should not be annotated.

```
-<sentence id="DrugDDI.d21753875.s0" origId="s0" text="Improvement of colchicine oral bioavailability by incorporating eugenol in the nanoemulsion as an oil excipient and enhancer.">
  <entity id="DrugDDI.d21753875.s0.e0" origId="" charOffset="15-24" type="drug" text="colchicine"/>
  <entity id="DrugDDI.d21753875.s0.e1" origId="s0.p2" charOffset="64-70" type="drug" text="eugenol"/>
</sentence>
```

Figure 97 There is no interaction between colchicine and eugenol because it acts like an excipient

However, drug interactions based on in vitro or ex vivo studies should be annotated.

```
-<sentence id="DrugDDI.d40.s2" origId="s2" text="Antagonism has been demonstrated between clindamycin and erythromycin in vitro.">
  <entity id="DrugDDI.d40.s2.e0" origId="s2.p25" charOffset="41-51" type="drug" text="clindamycin"/>
  <entity id="DrugDDI.d40.s2.e1" origId="s2.p27" charOffset="57-68" type="drug" text="erythromycin"/>
  <ddi id="DrugDDI.d40.s2.d0" e1="DrugDDI.d40.s2.e0" e2="DrugDDI.d40.s2.e1" type="effect"/>
</sentence>
```

Figure 98 Drug interactions based on in vitro and ex vivo studies should be annotated

4.5.7 Drug-protein interactions

The identification of interactions between drugs and proteins is a key area in drug discovery. However, these interactions are out of the scope of this corpus, and they are not included in the annotation.

```
-<sentence id="DrugDDI.d80.s5" origId="s5" text="Ketoconazole: Sensipar is metabolized in part by CYP3A4.">
  <entity id="DrugDDI.d80.s5.e0" origId="s5.p74" charOffset="0-11" type="drug" text="Ketoconazole"/>
  <entity id="DrugDDI.d80.s5.e1" origId="s5.p76" charOffset="14-21" type="brand" text="Sensipar"/>
</sentence>
```

Figure 99 Drug-protein interactions are not annotated

4.5.8 Abbreviations

As it was explained (section 3.1.3) abbreviations and acronyms that occur in the middle of a mention should be included in the annotation of that entity. However, if the abbreviation (or acronym) occurs just after a mention, it should be annotated as an independent entity. Similarly, if a sentence contains an interaction involving an entity whose acronym (or abbreviation) also appears just after it, annotators should add a new interaction involving this acronym. Figure 100 and Figure 102 contain some examples.

```

- <sentence id="DrugDDI.d249.s14" text="Certain drugs, including nonsteroidal anti-inflammatory agents (NSAIDs), salicylates, monoamine oxidase inhibitors, and non-selective beta-adrenergic-blocking agents may potentiate the hypoglycemic action of Starlix and other oral antidiabetic drugs.">
  <entity id="DrugDDI.d249.s14.e0" charOffset="25-61" type="group" text="nonsteroidal anti-inflammatory agents"/>
  <entity id="DrugDDI.d249.s14.e1" charOffset="64-69" type="group" text="NSAIDs"/>
  <entity id="DrugDDI.d249.s14.e2" charOffset="73-83" type="group" text="salicylates"/>
  <entity id="DrugDDI.d249.s14.e3" charOffset="86-113" type="group" text="monoamine oxidase inhibitors"/>
  <entity id="DrugDDI.d249.s14.e4" charOffset="120-164" type="group" text="non-selective beta-adrenergic-blocking agents"/>
  <entity id="DrugDDI.d249.s14.e5" charOffset="208-214" type="brand" text="Starlix"/>
  <entity id="DrugDDI.d249.s14.e6" charOffset="231-248" type="group" text="antidiabetic drugs"/>
  <ddi id="DrugDDI.d249.s14.d0" e1="DrugDDI.d249.s14.e0" e2="DrugDDI.d249.s14.e5" type="effect"/>
  <ddi id="DrugDDI.d249.s14.d1" e1="DrugDDI.d249.s14.e1" e2="DrugDDI.d249.s14.e5" type="effect"/>
  <ddi id="DrugDDI.d249.s14.d2" e1="DrugDDI.d249.s14.e2" e2="DrugDDI.d249.s14.e5" type="effect"/>
  <ddi id="DrugDDI.d249.s14.d3" e1="DrugDDI.d249.s14.e3" e2="DrugDDI.d249.s14.e5" type="effect"/>
  <ddi id="DrugDDI.d249.s14.d4" e1="DrugDDI.d249.s14.e4" e2="DrugDDI.d249.s14.e5" type="effect"/>
  <ddi id="DrugDDI.d249.s14.d5" e1="DrugDDI.d249.s14.e0" e2="DrugDDI.d249.s14.e6" type="effect"/>
  <ddi id="DrugDDI.d249.s14.d6" e1="DrugDDI.d249.s14.e1" e2="DrugDDI.d249.s14.e6" type="effect"/>
  <ddi id="DrugDDI.d249.s14.d7" e1="DrugDDI.d249.s14.e2" e2="DrugDDI.d249.s14.e6" type="effect"/>
  <ddi id="DrugDDI.d249.s14.d8" e1="DrugDDI.d249.s14.e3" e2="DrugDDI.d249.s14.e6" type="effect"/>
  <ddi id="DrugDDI.d249.s14.d9" e1="DrugDDI.d249.s14.e4" e2="DrugDDI.d249.s14.e6" type="effect"/>
</sentence>
```

Figure 100 Two different interactions were annotated between Starlix (e5) y nonsteroidal anti-inflammatory agents (e0) and its acronym (e1) (although they are the same interaction).

