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An ontological analysis of drug prescriptions

Jean-François Ethier [a,b,*,**], Adrien Barton [a,**] and Ryeyan Taseen [a,**]
[a] *GRIIS, Université de Sherbrooke, 2500, boul. de l'Université, Sherbrooke (Québec), J1K 2R, Canada*
[b] *INSERM UMR_S 1138 Eq. 22, Université Paris Descartes, Paris, France*

Abstract. The ambiguities and overspecificities of prescription semantics along with their lack of standardization hinders the adoption of electronic prescriptions in some countries, limit data interoperability and are potential sources of error. An ontology of drug prescriptions could help overcome such difficulties and ultimately reduce adverse drug events. This article presents the Prescription of Drugs Ontology (PDRO), a reference ontology founded on the Open Biomedical Ontology Foundry (OBO Foundry) realist principles and built on the upper ontology Basic Formal Ontology (BFO). It imports by the methodology Minimum Information to Reference an External Ontology Term (MIREOT) classes and object properties from the Information Artifact Ontology (IAO), the Ontology for Biomedical Investigations (OBI), the Ontology for General Medical Science (OGMS), the Ontology for Medically Related Social Entities (OMRSE) and the Drug Ontology (DRON). It categorizes a prescription and its parts as information content entities. It defines a key component of prescriptions, a drug administration specification, as an action specification that directs a process of drug administration. This article also discusses how to deal with synonymy and provides a pre-formal analysis of the social ontology underlying drug prescriptions, involving entities such as permissions, recommendations or mild obligations.

Keywords: Prescription, ontological realism, information content entity, social ontology, OBO Foundry

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1. Background

Modern health care extensively uses pharmaceutical drugs. But while the administration of a drug can mitigate, prevent, treat and cure disease, it can also cause unintended harm. Adverse drug events[1] cause about 5% of all hospital admissions (Lazarou, Pomeranz & Corey, 1998; Pirmohamed et al., 2004) and are estimated to be the 4th to 6th leading cause of death in the US (Lazarou et al., 1998; Kohn, Corrigan & Donaldson, 2000). As it happens, 37–51% of adverse drug events may be preventable (Baker et al., 2004). It has been estimated that the majority of these are a result of errors at the prescribing phase (Bates et al., 1999). Moreover, unclear dosing instructions (traditionally termed the "Sig.", for "signatura"; Liu, Burkhart & Bell, 2011) on drug product labeling have been shown to be especially susceptible in leading to medication errors and adverse drug events (Davis et al., 2006; 2009; Institute of Medicine, Aspden, Wolcott, Bootman & Cronenwett, 2007; Wolf et al., 2011). This motivates the development of an ontology of drug prescriptions that could represent prescriptions and support the prescribing process. This section will first elaborate on this motivation, and second provide a pre-formal analysis of the nature of drug prescriptions.

*Corresponding author. E-mail: ethierj@gmail.com.
**Equal contributors.
[1] An adverse drug event is a pathological bodily process that occurs after a drug administration and results in unintended harm to the patient (He et al., 2014; Institute of Medicine, Aspden, Wolcott, Bootman & Cronenwett, 2007, p. 37).

1.1. Motivation

This subsection will first present the insufficiency of existing solutions in representing electronic drug prescriptions; second, it will stress how ontologies could contribute to this task; third, it will show the necessity of supporting the prescription of drugs at the desired level of precision; and fourth, it will emphasize the necessity of dealing with homonymy.

1.1.1. The insufficiency of existing solutions for detecting inappropriate prescriptions

Drug prescriptions are a valuable source of information about the drug administrations intended to occur, and in a modern health care system, are required documents for distributing and administering prescription drugs. It follows that the interception of potentially harmful drug prescriptions could reduce the incidence of adverse drug events; this makes electronic prescriptions a compelling target of patient safety improvement due to their susceptibility to detection by health information technology systems (Shekelle et al., 2013). There is evidence of benefit in the use of electronic prescriptions for detecting inappropriate prescriptions and thereby reducing the incidence of adverse drug events (Ammenwerth, Schnell-Inderst, Machan & Siebert, 2008; Kannry, 2011; Nuckols et al., 2014). Important challenges remain in the implementation and adoption of these systems. Among the most frequently cited of these issues is the lack of data standardization (Gagnon, Nsangou, Payne-Gagnon, Grenier & Sicotte, 2014; Motulsky et al., 2015). In Canada, where there is currently no national standard for electronic prescriptions, this reduces system quality, hinders adoption and limits interoperability (Gagnon, Payne-Gagnon, Sicotte, Langué-Dubé & Motulsky, 2015).

While electronic prescriptions may be widespread in the United States, their dosing instructions are not yet standardized. The NCPDP "Structured and Codified Sig Format" (SCSF) is a specification for the standard fields and code sets to use for the dosing instructions of electronic prescriptions. Unlike the NCPDP SCRIPT, an accepted US standard for the computer-to-computer transfer of prescriptions (National Council for Prescription Drug Programs, 2014, p. 2), the SCSF is not itself an accredited standard by ANSI (American National Standards Institute), and is not intended to be (National Council for Prescription Drug Programs, 2017a, p. 61). Its use is not federally mandated, and according to health information technology industry consultants, is rarely supported by electronic health records vendors (Burger & Fisher, 2016). With the implementation of the SCSF being dependent on the implementation of the SCRIPT (National Council for Prescription Drug Programs, 2017c, p. 63), and the SCRIPT being tied to US stakeholder perspectives and national policy (National Council for Prescription Drug Programs, 2017b), porting the SCSF outside of the United States would raise significant challenges.