4.5.9 Titles

In this corpus, it is very common to find sentences that begin with a mention of any of the entity types followed by dot-point. Normally, the text after the dot-point is a shorter and well-formed sub-subsentence that describes an interaction (see Figure 101).

```

- <sentence id="DrugDDI.d523.s9" text="ACE inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors.">
  <entity id="DrugDDI.d523.s9.e0" charOffset="0-13" type="group" text="ACE inhibitors"/>
  <entity id="DrugDDI.d523.s9.e1" charOffset="37-42" type="group" text="NSAIDs"/>
  <entity id="DrugDDI.d523.s9.e2" charOffset="88-133" type="group" text="Angiotensin Converting Enzyme (ACE) inhibitors"/>
  <ddi id="DrugDDI.d523.s9.d0" e1="DrugDDI.d523.s9.e1" e2="DrugDDI.d523.s9.e2" type="effect"/>
</sentence>
- <sentence id="DrugDDI.d38.s1" text="Aspirin: Concomitant aspirin may decrease the metabolic clearance of nicotinic acid.">
  <entity id="DrugDDI.d38.s1.e0" charOffset="0-6" type="brand" text="Aspirin"/>
  <entity id="DrugDDI.d38.s1.e1" charOffset="21-27" type="brand" text="aspirin"/>
  <entity id="DrugDDI.d38.s1.e2" charOffset="69-82" type="drug" text="nicotinic acid"/>
  <ddi id="DrugDDI.d38.s1.d0" e1="DrugDDI.d38.s1.e1" e2="DrugDDI.d38.s1.e2" type="mechanism"/>
</sentence>
```

Figure 101 These sentences include a title (an entity name followed by a dot-point) and a well-formed subsentence containing an interaction.

However, sometimes the text of the title is the subject of the sub-sentence. In these cases, the entities in the title are usually involved in the interactions described in the sub-sentence. For example, the title of the sentence shown in Figure 102 is the subject of the sub-sentence. Also, the entities contained in the title ('Corticosteroids' and 'Corticotropin') are involved in the interactions described in the sentence, and thereby, are annotated as interacting drugs. Note that the abbreviation of 'Corticotropin', ACTH, is annotated as an independent entity, and also, annotators added an interaction (d2) involving it.

```

- <sentence id="DrugDDI.d23.s2" text="Corticosteroids and Corticotropin (ACTH): may potentiate amphotericin B-induced hypokalemia which may predispose the patient to cardiac dysfunction.">
  <entity id="DrugDDI.d23.s2.e0" charOffset="0-14" type="group" text="Corticosteroids"/>
  <entity id="DrugDDI.d23.s2.e1" charOffset="20-32" type="drug" text="Corticotropin"/>
  <entity id="DrugDDI.d23.s2.e2" charOffset="35-38" type="group" text="ACTH"/>
  <entity id="DrugDDI.d23.s2.e3" charOffset="57-70" type="drug" text="amphotericin B"/>
  <ddi id="DrugDDI.d23.s2.d0" e1="DrugDDI.d23.s2.e0" e2="DrugDDI.d23.s2.e3" type="effect"/>
  <ddi id="DrugDDI.d23.s2.d1" e1="DrugDDI.d23.s2.e1" e2="DrugDDI.d23.s2.e3" type="effect"/>
  <ddi id="DrugDDI.d23.s2.d2" e1="DrugDDI.d23.s2.e2" e2="DrugDDI.d23.s2.e3" type="effect"/>
</sentence>
```

Figure 102The title is the subject of the sub-sentence

4.5.10 Interactions involving hypernymc propositions

A hypernymic proposition represents a taxonomic relation between a hyponym and a hypernym. Hypernymic propositions, in particular appositive structures, consisting of several entities are very common in our texts. The following sentence contains two appositive structures: ‘Quinilones, including cinoxacin’ and ‘oral anticoagulants, such as warfarin or its derivates’.

```

- <sentence id="DrugDDI.d462.s8" origId="s8" text="Quinilones, including cinoxacin, may enhance the effects of oral anticoagulants, such as warfarin or its derivatives.">
  <entity id="DrugDDI.d462.s8.e0" origId="s8.p90" charOffset="0-9" type="group" text="Quinilones"/>
  <entity id="DrugDDI.d462.s8.e1" origId="s8.p92" charOffset="22-30" type="drug" text="cinoxacin"/>
  <entity id="DrugDDI.d462.s8.e2" origId="s8.p96" charOffset="65-78" type="group" text="anticoagulants"/>
  <entity id="DrugDDI.d462.s8.e3" origId="s8.p97" charOffset="89-96" type="drug" text="warfarin"/>
  <ddi id="DrugDDI.d462.s8.d0" e1="DrugDDI.d462.s8.e0" e2="DrugDDI.d462.s8.e2" type="effect"/>
  <ddi id="DrugDDI.d462.s8.d1" e1="DrugDDI.d462.s8.e0" e2="DrugDDI.d462.s8.e3" type="effect"/>
  <ddi id="DrugDDI.d462.s8.d2" e1="DrugDDI.d462.s8.e1" e2="DrugDDI.d462.s8.e2" type="effect"/>
  <ddi id="DrugDDI.d462.s8.d3" e1="DrugDDI.d462.s8.e1" e2="DrugDDI.d462.s8.e3" type="effect"/>
</sentence>
```

Figure 103 Example of appositive structures that are involved in interactions

If there is some interaction involving the entities described in the appositive interaction, then both its hypernym and its hyponyms should be annotated as interacting entities, and thereby, an interaction for each of them should be added (seeFigure 104).

```

- <sentence id="DrugDDI.d131.s4" text="The effects of adenosine are antagonized by methylxanthines such as caffeine and theophylline.">
  <entity id="DrugDDI.d131.s4.e0" charOffset="15-23" type="drug" text="adenosine"/>
  <entity id="DrugDDI.d131.s4.e1" charOffset="44-58" type="group" text="methylxanthines"/>
  <entity id="DrugDDI.d131.s4.e2" charOffset="68-75" type="drug" text="caffeine"/>
  <entity id="DrugDDI.d131.s4.e3" charOffset="81-92" type="drug" text="theophylline"/>
  <ddi id="DrugDDI.d131.s4.d0" e1="DrugDDI.d131.s4.e0" e2="DrugDDI.d131.s4.e1" type="effect"/>
  <ddi id="DrugDDI.d131.s4.d1" e1="DrugDDI.d131.s4.e0" e2="DrugDDI.d131.s4.e2" type="effect"/>
  <ddi id="DrugDDI.d131.s4.d2" e1="DrugDDI.d131.s4.e0" e2="DrugDDI.d131.s4.e3" type="effect"/>
</sentence>
```

Figure 104Bothhypernym and hyonyms should be annotated as interacting drugs.

However, in some appositive structures, the scope of the interaction only remains the hyponym and not the hypernym.

```

- <sentence id="DrugDDI.d1225.s3" text="In addition to this pharmacological interaction, this report describes a novel chemical reaction between temazepam (a benzodiazepine) and ethanol under acidic conditions similar to those found in vivo, resulting in a 3-ethoxylated product. ">
  <entity id="DrugDDI.d1225.s3.e0" charOffset="105-113" type="drug" text="temazepam"/>
  <entity id="DrugDDI.d1225.s3.e1" charOffset="132-145" type="group" text="benzodiazepine"/>
  <entity id="DrugDDI.d1225.s3.e2" charOffset="152-158" type="drug" text="ethanol"/>
  <ddi id="DrugDDI.d1225.s3.d0" e1="DrugDDI.d1225.s3.e0" e2="DrugDDI.d1225.s3.e2" type="mechanism"/>
</sentence>
```

Figure 105 ‘benzodiazepine’ should not be annotated as an interacting drug

```

- <sentence id="DrugDDI.d240.s14" text="Antacids: In a single dose study (n=6), ingestion of an antacid containing 1.7-gram of magnesium hydroxide with 500-mg of mefenamic acid increased the Cmax and AUC of mefenamic acid by 125% and 36%, respectively. A number of compounds are inhibitors of CYP2C9 including fluconazole, lovastatin and trimethoprim.">
  <entity id="DrugDDI.d240.s14.e0" charOffset="0-7" type="group" text="Antacids"/>
  <entity id="DrugDDI.d240.s14.e1" charOffset="56-62" type="group" text="antacid"/>
  <entity id="DrugDDI.d240.s14.e2" charOffset="87-105" type="drug" text="magnesium hydroxide"/>
  <entity id="DrugDDI.d240.s14.e3" charOffset="122-135" type="drug" text="mefenamic acid"/>
  <entity id="DrugDDI.d240.s14.e4" charOffset="167-180" type="drug" text="mefenamic acid"/>
  <entity id="DrugDDI.d240.s14.e5" charOffset="271-281" type="drug" text="fluconazole"/>
  <entity id="DrugDDI.d240.s14.e6" charOffset="284-293" type="drug" text="lovastatin"/>
  <entity id="DrugDDI.d240.s14.e7" charOffset="299-310" type="drug" text="trimethoprim"/>
  <ddi id="DrugDDI.d240.s14.d0" e1="DrugDDI.d240.s14.e2" e2="DrugDDI.d240.s14.e3" type="mechanism"/>
</sentence>
```

Figure 106 ‘antacid’ should not be annotated as an interacting drug.

4.5.11 Annotation rules for interacting drugs

Some interactions involve drugs that are mentioned multiple times in a sentence. When there are multiple mentions of the same entity, it may not be obvious to decide what pair of mentions should be annotated as interacting drugs. In these cases, annotators should only annotate as interacting drugs the pair of mentions most logically linked with the textual evidence of the interaction.

```

- <sentence id="DrugDDI.d463.s9" origId="s9" text="Data from in vitro studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine.">
  <entity id="DrugDDI.d463.s9.e0" origId="s9.p172" charOffset="30-39" type="drug" text="alprazolam"/>
  <entity id="DrugDDI.d463.s9.e1" origId="s9.p175" charOffset="82-91" type="drug" text="alprazolam"/>
  <entity id="DrugDDI.d463.s9.e2" origId="s9.p178" charOffset="112-121" type="drug" text="sertraline"/>
  <entity id="DrugDDI.d463.s9.e3" origId="s9.p180" charOffset="127-136" type="drug" text="paroxetine"/>
  <ddi id="DrugDDI.d463.s9.d0" e1="DrugDDI.d463.s9.e1" e2="DrugDDI.d463.s9.e2" type="int"/>
  <ddi id="DrugDDI.d463.s9.d1" e1="DrugDDI.d463.s9.e1" e2="DrugDDI.d463.s9.e3" type="int"/>
</sentence>
```

Figure 107 The second mention of ‘alprazolam’ is most logically linked with the textual evidence of the interaction.

Figure 108 contains a sentence with two mentions of ‘methotrexate’ and three different interactions with ‘methotrexate’. Annotators decided to annotate only the first mention of ‘methotrexate’ as an interacting drug. Although the text ‘possibly increasing the toxicity of methotrexate’, which is a consequence of the previous interaction, also seems to indicate an interaction, however its mention of ‘methotrexate’ it is not annotated as interacting drug, while the previous mention of ‘methotrexate’ is annotated by its proximity to the other drugs.

```

- <sentence id="DrugDDI.d159.s12" origId="s12" text="Naproxen, naproxen sodium and other NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model, possibly increasing the toxicity of methotrexate.">
  <entity id="DrugDDI.d159.s12.e0" origId="s12.p128" charOffset="0-7" type="drug" text="Naproxen"/>
  <entity id="DrugDDI.d159.s12.e1" origId="s12.p129" charOffset="10-24" type="drug" text="naproxen sodium"/>
  <entity id="DrugDDI.d159.s12.e2" origId="s12.p131" charOffset="36-41" type="group" text="NSAIDs"/>
  <entity id="DrugDDI.d159.s12.e3" origId="s12.p138" charOffset="97-108" type="drug" text="methotrexate"/>
  <entity id="DrugDDI.d159.s12.e4" origId="s12.p143" charOffset="166-177" type="drug" text="methotrexate"/>
  <ddi id="DrugDDI.d159.s12.d0" e1="DrugDDI.d159.s12.e0" e2="DrugDDI.d159.s12.e3" type="mechanism"/>
  <ddi id="DrugDDI.d159.s12.d1" e1="DrugDDI.d159.s12.e1" e2="DrugDDI.d159.s12.e3" type="mechanism"/>
  <ddi id="DrugDDI.d159.s12.d2" e1="DrugDDI.d159.s12.e2" e2="DrugDDI.d159.s12.e3" type="mechanism"/>
</sentence>
```