1.1.2. The role of ontologies

In recent years, open source ontologies have emerged as a reliable solution to the Tower of Babel problem in medical informatics (Arp, Smith & Spear, 2015) as exemplified by ontologies in the consortium of the Open Biomedical Ontologies (OBO, Smith et al., 2007). The goal of this consortium is to support biomedical data integration by using a shared, tested set of best practices in the building of ontologies. Each ontology aims at providing a logical, scientifically accurate and orthogonal representation of its domain.

Currently, the OBO Foundry includes ontologies for the domains of drug products (the drug ontology [DRON], Hanna, Joseph, Brochhausen & Hogan, 2013), adverse events (Ontology of adverse events [OAE], He et al., 2014; Adverse event reporting ontology [AERO], Courtot, Brinkman & Ruttenberg, 2014), and potential drug-drug interactions (Drug Interaction and Evidence Ontology [DIDEO],

Brochhausen et al., 2014). While those ontologies address to various degrees drug-related entities, a realist ontology for drug prescriptions is still missing. Such an ontology could help standardize a key source of data for the potential clinical applications that motivated the afore-mentioned ontologies. Conversely, the adoption of a data standard that is within the fold of the OBO Foundry would facilitate the development of cross-domain health care applications, such as those for detecting inappropriate prescriptions by comparing electronic prescriptions against diagnosis data, demographic data, lab and medical imaging data, and drug-drug interaction data. The Prescription of Drugs Ontology (PDRO; pronounced "Pedro") is a realist ontology of drug prescriptions that was developed with this objective in mind.

1.1.3. Levels of generality in drug product specifications

Consider two instructions (each termed a "Drug administration specification" [DAS]) to take metoprolol: $\mathbf{DAS_1}$ = 'Metoprolol 50 mg PO bid', which instructs taking Metoprolol 50 mg per mouth ("PO" for *per os*) twice a day ("bid"), and $\mathbf{DAS_2}$ = 'Apo-Metoprolol 50 mg tab, 1 tab PO bid', which instructs taking 1 tab of Apo-Metoprolol 50 mg per mouth twice a day. Most clinicians would intend to prescribe $\mathbf{DAS_1}$ as they want to indicate the active ingredient Metoprolol, rather than a specific drug product name manufactured by a specific company like Apo-Metoprolol, because all pharmacies do not have in inventory every possible brand. However, many e-prescribing platforms can only prescribe a uniquely registered drug (e.g., Apo-Metoprolol[2] 50 mg tab) as in $\mathbf{DAS_2}$, which artificially restricts the collection of drugs that satisfy the intention of the prescriber (e.g., any drug product containing the active ingredient metoprolol and suitable for an administration by mouth of 50 mg of active ingredient at a time twice daily; Motulsky et al., 2015); that is, $\mathbf{DAS_2}$ is overspecific. This inability of the prescriber to specify a drug at different levels of generality poses several problems for different users. For the pharmacist, it means having to contact the prescriber and/or modify the prescription when the drug that was specified is not in stock or when it does not match patient insurance eligibility. This reduces efficiency and increases the risk of error (Gagnon et al., 2015; Odukoya & Chui, 2012). For prescribers, it is frustrating to have to deal with the mismatch between the initial prescription and what appears on the prescription returned from the pharmacy, since there may not be any resemblance between the written names of the drug product specified and the drug product dispensed (Gagnon et al., 2015). For the patient, if the medication that is prescribed is not covered by their insurance, it can increase out-of-pocket costs (Lapane, Rosen & Dubé, 2011).

To address these issues, a representation of drug prescriptions should formalize the specification of a drug product such that the informational entity referring to the collection of drug products acceptable to dispense and administer on a prescription can be as general (or as specific) as the prescriber's intention.

1.1.4. Homonymy

Modelling informational entities that are commonly viewed as strings, such as prescriptions, requires distinguishing between homonyms (a common problem for ontologists): strings that are identical in their composition and order of characters, but have different meanings. For example, 'Metoprolol' in $\mathbf{DAS_1}$ would usually refer to any drug product containing metoprolol or to the active ingredient metoprolol itself, although in some cases it might instead refer to the generic drug product branded with the name "Metoprolol" (Sanis Health Inc., 2014).

Cases of homonymy can be especially problematic. For example, the term "PRN" is a shortcut for "pro re nata" that can be translated as "as needed". However, it can have two different meanings. For example, "Nitro 0.4 mg/spray 1 dose SL q5min ×3 max PRN chest pain" instructs taking one dose sublingual

[2] This is a generic drug brand name. Note that non-generic drugs are often referred to as "brand name drugs", yet what is referred to as a "generic drug" is also branded by its production company.

("SL") of nitroglycerin 0.4 mg/spray every 5 minutes ("q5min"), 3 doses max, in case ("PRN") of chest pain. A doctor writing this instruction would strongly recommend taking the Nitro drug in case of chest pain – as untreated angina could lead to a myocardial infarction. On the other hand, "Ativan 1 mg SL HS PRN insomnia" instructs taking one dose sublingual of Ativan 1 mg before bedtime ("HS"), in case of insomnia. A doctor writing this instruction may simply allow the patient to buy Ativan and inform him that he could take it in case he deems it important for his own well-being, without recommending it: the agent can judge whether he will take it on a given night. Note however that drug prescriptions are often not explicitly specified as informative or recommendative, as this dimension is generally stated orally, or not explicitly stated at all. This can be problematic as it places the onus of interpretation onto patients, who are generally less informed than prescribers about the diseases, the drugs and their effects.