Figure 108 Only the first mention of ‘methotrexate’ should be annotated as an interacting drug, since the second mention is in an independent sentence.

Normally, those mentions that occur in phrases such as “coadministration of X and/with Y”, “concomitant administration of X and Y”, “X during therapy with Y” or “When X was administered with Y” should be annotated as the pair of interacting substances.

```

- <sentence id="DrugDDI.d54.s4" origId="s4" text="Aspirin: Concomitant administration of aspirin with valdecoxib may result in an increased risk of GI ulceration and complications compared to valdecoxib alone.">
  <entity id="DrugDDI.d54.s4.e0" origId="s4.p81" charOffset="0-6" type="brand" text="Aspirin"/>
  <entity id="DrugDDI.d54.s4.e1" origId="s4.p84" charOffset="39-45" type="brand" text="aspirin"/>
  <entity id="DrugDDI.d54.s4.e2" origId="s4.p85" charOffset="52-61" type="drug" text="valdecoxib"/>
  <entity id="DrugDDI.d54.s4.e3" origId="s4.p94" charOffset="142-151" type="drug" text="valdecoxib"/>
  <ddi id="DrugDDI.d54.s4.d0" e1="DrugDDI.d54.s4.e1" e2="DrugDDI.d54.s4.e2" type="effect"/>
</sentence>

- <sentence id="DrugDDI.d53.s2" origId="s2" text="Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.">
  <entity id="DrugDDI.d53.s2.e0" origId="s2.p14" charOffset="29-43" type="drug" text="oxyphenbutazone"/>
  <entity id="DrugDDI.d53.s2.e1" origId="s2.p16" charOffset="49-57" type="group" text="androgens"/>
  <entity id="DrugDDI.d53.s2.e2" origId="s2.p20" charOffset="98-112" type="drug" text="oxyphenbutazone"/>
  <ddi id="DrugDDI.d53.s2.d0" e1="DrugDDI.d53.s2.e0" e2="DrugDDI.d53.s2.e1" type="mechanism"/>
</sentence>

- <sentence id="DrugDDI.d54.s33" origId="s33" text="Coadministration of valdecoxib (40 mg BID (day 1) and 40 mg QD (days 2-7)) with glyburide (10 mg glyburide BID) resulted in 21% increase in glyburide AUC0-12 and a 16% increase in glyburide Cmax leading to a 16% decrease in glucose AUC0-24.">
  <entity id="DrugDDI.d54.s33.e0" origId="s33.p486" charOffset="20-29" type="drug" text="valdecoxib"/>
  <entity id="DrugDDI.d54.s33.e1" origId="s33.p498" charOffset="80-88" type="drug" text="glyburide"/>
  <entity id="DrugDDI.d54.s33.e2" origId="s33.p500" charOffset="97-105" type="drug" text="glyburide"/>
  <entity id="DrugDDI.d54.s33.e3" origId="s33.p504" charOffset="140-148" type="drug" text="glyburide"/>
  <entity id="DrugDDI.d54.s33.e4" origId="s33.p507" charOffset="180-188" type="drug" text="glyburide"/>
  <ddi id="DrugDDI.d54.s33.d0" e1="DrugDDI.d54.s33.e0" e2="DrugDDI.d54.s33.e1" type="mechanism"/>
</sentence>

```

Figure 109 If a sentence asserts an interaction, entities mentioned in phrases such as ‘concurrent administration of X and Y’ should be considered as the pair of interacting drugs.

However, sometimes these phrases (meaning coadministration) are part of compound sentences that contain simpler sentences describing interactions. When a phrase of this type is followed by a simpler sentence that asserts an interaction between two drugs contained in it, this pair of drugs should be annotated as the pair of interacting drugs.

```

- <sentence id="DrugDDI.d124.s0" origId="s0" text="When ertapenem is co-administered with probenecid (500 mg p.o. every 6 hours), probenecid competes for active tubular secretion and reduces the renal clearance of ertapenem.">
  <entity id="DrugDDI.d124.s0.e0" origId="s0.p1" charOffset="5-13" type="drug" text="ertapenem"/>
  <entity id="DrugDDI.d124.s0.e1" origId="s0.p4" charOffset="39-48" type="drug" text="probenecid"/>
  <entity id="DrugDDI.d124.s0.e2" origId="s0.p9" charOffset="79-88" type="drug" text="probenecid"/>
  <entity id="DrugDDI.d124.s0.e3" origId="s0.p14" charOffset="163-171" type="drug" text="ertapenem"/>
  <ddi id="DrugDDI.d124.s0.d0" e1="DrugDDI.d124.s0.e2" e2="DrugDDI.d124.s0.e3" type="mechanism"/>
</sentence>

```

Figure 110 Although the first mention of drugs ‘ertapenem’ and ‘probenecid’ indicates a coadministration, the second pair of entities must be chose as the interacting drug pair.

Biomedical texts usually consist of extremely long sentences, which are usually complex or compound-complex sentences (with two or more clauses). In some cases, compound sentences can be divided into simpler sentences describing different interactions, or even, different occurrences of the same interaction. In these cases, annotators decided to consider each occurrence as a different interaction. The following figure shows a compound sentence that can be divided into two simple sentences, each of them describes an interaction between ‘erythromycin’ and ‘trialozam’ (though the interaction is the same).

```

- <sentence id="DrugDDI.d29.s19" text="Triazolam: Erythromycin has been reported to decrease the clearance of triazolam and, thus, may increase the pharmacologic effect of triazolam.">
  <entity id="DrugDDI.d29.s19.e0" charOffset="0-8" type="drug" text="Triazolam"/>
  <entity id="DrugDDI.d29.s19.e1" charOffset="11-22" type="drug" text="Erythromycin"/>
  <entity id="DrugDDI.d29.s19.e2" charOffset="71-79" type="drug" text="triazolam"/>
  <entity id="DrugDDI.d29.s19.e3" charOffset="133-141" type="drug" text="triazolam"/>
  <ddi id="DrugDDI.d29.s19.d0" e1="DrugDDI.d29.s19.e1" e2="DrugDDI.d29.s19.e2" type="mechanism"/>
  <ddi id="DrugDDI.d29.s19.d1" e1="DrugDDI.d29.s19.e1" e2="DrugDDI.d29.s19.e3" type="effect"/>
</sentence>
```

Figure 111This sentence describes an interaction and its subsequent effect.

Also, in the first example above (Figure 111), the first simple sentence describes the mechanism of the interaction, while the second one describes its subsequent effect. In the following example (Figure 112), the simpler sentences describe the same interaction but provide different information of the same interaction.

```

- <sentence id="DrugDDI.d444.s15" text="Probenecid: Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in serum.">
  <entity id="DrugDDI.d444.s15.e0" charOffset="0-9" type="drug" text="Probenecid"/>
  <entity id="DrugDDI.d444.s15.e1" charOffset="12-21" type="drug" text="Probenecid"/>
  <entity id="DrugDDI.d444.s15.e2" charOffset="66-78" type="drug" text="ciprofloxacin"/>
  <entity id="DrugDDI.d444.s15.e3" charOffset="121-133" type="drug" text="ciprofloxacin"/>
  <ddi id="DrugDDI.d444.s15.d0" e1="DrugDDI.d444.s15.e1" e2="DrugDDI.d444.s15.e2" type="mechanism"/>
  <ddi id="DrugDDI.d444.s15.d1" e1="DrugDDI.d444.s15.e1" e2="DrugDDI.d444.s15.e3" type="mechanism"/>
</sentence>
```

Figure 112 Simple sentences describing interactions should be considered as independent sentences. All occurrences of interactions should be annotated.

```

- <sentence id="DrugDDI.d561.s9" origId="s9" text="Antacids: In a clinical pharmacology study, coadministration of an antacid (aluminum hydroxide, magnesium hydroxide, and simethicone) with fosinopril reduced serum levels and urinary excretion of fosinoprilat as compared with fosinopril administered alone, suggesting that antacids may impair absorption of fosinopril.">
  <entity id="DrugDDI.d561.s9.e0" origId="s9.p131" charOffset="0-7" type="group" text="Antacids"/>
  <entity id="DrugDDI.d561.s9.e1" origId="s9.p135" charOffset="67-73" type="group" text="antacid"/>
  <entity id="DrugDDI.d561.s9.e2" origId="s9.p137" charOffset="76-93" type="drug" text="aluminum hydroxide"/>
  <entity id="DrugDDI.d561.s9.e3" origId="s9.p138" charOffset="96-114" type="drug" text="magnesium hydroxide"/>
  <entity id="DrugDDI.d561.s9.e4" origId="s9.p140" charOffset="121-131" type="drug" text="simethicone"/>
  <entity id="DrugDDI.d561.s9.e5" origId="s9.p142" charOffset="139-148" type="drug" text="fisinopril"/>
  <entity id="DrugDDI.d561.s9.e6" origId="s9.p147" charOffset="196-207" type="drug_n" text="fisinoprilat"/>
  <entity id="DrugDDI.d561.s9.e7" origId="s9.p150" charOffset="226-235" type="drug" text="fisinopril"/>
  <entity id="DrugDDI.d561.s9.e8" origId="s9.p154" charOffset="273-280" type="group" text="antacids"/>
  <entity id="DrugDDI.d561.s9.e9" origId="s9.p158" charOffset="307-316" type="drug" text="fisinopril"/>
  <ddi id="DrugDDI.d561.s9.d0" e1="DrugDDI.d561.s9.e1" e2="DrugDDI.d561.s9.e5" type="mechanism"/>
  <ddi id="DrugDDI.d561.s9.d1" e1="DrugDDI.d561.s9.e2" e2="DrugDDI.d561.s9.e5" type="mechanism"/>
  <ddi id="DrugDDI.d561.s9.d2" e1="DrugDDI.d561.s9.e3" e2="DrugDDI.d561.s9.e5" type="mechanism"/>
  <ddi id="DrugDDI.d561.s9.d3" e1="DrugDDI.d561.s9.e4" e2="DrugDDI.d561.s9.e5" type="mechanism"/>
  <ddi id="DrugDDI.d561.s9.d4" e1="DrugDDI.d561.s9.e8" e2="DrugDDI.d561.s9.e9" type="mechanism"/>
</sentence>
```