Thus, a representation of drug prescriptions must not only consider the strings themselves that a prescription may be composed of, but must consider the intention behind them, that is, what these strings might refer to.

1.2. The domain of prescriptions

PDRO is intended as a reference ontology of drug prescriptions. The first step is therefore to clarify what is a drug prescription. All medical prescriptions are not drug prescriptions, as some do prescribe other actions than taking drugs – such as physiotherapy. Moreover, the term "prescription" can also be used outside the medical domain – for example, an economist can prescribe an economic policy.

The Oxford Advanced Learner's dictionary (Turnbull et al., 2010) suggests three definitions for the term "prescription":

- Definition 1: "an official piece of paper on which a doctor writes the type of medicine you should have, and which enables you to get it from a chemist's shop/drugstore".
- Definition 2: "the act of prescribing medicine".
- Definition 3: "a plan or a suggestion for making something happen or for improving it" (note that this definition is not restricted to medical prescriptions).

Those definitions point to four different kinds of entities that are sometimes called "prescription" in a medical context: a material object (namely, a piece of paper); an action; a plan; and a suggestion. There is at least one further entity that could be called "prescription": the informational entity that is borne by a piece of paper such as described in Definition 1. This informational entity can be concretized on a piece of paper, but also on other media – like a computer screen, a hard drive, etc. This dual nature is common for several terms which commonly refer to both informational entities and their physical bearers, such as "book", "recipe", "report", etc. (Smith & Ceusters, 2015).

Thus, the term "prescription" can refer to at least five different entities in a medical context:

- An informational entity, as in the sentence "Send me his prescription by email."
- A bearer of such an informational entity, such as a physical piece of paper, as in "He burned his prescription.", or a pattern on a computer screen or on a hard drive.
- The process of creating such an informational entity, as in "The prescription of drugs is a doctor's responsibility." (Turnbull et al., 2010)
- The plan that this informational entity describes, as in "I have been following his prescription."
- The suggestion or recommendation to follow such a plan, as in "Dr. Jones' prescription was contradicting Dr. Williams' prescription."

In this article, the term "prescription" (or sometimes "informational prescription", to avoid ambiguity) will be reserved to the first entity, the term "prescription paper" will refer to the second entity (when the bearer is a piece of paper), "prescribing process" to the process of prescribing, and "prescription plan" to a plan that is specified in a prescription. The central task of an ontology of drug prescriptions will therefore be to analyze the structure of drug prescriptions by determining what are the informational entities that compose such documents.

Moreover, Definition 1 above suggests two ways in which a prescription could interact with the social ontology: a doctor writes on a prescription "the type of medicine you should have", and a prescription "enables you to get it from a chemist's shop/drugstore". Thus, a prescription may be linked with two kind of deontic entities: a mild obligation ("should"); and a permission ("enables"). Definition 3 also mentions a "suggestion or recommendation", which is a social entity too. Thus, an ontological analysis of drug prescriptions has the potential to contribute to an ontology of social reality by analyzing such entities.

The next section will present the OBO Foundry methodology underlying our ontology of drug prescriptions to address the above-mentioned issues.

2. Methods

This part will present first the realist OBO-Foundry methodology that will be used and its theory of information content entities (ICE); second, the relations of parthood and aboutness for ICEs; third, some ICEs that are relevant for formalizing the parts of a drug prescription; and fourth, a proposal that has been made for a social ontology in the OBO Foundry.

2.1. The realist methodology

PDRO is a reference ontology built according to the OBO Foundry principles, which endorse a realist methodology. It is available online and open for discussion at https://www.github.com/openLHS/PDRO (see also http://www.obofoundry.org/ontology/pdro.html). In what follows, universals or classes will be written in italics such as *Aspirin tablet* (the class of aspirin tablets), whereas particulars will be written in bold, such as **Aspirin tablet$_1$** or **Aspirin tablet$_2$** to refer to two specific tablets. PDRO uses the Basic Formal Ontology BFO 2.0 as an upper ontology and imports 34 classes and 20 relationships from various OBO Foundry ontologies using the Minimum Information to Reference an External Ontology Term methodology (MIREOT; Courtot et al., 2011), as per the OBO principle of orthogonality (Smith et al., 2007): the Information Artifact Ontology (IAO; Ceusters, 2012; Smith & Ceusters, 2015), the Ontology for Biomedical Investigations (OBI; Bandrowski et al., 2016), the Ontology for General Medical Science (OGMS; Scheuermann, Ceusters & Smith, 2009), the Drug Ontology (DRON; Hanna et al., 2013), the Ontology for Medically Related Social Entities (OMRSE; Hicks, Hanna, Welch, Brochhausen & Hogan, 2016), and the phenotypic quality ontology (PATO; Mungall et al., 2016). 135 additional classes were created in PDRO.

BFO makes the distinction between *Independent continuant*: things whose existence is ontologically independent of the existence of other continuants, like an aspirin 81 mg tablet (instance of *Material Entity*); *Specifically dependent continuant*: things whose existence depends on a specific independent continuant, like the shape or color of an aspirin 81 mg tablet (instances of *Quality*); and *Generically dependent continuant*: things whose existence depends on some independent continuant, but not a specific one, and can thus migrate from bearer to bearer.

A subclass of *Generically dependent continuant* is IAO: *Information content entity* (ICE) which has the property of being *about* something (Smith & Ceusters, 2015). For example, the information 'Tylenol' on a drug product monograph is an ICE that is about the class of Tylenol drug products. Following Smith and Ceusters (2015), an ICE is concretized by some *Information Quality Entity* (IQE; subclass of BFO:*Quality*). For example, an ICE can be concretized by the outline of a string of characters on a sheet of paper, by some pixels on a computer screen or even by some neuronal configuration inhering in the doctor or the patient. In the following, single quotes such as in 'Amoxicillin' will be used to refer to an ICE instance and double quotes such as in "Amoxicillin" will be used to refer to a string of characters.