Figure 113Note that the pair (antacids, fosinopril) (at the end of the sentence) was annotated as an interaction. This is due to the sentence can be divided in two sentences.

```

- <sentence id="DrugDDI.d66.s20" origId="s20" text="Chlorpropamide: Chlorpropamide plasma half-life may be prolonged by allopurinol, since allopurinol and chlorpropamide may compete for excretion in the renal tubule.">
  <entity id="DrugDDI.d66.s20.e0" origId="s20.p334" charOffset="0-13" type="drug" text="Chlorpropamide"/>
  <entity id="DrugDDI.d66.s20.e1" origId="s20.p336" charOffset="16-29" type="drug" text="Chlorpropamide"/>
  <entity id="DrugDDI.d66.s20.e2" origId="s20.p342" charOffset="69-79" type="drug" text="allopurinol"/>
  <entity id="DrugDDI.d66.s20.e3" origId="s20.p344" charOffset="88-98" type="drug" text="allopurinol"/>
  <entity id="DrugDDI.d66.s20.e4" origId="s20.p346" charOffset="104-117" type="drug" text="chlorpropamide"/>
  <ddi id="DrugDDI.d66.s20.d0" e1="DrugDDI.d66.s20.e1" e2="DrugDDI.d66.s20.e2" type="mechanism"/>
  <ddi id="DrugDDI.d66.s20.d1" e1="DrugDDI.d66.s20.e3" e2="DrugDDI.d66.s20.e4" type="mechanism"/>
</sentence>
```

Figure 114In a compound sentence, each interaction described in its simple sentences should be annotated.

Sometimes it is not obvious to decide the type of the interaction because the sentence provides different information about the same interaction. The following sentence (Figure 115)

asserts an interaction and provides clues indicating that this interaction may be classified as ‘mechanism’ (‘increased theophylline levels’) as well as ‘effect’ (‘theophylline toxicity’). In order to reduce the difficulty level of the task, we decided only to annotate a type for each interaction. If an interaction may be classified with several types, the following priority order should be applied: (1) mechanism, (2) effect, (3) advice.

```
- <sentence id="DrugDDI.d1378.s2" text="Concomitant administration of TRENTAL and theophylline-containing drugs leads to increased theophylline levels and theophylline toxicity in some individuals.">
  <entity id="DrugDDI.d1378.s2.e0" charOffset="30-36" type="brand" text="TRENTAL"/>
  <entity id="DrugDDI.d1378.s2.e1" charOffset="42-53" type="drug" text="theophylline"/>
  <entity id="DrugDDI.d1378.s2.e2" charOffset="91-102" type="drug" text="theophylline"/>
  <entity id="DrugDDI.d1378.s2.e3" charOffset="115-126" type="drug" text="theophylline"/>
  <ddi id="DrugDDI.d1378.s2.d0" e1="DrugDDI.d1378.s2.e0" e2="DrugDDI.d1378.s2.e1" type="mechanism"/>
</sentence>
```

Figure 115When an interaction may be classified with several types, annotator should apply the following priority order: mechanism -> effect ->advice.

However, when a phrase containing a pair of interacting entities is followed by a simpler sentence describing a different type of information, annotator should annotate the type of interaction described in the phrase containing the pair of interacting drugs.

```
- <sentence id="DrugDDI.d85.s0" text="Cevimeline should be administered with caution to patients taking beta adrenergic antagonists, because of the possibility of conduction disturbances.">
  <entity id="DrugDDI.d85.s0.e0" charOffset="0-9" type="drug" text="Cevimeline"/>
  <entity id="DrugDDI.d85.s0.e1" charOffset="66-92" type="group" text="beta adrenergic antagonists"/>
  <ddi id="DrugDDI.d85.s0.d0" e1="DrugDDI.d85.s0.e0" e2="DrugDDI.d85.s0.e1" type="advise"/>
</sentence>
```

Figure 116Although the effect of the interaction is described at the end of the sentence, annotators should assigned the type ‘advice’.

5 Appendix

5.1 Introduction:

This appendix includes several terms that can be helpful for a better comprehension of texts about drug-drug interactions. These terms were chosen for their relevance and frequent occurrence in the texts within the DrugDDI Corpus. Therefore, it should be noted that it does not include the entire vocabulary that can be used to describe drug interactions.

Each term is described by a definition, which has been selected or adapted from various sources (see bibliography) in function of the objectives of this corpus, and a number of examples of simple sentences similar to those that can appear in the texts of the corpus. Sometimes, several lexical patterns describing events and relations concerning these terms are given. Similarly, these examples do not cover all possibilities and can appear other sentences. In some cases, a section of synonyms and other related terms is also included.

5.2 Pharmacokinetic vocabulary:

PHARMACOKINETICS
Some synonyms and related terms: http://www.ncbi.nlm.nih.gov/mesh/68010599
Definition: Pharmacokinetics refers to the study of absorption, distribution, metabolism and excretion (ADME) of bioactive compounds in a higher organism.
Some ways PHARMACOKINETICS can be described: <i>The pharmacokinetic parameters of X were altered when mixed with Y.</i> <i>The pharmacokinetic interactions listed below are [...]</i> <i>X's pharmacokinetics are affected by Y.</i>
<i>Note: X and Y are drug substances (generic drugs, brand drugs, group of drugs and substances not approved for human use)</i>

ABSORPTION
Some synonyms and related terms: http://www.ncbi.nlm.nih.gov/mesh/68000042
Definition: Drug absorption is the movement of the drug from its site of administration into the bloodstream.
Some ways ABSORPTION can be described: <i>X appears to interfere with the absorption of Y.</i> <i>X slows the intestinal absorption of Y.</i> <i>X causes a 60% reduction in the absorption of Y.</i> <i>X reduced the apparent rate of absorption of Y.</i>

AREA UNDER THE CURVE

Some synonyms and related terms:

AUC

AUMC

Area Under the Moment Curve

<http://www.ncbi.nlm.nih.gov/mesh?term=area%20under%20curve>

Definition: Area between a curve and the horizontal axis, i.e., the area underneath the graph of a function: often, the area under the tissue (plasma) concentration curve of a substance expressed as a function of time.

Some ways AREA UNDER THE CURVE can be described:

X increased the AUC of Y.

X decreased Y steady-state AUC by an average of 82%.