2.2. Aboutness and parthood for ICEs

An ICE is about something. Smith & Ceusters (2015) distinguishes two senses of aboutness. First, an ICE such as 'The Eiffel Tower is in France' is about the various elements specified in its parts: the Eiffel Tower and the country France. Second, this ICE is about a configuration relating those various elements, namely the configuration of the Eiffel tower being located in France.

Aboutness can be used to clarify relations of synonymy and homonymy. ICEs will here be said synonyms if they are about the same portion of reality (as defined in Smith & Ceusters, 2015) with the second sense of aboutness mentioned above. For example, the ICEs 'sun' and 'closest star to earth' both refer to the same entity and are therefore synonyms. To take a pharmaceutical example, consider the strings "Aspirin 81 mg PO once daily" and "if one day has elapsed since the previous dose of Aspirin 81 mg in oral dose form, take 81 mg by mouth of this drug": they concretize ICEs which are about the same thing and are therefore synonyms (for more on dealing with synonymy, see Section 4.1).

Conversely, two ICEs could be concretized by similar strings but be about different entities and thus be different ICEs. For example, the ICE 'Metoprolol'$_1$ referring to the generic drug *Metoprolol* and the ICE 'Metoprolol'$_2$ referring to the active ingredient *Metropolol* are not about the same thing (and their aboutness are determined by the intention of the agent who created them in a cognitive act – see Section 4.1 for more details) and thus they are not the same ICE, even if they can be concretized by similar strings; this is a case of homonymy.

To determine the ICEs that compose an informational drug prescription, consider the prescription on Fig. 1. It contains various parts: ICEs specifying the name and date of birth of the patient, the date, the name of the doctor, and three instructions, each directing a drug administration. As a reference ontology of drug prescriptions, PDRO needs to create categories to describe them and relate those parts, even if most of them do not have well-established names in medical's practice (in the following, whenever the ontology name is omitted in the name of an entity that was not introduced earlier, this means that the entity is introduced by PDRO – so we will write e.g. "*Prescription*" instead of "PDRO:*Prescription*"). Information content entities such as *Patient identification* or *Prescriber identification* do not raise any special difficulties. PDRO focuses on describing various parts of a *Drug prescription*, such as *Drug administration specification* (e.g. 'Amoxicillin 500 mg PO tid', where "tid" means "three times a day") or *Drug product specification* (e.g. 'Amoxicillin'). The relations BFO: **has_part** and BFO: **part_of** will be used to describe mereological associations.

2.3. Relevant ICEs

Following the pre-formal analysis described in Section 1.2 and the OBO Foundry methodology described above, PDRO:*Health care prescription* is classified as a subclass of IAO:*Document*, which is

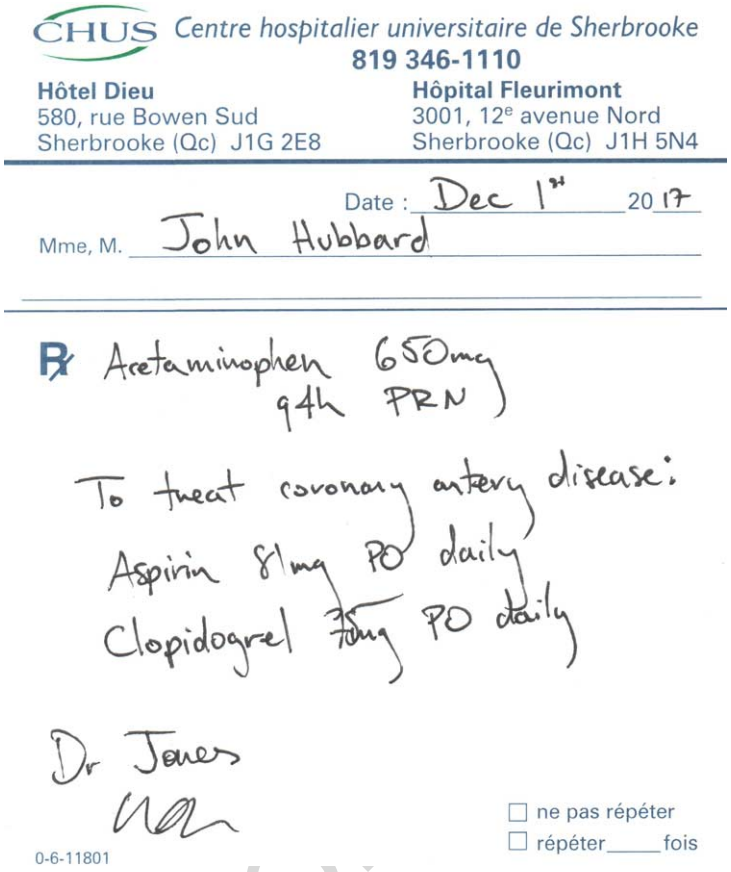

Fig. 1. An example of prescription.

defined as "A collection of information content entities intended to be understood together as a whole". The main goal will therefore be to determine what are the parts of such a document. To answer, the relevant entities in IAO need first to be identified.

Some parts of a drug prescriptions specify the action to take (or administer) some drugs; an important class from IAO will therefore be *Action specification*. A related entity in IAO is *Plan specification*, which has as parts both *Action specification* and IAO:*Objective specification*. Consider for example a chocolate cake recipe that has as parts a title 'How to make a chocolate cake' (the objective specification) as well as an action specification stating the action(s) required to complete this task (we suppose here that several actions can compose together a more complex action). This recipe is a plan specification that directs the process of making a chocolate cake by performing the actions described in this recipe. A plan specification may give rise to a OBI:*Plan* (a subclass of *Realizable entity*) by a relation called here "**specifies**":[3]

[3]We do not discuss here this formal relation **specifies**, as this is a matter for OBI, which is still being discussed in the OBO community. Currently, according to OBI, a plan specification can be concretized by a plan. However, Smith & Ceusters (2015) argue that ICEs (including plan specifications) can only be concretized by an information quality entity. If we follow Smith and Ceusters' account, the IQE concretizing a plan specification could then bring about a disposition to act according to this plan specification – and we might view this disposition as a plan. Thus, the nature of the relation **specifies** is not the same if we follow OBI or Smith & Ceusters (2015). This debate has no consequence for PDRO, which currently formalizes action

Plan specification subClassOf **specifies** only *Plan*.

A plan is a realizable entity that inheres in an agent who intends to fulfill the objective by performing the action, and this plan can be realized by a OBI:*Planned process*. For example, when Mr. Hubbard decides to follow the chocolate cake recipe, this brings about an instance of *Plan* inhering in himself; and when he follows the recipe, this plan is realized in the planned process of making the cake. Note that a plan specification can exist even if it does not give rise to a plan (consider a recipe that nobody intends to follow), and a plan can exist without ever being realized in a planned process (consider a recipe that a person initially intends to follow, before eventually changing her plans).

2.4. The social ontology

To analyze the relation between a drug prescription and the social reality, this article will build on the theory of social entities developed by Brochhausen, Almeida & Slaughter (2013) and Smith (2012; 2014), that will now be presented.

The philosophical roots of the ontology of permissions as they are presently accepted in the OBO Foundry (Smith, 2014) go back to Reinach (1989). The German philosopher refers to acts arising from the internal activity of the subject (rather than as produced passively by the agent) such as deciding, asking, commanding, permitting or forgiving as "spontaneous acts". Some spontaneous acts, like deciding or forgiving, do not need to be perceived by other agents to exist, and Reinach calls them "internal acts". But some other spontaneous acts, like commanding or permitting, need to be perceived to exist, and are directed towards another conscious being: they are called "social acts". According to Reinach, some social acts can bring about social entities such as claims, rights, permissions or obligations (this theory can be seen as a precursor of Austin-Searle's speech acts theory – Austin, 1975, Searle, 1969 – although it may have different ontological commitments).

Such entities are categorized by Brochhausen et al. (2013) as socio-legal generically dependent continuants, which are generically dependent continuants that come into existence through social acts and are concretized by roles. For example, the claim to a piece of land is a socio-legal generically dependent continuant that comes into existence through a social act process, and is concretized by the role of land owner. Smith (2012) note that such social acts can be put in an enduring form, by validating a document: this process is a document act. Thus, document acts can create, revoke or transfer socio-legal generically dependent continuants. For example, a document act can create a claim to a piece of land from an agent, revoke his former claim, or transfer his claim to another agent. Socio-legal generically dependent continuants differ from ICEs in at least two respects (Brochhausen et al., 2013): they are not about something; and they are not concretized by qualities, but by roles.

PDRO currently formalizes the structure of informational drug prescriptions, rather than the social ontology underlying drug prescriptions. There are two reasons for this. First, the categories pertaining to the underlying social ontology will arguably not be necessary for most potential applications of PDRO – contrarily to the informational parts of drug prescriptions. Second, the foundations for social ontology in BFO are still being discussed and under development, as illustrated e.g. by Donohue (2017). Building a systematic and comprehensive social ontology in this context will require input from several fields – drug prescriptions being one of those fields. Therefore, this article will contribute to this overarching goal by discussing the social ontology behind drug prescriptions and making proposals in this respect,

specifications and plan specifications, but not the plans that they might specify.

that will be formalized in the future in PDRO when a consensus involving various relevant domains will have been obtained.

3. Results

The first subsection will characterize a central entity in a drug prescription named "Drug administration specification" as an action specification that is part of a plan specification that can specify a plan, which can be realized in a process of drug administration. It will also characterize an entity named "Drug distribution specification" which complements a "Drug administration specification". The second subsection will detail the parts of a drug administration specification.

3.1. Drug administration specification and drug distribution specification

3.1.1. Drug administration specification as an action specification

While medical prescriptions can have non-pharmaceutical uses, e.g. physiotherapy, a *Drug prescription* is differentiated as a type of *Health care prescription* that has as part a *Drug administration specification* (DAS), which specifies how to realize the administration of a drug. In the Web Ontology Language (OWL):

> *Drug prescription* subClassOf (*Health care prescription* and **has_part** some *Drug administration specification*).

A DAS specifies an action of drug administration; therefore, it is classified under IAO:*Action specification*. Some drug prescriptions contain not only a DAS, but also an instance of PDRO:*Health care objective specification* (subclass of *Objective specification*) related to this DAS; such health care objective specifications could be e.g. 'prevention of malaria', 'alleviation of cough', etc. The mereological fusion of this DAS and this objective specification is a *Plan specification*. Some drug prescriptions, however, do not encompass any objective specification: in such cases, the doctor has some objective in mind, but does not write it on the prescription. He generally communicates it orally to the patient ("Mr. Williams, you should take this drug to cure your otitis" while handing over the prescription), but not always – think about a doctor prescribing drugs for a patient who is in coma. In every case though, there is a healthcare objective specification concretized by some cognitive representation (Smith & Ceusters, 2015), even if it is not concretized on a prescription paper or communicated orally.