BIOAVAILABILITY

Some synonyms and related terms:

biological availability

physiological availability

<http://www.ncbi.nlm.nih.gov/mesh?term=Bioavailability>

Definition: The extent to which the active ingredient of a drug dosage form becomes available at the site of drug action or in a biological medium believed to reflect accessibility to a site of action.

Some ways BIOAVAILABILITY can be described:

The bioavailability of X was reduced by Y.

X affects the biological availability of Y.

The oral bioavailability of X is decreased 80% by Y.

HALF LIFE

Some synonyms and related terms:

$t_{1/2}$

<http://www.ncbi.nlm.nih.gov/mesh?term=HALF%20LIFE>

Definition: For a substance, the time required for the amount of that substance in a biological system to be reduced to one half of its value by biological processes, when the rate of removal is approximately exponential.

Some ways HALF LIFE can be described:

X has been shown to shorten serum half-life of Y.

X elimination half life was increased by 29%.

CONCENTRATION

Some synonyms and related terms:

Level

Drug exposure

Definition: The amount of drug in a given volume.

Some ways CONCENTRATION can be described:

The steady-state plasma concentrations of X were increased.

The plasma levels of X were decreased.

*Serum levels of X must be monitorized.
20% increase in steady-state plasma concentrations of Y.
X may significantly decrease exposure to Y.*

MAXIMUM CONCENTRATION

Some synonyms and related terms:

Cmax

Peak concentration

Definition: Observed maximum plasma or serum concentration after administration.⁸

Some ways MAXIMUM CONCENTRATION can be described:

X has been shown to increase Cmax of Y.

X mean cmax was increased 11-fold.

Mean X Cmax was significantly affected.

Co-administration of X with Y resulted in increases in Y peak plasma levels of 42%

STEADY-STATE

Some synonyms and related terms:

ss

Definition: State of a system in which the conditions do not change in time.

Some ways STEADY-STATE can be described:

Steady state plasma exposure (AUC) of X was decreased by 27% when co-administered with Y.

DISTRIBUTION

Definition: The movement of drug from the blood into the tissue.

Some ways DISTRIBUTION can be described:

See Distribution Volume

DISTRIBUTION VOLUME

Some synonyms and related terms:

V

Vd

Definition: Theoretical volume of a body compartment throughout which a substance is calculated to be distributed.

Some ways DISTRIBUTION VOLUME can be described:

Volume of distribution for X was reduced by 20%

X reduces Y's apparent volume of distribution.

⁸ (3) Collection of terms, symbols, equations, and explanations of common pharmacokinetic and pharmacodynamic parameters and some statistical functions Publisher: The pharmacokinetics working group of the AGAH

PROTEIN BINDING

Some synonyms and related terms:

<http://www.ncbi.nlm.nih.gov/mesh/68011485>

Definition: The process in which substances bind to plasma proteins.

Some ways PROTEIN BINDING can be described:

X is approximately 90% bound to plasma proteins.

[...] clinically significant protein binding interactions with other highly protein bound drugs.

The binding of X was reduced from approximately 99.2% to 97.5%, representing a potential twofold increase in unbound X plasma levels.

In vitro, X may displace less firmly bound drugs like Y.

FREE FRACTION

Some synonyms and related terms:

Unbound fraction

f_u

f_{ut}

Definition: Fraction of unbound (not protein bound or free) drug in plasma or serum.

Some ways TERM can be described:

X free fraction was increased.

X administration was associated with a 60% increase in the free fraction of Y.

X increased the unbound fraction of Y.

X is highly bound to plasma proteins.

X displaces other protein-bound drugs.

BIOTRANSFORMATION

Some synonyms and related terms:

Metabolism.

<http://www.ncbi.nlm.nih.gov/mesh/68001711>

Definition: Biotransformation is the chemical conversion of substances by living organisms or enzyme preparations.

Some ways BIOTRANSFORMATION can be described:

The extent of biotransformation of X to the active metabolite is reduced by Y.

METABOLISM

Some synonyms and related terms:

Biotransformation.

<http://www.ncbi.nlm.nih.gov/mesh/68008660>

Definition: In medicinal chemistry the term metabolism refers to the biotransformation of xenobiotics and particularly drugs.

Some ways METABOLISM can be described:

X appears to enhance the metabolism of Y.

X inhibits the metabolism of Y.

X induces its own metabolism.

X did not alter the metabolism of Y.

FIRST PASS METABOLISM

Some synonyms and related terms:

First-pass effect

Definition: Biotransformation and, in some cases, elimination of a substance in the liver after absorption from the intestine and before it reaches the systemic circulation.

Some ways FIRST PASS METABOLISM can be described:

X and Y co-administration resulted in inhibition of the first-pass metabolism of Y.

ENZYME INDUCTION

Some synonyms and related terms:

<http://www.ncbi.nlm.nih.gov/mesh?term=enzyme%20induction>

Definition: Process whereby an enzyme is synthesized in response to the presence of a specific substance or to other agents.

Some ways ENZYME INDUCTION can be described:

This mechanism is probably through the induction of hepatic microsomal enzymes.

X is known to induce certain cytochrome P-450 enzymes.

X is an inductor of P-glycoprotein.

Enzyme induction occurred when [...]

ENZYME INHIBITION

Some synonyms and related terms:

Enzymerepression

Definition: The process by which a drug reduces the catalytic activity of a specific enzyme.

Some ways ENZYME INHIBITION can be described:

X inhibits the metabolism of Y.

X is an inhibitor of metabolism of Y.

X is an inhibitor of CYP450.

ENZYME

Some synonyms and related terms:

<http://www.ncbi.nlm.nih.gov/mesh/68004798>

Definition: An enzyme is a macromolecule, usually a protein, which functions as a (bio) catalyst by increasing the reaction rate.

Some ways ENZYME can be described:

X reduces the plasma concentrations of drugs metabolized by those enzymes.