Thus, a DAS is an action specification concretized by both a doctor's cognitive representation and by some IQE on a shareable medium (such as a prescription paper), which is a part of a plan specification concretized – at least – by a doctor's cognitive representation; thus:

> *Drug administration specification* subClassOf (*Action specification* and **part_of** some *Plan specification*).

In the case where the objective specification is communicated (in writing or orally) to the patient, it may give rise to an instance of *Plan* in the patient, that may be realized by an instance of *Planned process* if the patient follows the plan specification by taking his drugs.

To illustrate this, consider a (fictional) instance of *Prescription* named **prescription$_0$** that Dr. Jones writes on a paper represented on Fig. 1, in presence of his patient Mr. Hubbard. **prescription$_0$** has as parts three DAS:

- **DAS$_a$**: 'Acetaminophen 650 mg q4h PRN'.
- **DAS$_b$**: 'Aspirin 81 mg PO daily'.
- **DAS$_c$**: 'Clopidogrel 75 mg PO daily'.

As well as one objective specification **OS$_{b\text{-}c}$**: 'To treat coronary artery disease'.

There is an instance of plan specification **PS$_{b–c}$** concretized on the prescription paper that has as parts **DAS$_b$** and **DAS$_c$** and the objective specification **OS$_{b\text{-}c}$**:

DAS$_b$ part_of PS$_{b–c}$.

DAS$_c$ part_of PS$_{b–c}$.

OS$_{b\text{-}c}$ part_of PS$_{b–c}$.

There is also an instance of plan specification **PS$_a$** concretized by a cognitive representation in Dr. Jones (Smith & Ceusters, 2015). If Dr. Jones explains to Mr. Hubbard the objective of taking acetaminophen, then **PS$_a$** is also concretized by a cognitive representation in Mr. Hubbard. **PS$_a$** has as part an objective specification **OS$_a$** specifying the objective of treating pain, and the action specification **DAS$_a$**. **DAS$_a$** is a part of **prescription$_0$**, but **OS$_a$** is not:

DAS$_a$ part_of PS$_a$.

OS$_a$ part_of PS$_a$.

DAS$_a$ part_of prescription$_0$.

3.1.2. Drug dispensing specification as an action specification

A DAS can be complemented by an ICE specifying how the drug should be distributed to the patient, called a "DDS" (drug dispensing specification). For example, a DAS 'Amoxicillin 500 mg 1 tab PO TID × 7 days start if bronchitis' could be completed with the DDS '21 pills × 1', which refers to the number of pills that should be distributed. Thus, the DDS is an action specification that is part of a plan specification inhering at least in the mind of the doctor; in this example, the DDS can bring about a plan in a drug dispenser that can be realized in a planned process of distributing at one time 21 drug pills as specified in the DAS. The DAS and the DDS together would read 'Amoxicillin 500 mg 1 tab PO TID × 7 days start if bronchitis 21 pills × 1'. This entity will be named a *Drug administration and dispensing specification*, which has as parts a DAS and a DDS (note that it is neither a DAS, nor a DDS):

Drug administration and dispensing specification subClassOf [(**has_part** some *Drug administration specification*) and (**has_part** some *Drug dispensing specification*)].

3.2. The parts of a drug administration specification

3.2.1. Process of drug administration vs. dose administration

To clarify the parts of a DAS, the relevant underlying processes need first to be clarified. The administration of a drug aims at fulfilling some health-related objective such as curing a disease, alleviating

a symptom, preventing a disease, etc. To fulfill this objective, a drug is often administered in several individual doses that will be taken over some period. Accordingly, the administration process of a drug involves two related processual entities: a *Dose administration* such as the administration of 500 mg of Amoxicillin on February 24th, 2016 at 1 PM; and a *Drug administration*, which is a mereological sum of one or several instances of *Dose administration*, such as the administration of 500 mg of Amoxicillin three times a day during 7 days, starting on February 19th, 2016. Inspired by DRON's definition of *Drug administration*, a *Dose administration* is defined as "A process that has as participants an extended organism and a drug product and that results in a single dose of the drug product being located in the extended organism."

3.3. The parts of a DAS

Each *DAS* has as part at least one *Drug product specification* (defined as "An information content entity specifying a class of drug product.") and at least one *Dose administration specification* (defined as "An action specification that specifies a dose administration.")

> *Drug administration specification* subClassOf [(**has_part** some *Drug product specification*) and (**has_part** some *Dose administration specification*)].

In $\mathbf{DAS_1}$ (as defined on Section 1.1.3), the string "Metoprolol" specifies a class of drug products, namely those which contain the active ingredient metoprolol, thus it is a *Drug product specification*. $\mathbf{DAS_1}$ also has as part an instance of *Dose administration specification* written '50 mg PO bid', which has parts that specify that the quantity in a dose should be 50 mg (*Dose quantification specification*, defined as "An information content entity that specifies a quantity of a drug product to be administered in a dose."[4]) and that the route of administration should be by mouth ('PO' is a *Route of administration specification*, defined as "An information content entity that specifies a route of administration of a drug product."). The part 'bid' informs when a dose should be taken; this is covered in the next subsection.

The '50 mg' that appears in $\mathbf{DAS_2}$, on the other hand, specifies the strength of the drug product intended by the prescriber, i.e., that 50 mg of active ingredient should be contained in one pill – and not split, for example, between two pills of 25 mg each. Accordingly, it is part of '50 mg tab', an instance of *Drug strength specification* ("An information content entity that specifies the strength of a drug product."), which is a part of the *Drug product specification*, along with 'Apo-Metoprolol'. The *Dose administration specification* in $\mathbf{DAS_2}$ is '1 tab PO', where '1 tab' specifies the quantity in a dose and is therefore an instance of *Dose quantification specification*.

[4] An additional question raised by a reviewer is how to model the data value in the ICE above '50 mg'. Currently, OBI and IAO introduce to this effect the entity *Value specification*, such that several ICEs that read '50 mg', but are about different entities, share the same value specification. Those ontologies also introduce the object properties **has value specification** and **has measurement unit label**, as well as the data property **has specified value**, such that the ICE '50 mg' is related by **has value specification** to an instance of *Value specification* that **has specified value** 50 and **has measurement unit label** 'mg'. Overall, this leads to the following formalization:

- '50 mg' **has value specification** o **has specified value** 50.
- '50 mg' **has value specification** o **has measurement unit label** 'mg'.

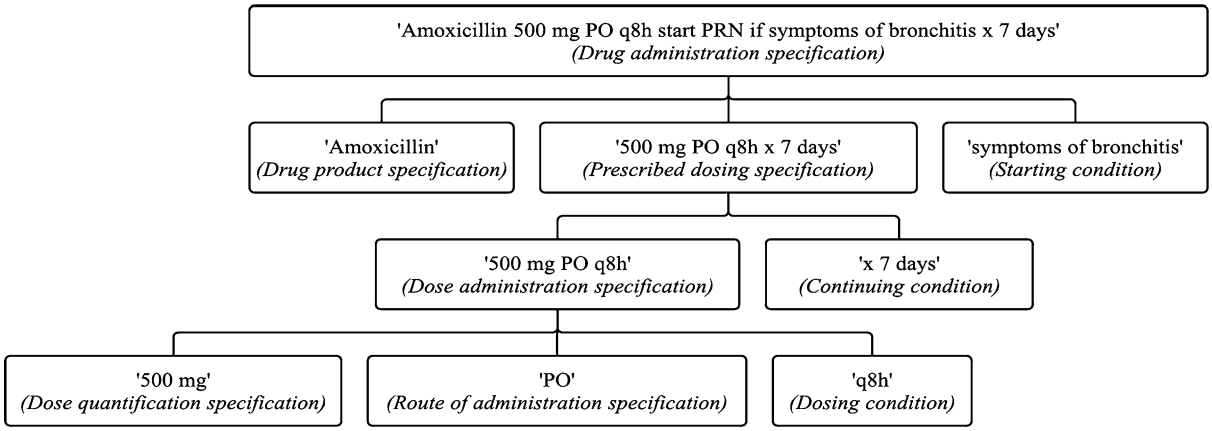

Fig. 2. Mereology of particulars and corresponding universals in $\mathbf{DAS_3}$.[5]

3.4. Condition statements

The mereological structure of a DAS will now be analyzed. A *DAS* specifies both the condition(s) for permitting a *Drug administration*, and the condition(s) for permitting the *Dose administration*(s) of that *Drug administration*. Consider the informational parts of the following *DAS* (Fig. 2):

$\mathbf{DAS_3}$: 'Amoxicillin 500 mg PO q8h start if symptoms of bronchitis $\times$ 7 days'.

In common language, $\mathbf{DAS_3}$ specifies to start a treatment of Amoxicillin, 500 mg by mouth ("PO") in case of symptoms of bronchitis; and to continue the treatment for 7 days, by taking 500 mg of Amoxicillin every 8 hours ("q8h").

To analyze the logical structure of $\mathbf{DAS_3}$, let us introduce the following time-indexed condition statements $\mathbf{C_1}$, $\mathbf{C_2}$ and $\mathbf{C_3}$, all instances of *Condition statement*, which is a subclass of *ICE*:

$\mathbf{C_1(t)}$: 'at t, symptoms of bronchitis are present'.
$\mathbf{C_2(t)}$: 'at t, less than 7×24 h have elapsed since the administration of a first dose or no first dose has been administered'.
$\mathbf{C_2(t)}$: 'at t, 8 hours have elapsed since the administration of the last dose during the current drug administration or no first dose has been administered'.

$\mathbf{DAS_3}$ is synonymous (for more on synonym, see Section 4.1) with $\mathbf{DAS_3'}$, which reads as follows:

$\mathbf{DAS_3'}$: 'for every t_0, if $\mathbf{C_1(t_0)}$, complete the administration of Amoxicillin as directed by $\mathbf{PDS'(t_0)}$, in case such a drug administration is not already ongoing',

where $\mathbf{PDS'(t_0)}$ is an instance of *Prescribed dosing specification*, which is also termed the "Sig.", defined as an *Action specification* that specifies which doses of a drug product should be administered, and under which modalities:

$\mathbf{PDS'(t_0)}$: 'for every $t > t_0$, if $\mathbf{C_2(t)}$ then $\mathbf{DoAS'(t)}$',

where the dose administration specification $\mathbf{DoAS'(t)}$ is defined as:

$\mathbf{DoAS'(t)}$: 'if $\mathbf{C_3(t)}$ then administer a dose of 500 mg PO of drug at t'.

The process directed by $\mathbf{DAS'_3}$ is a drug administration over seven days in order to achieve some health-related objective, specifically that of treating an acute bronchitis. By contrast, $\mathbf{DoAS'(t)}$ directs a process whose extension in time is much more limited, namely a dose administration at time t. To summarize, a DAS specifies the conditional action of administering doses of the specified drug product, as specified in the prescribed dosing specification (PDS), if the starting condition is true.