CYTOCHROME P450 ENZYME SYSTEM

Some synonyms and related terms:

<http://www.ncbi.nlm.nih.gov/mesh/68003577>

Definition: A superfamily of enzymes that takes part in the metabolism of many drugs

Some ways CYTOCHROME P450 ENZYME SYSTEM can be described:

As a potent inhibitor of CYP3A, X increases plasma concentration of Y.

P-GLYCOPROTEIN

Some synonyms and related terms:

<http://www.ncbi.nlm.nih.gov/mesh/68020168>

Definition: P-glycoprotein is a transmembrane protein located in a number of tissues, including the blood-brain barrier, the mucosal lining of the intestinal and hepatobiliary tract and the placenta and which acts as a transport protein that carries certain drugs from inside to the outside of the cell.

Some ways P-GLYCOPROTEIN can be described:

X inhibits p-glycoprotein transport.

X is a p-glycoprotein substrate.

METABOLITE

Definition: A metabolite is any intermediate or product resulting from metabolism.

Some ways METABOLITE can be described:

The effects of this interaction in X or its metabolites have been studied.

PRODRUG

Some synonyms and related terms:

<http://www.ncbi.nlm.nih.gov/mesh?term=pro%20drugs>

Definition: A compound that, on administration, must undergo chemical conversion by metabolic processes before becoming the pharmacologically active drug for which it is a prodrug.

Some ways PRODRUG can be described:

X₁ is a prodrug of X.

ELIMINATION

Definition: Disappearance of a substance from an organism or a part thereof, by processes of metabolism, secretion, or excretion.

Some ways ELIMINATION can be described:

Hepatic elimination of X may be accelerated by co-administration of Y.

X decreases the elimination of Y.

ELIMINATION RATE CONSTANT

Definition: Differential with respect to time of the concentration or amount of a substance in the body, or a part thereof, resulting from elimination.

Some ways ELIMINATION RATE CONSTANT can be described:

The rate and extent of X elimination is affected by concomitant Y.

EXCRETION

Definition: Discharge or elimination of an absorbed or endogenous substance, or of a waste product, and/or its metabolites, through some tissue of the body and its appearance in urine, feces, or other products normally leaving the body. Excretion does not include the passing of

a substance through the intestines without absorption.

Some ways EXCRETION can be described:

X may enhance Y excretion.

X may reduce the excretion of Y.

X significant decrease in urinary excretion of Y.

CLEARANCE

Some synonyms and related terms:

CL

<http://www.ncbi.nlm.nih.gov/mesh/68008657>

Definition: Volume of blood or plasma or mass of an organ effectively cleared of a substance by elimination (metabolism and excretion) divided by time of elimination. Total clearance is the sum of the clearances of each eliminating organ or tissue for a given substance.

Some ways CLEARANCE can be described:

X is expected to inhibit clearance of Y.

X induces the clearance of drugs metabolized by CYP-450.

X decreases the oral clearance of Y by about 20%.

Hepatic clearance of X is significantly reduced during treatment with Y.

5.3 Pharmacodynamic vocabulary

PHARMACODYNAMICS

Definition: The science and study of how *chemicals* produce their biologic effects.

Some ways PHARMACODYNAMICS can be described:

Preliminary data suggest that there may be a pharmacodynamic interaction between X and Y.

X could theoretically affect Y pharmacodynamics.

DRUG SYNERGISM

Some synonyms and related terms:

<http://www.ncbi.nlm.nih.gov/mesh?term=drug%20potentiation>

Definition: The action of a drug in promoting or enhancing the effectiveness of another drug

Some ways DRUG SYNERGISM can be described:

X synergistic effect is expected when Y is given concurrently with B.

ADDITIVE EFFECT

Definition: The effect of two drugs, which have the same pharmacological effect, when are given together.

Some ways ADDITIVE EFFECT can be described:

The concomitant use of X and Y may produce additive(depressant) effects.

X actions may be additive to those of other drugs.

X may demonstrate additive toxicity when used in combination with Y.

X and Y cause additive CNS depression.

POTENTIATION

Some synonyms and related terms:

Potentiated Effect

Definition: Is the enhancement of one drug effect by another, resulting in a greater effect than those of the two drugs given alone.

Some ways POTENTIATION can be described:

The response of X may be potentiated by Y.

X may potentiate the hypotensive effects of Y.

ANTAGONISM

Definition: The action of a drug diminishes or disappears in presence of other drugs. Different mechanism may exist: both drugs bind to the same receptor; the antagonist drug interrupts the union receptor-drug or both drugs have opposed physiological effects

Some ways ANTAGONISM can be described:

X may antagonized the effect of Y.

5.4 Other common terms

MONITORIZATION

Some synonyms and related terms:

biological monitoring

biomonitoring

Definition: Continuous or repeated measurement of potentially toxic substances or their metabolites or biochemical effects in tissues, secreta, excreta, expired air, or any combination of these in order to evaluate occupational or environmental exposure and health risk by comparison with appropriate reference values based on knowledge of the probable relationship between ambient exposure and resultant adverse(health) effects.

Some ways MONITORIZATION can be described:

If X and Y are administered concurrently, the clinical response to Y should be monitored closely.

Frequent monitoring of X whole blood trough concentrations should be performed.

Patients should be monitored closely for adverse events.

6 Glossary:

AEMPS: Spanish Agency for Medicines and Healthcare Products

ATC :Anatomical Therapeutic Chemical.

ATCvet: Anatomical Therapeutic Chemical system for classification of veterinary medicines.

CIMA: AEMPS Medicines Online Information Center.

DDI: drug-drug interaction.

EMA:European Medicines Agency.

FDA: Food and Drug Administration.

INN: International Nonproprietary Names.

INNM: International Nonproprietary Name Modified.

IUPAC: International Union of Pure and Applied Chemistry.

MAO: MonoaminoOxidasa.

MeSH: Medical Subject Headings.

USAN: United States Adopted Name.

WHO: World Health Organization.

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