$\mathbf{C_1}$ is an instance of *Drug administration starting condition statement*.[6] Moreover, $\mathbf{C_1}$ is here an instance of *Presence of symptom statement*, but in another instance of *DAS*, the condition for starting the drug administration might be e.g., an instance of *Current time statement* (such as 'at t, it is July 2nd, 2016').

If $\mathbf{C_2(t)}$ and $\mathbf{C_3(t)}$ are both true at some time t, subsequent dose administration(s) should occur as part of a drug administration. However, once the drug administration has begun, $\mathbf{C_2}$ remains true until it becomes false, playing the role of an upper bound for the drug administration, whereas $\mathbf{C_3}$ can alternate truth values with some periodicity during the drug administration. Therefore, $\mathbf{C_2}$ is classified as a *Drug administration continuing condition* and $\mathbf{C_3}$ as a *Dosing condition*.

Here, $\mathbf{C_2}$ is an instance of *Time elapsed since first dose statement* and $\mathbf{C_3}$ is an instance of *Time elapsed since previous dose statement*. In another instance of *DAS*, the condition for continuing a drug administration might be e.g., an instance of *Number of doses statement* (such as 'at t, less than 21 doses of this drug have been given') or *Current time statement* (such as 'time t is before July 2nd, 2016'), and the dosing condition might be e.g., an instance of *Presence of symptom statement* (such as 'at t, the patient has chest pain') or *Total dosage statement* (such as 'at t, less than 4 grams of this drug have been administered in the last 24 hours').

Although $\mathbf{DoAS'(t)}$ directs the administration of some dose at some time t, other dose administration specifications may direct the administration of a dose over a temporally extended period, as in instructions with "die" or "once a day", without specifying the exact instant of time at which to take the dose. It may also specify the administration of *several doses* over a temporally extended period, as in instructions with "bid" or "twice a day". A dose administration specification containing such instructions would be synonymous to an action specification having as part the condition: 'less than two doses have been administered during the day of which t is part', which, if true, would direct the administration of a total of two doses during the day of which t is part, without specifying the time at which these dose administrations should occur, nor the interval between them.

4. Discussion

PDRO raise a few issues that will now be discussed. First, the question of the synonymy between ICEs, which has been invoked a few times earlier, will be addressed by considering the question of the identity of ICEs; the article will suggest that one can deal, for some applied purposes, with classes of synonymous ICEs. Second, the ontology of socio-legal entities will be discussed. Third, a conclusion will follow.

[5]Note that the labels of *Drug administration starting condition statement*, *Drug administration continuing condition statement* and *Dosing condition statement* have been truncated.

[6]Note that $\mathbf{C_1(t)}$ is a *Drug administration starting condition* only because it is used in some way in the prescription. Therefore, *Drug administration starting condition* can be seen as equivalent to an *ICE* that is BFO:**bearer_of** some *Drug administration starting condition role* (and similar considerations could hold for $\mathbf{C_2(t)}$ and $\mathbf{C_3(t)}$ defined above). Since the use of roles has not yet been systematized in BFO and IAO for ICEs, we have not defined these role classes in PDRO yet.

Table 1
List of information quality entities

IQE$_2$	The cognitive representation of Dr. Jones that is about the active ingredient Metoprolol.
IQE$_3$	"Metoprolol" handwritten by Dr. Jones in blue and cursive letters on a paper, which is conformant to his cognitive representation **IQE$_2$**.
IQE$_4$	The cognitive representation of Dr. Williams (that is about the active ingredient Metoprolol) when he reads **IQE$_3$**.
IQE$_5$	"Metoprolol" written in black and block letters on a computer screen, written by Dr. Williams as a copy of **IQE$_3$**, and conformant to his cognitive representation **IQE$_4$**.
IQE$_6$	The configuration in the computer hard drive coding the string "Metoprolol" that leads to **IQE$_5$** appearing on the computer screen.
IQE$_7$	"Metoprolol (active ingredient)" written in black and block letters by Dr. Williams, with the intention to disambiguate the meaning of the pattern **IQE$_5$**.
IQE$_8$	"Metoprolol (ingrédient actif)" written (in French) in black and block letters by Dr. Williams, as a French translation of **IQE$_7$**.
IQE$_9$	A string "51384-51-1" referring to the active ingredient Metoprolol, following the PubChem classification (Wang et al., 2009).
IQE$_{10}$	"Metoprolol" handwritten by Dr. Smith on a paper with the intention to refer to the active ingredient Metoprolol, independently of what was written by Dr. Jones and Dr. Williams.

4.1. The identity of an ICE and dealing with synonymy

This subsection will mention the complexities and debates surrounding the issue of the identity of ICEs in the OBO Foundry. Despite those complexities, a simple solution to deal with synonymy for applied purposes will be suggested.

IAO understands ICEs as created by cognitive acts (Smith & Ceusters, 2015), and endorses the "primacy of the intentional" (Chisholm, 1984): their aboutness is determined by the cognitive acts that brings them into existence. There are several factors that are relevant for the identity of an ICE.

First, two particular ICEs that are about different portions of reality are not the same ICE. For example, let's call **IQE$_1$** the outline on a paper of a string "Metoprolol" written with the intention to refer to the generic drug Metoprolol, and **IQE$'_1$** the outline on another paper of a string "Metoprolol" written with the intention to refer to the active ingredient Metoprolol: **ICE$_1$**, which is concretized by **IQE$_1$**, and **ICE$'_1$**, which is concretized by **IQE$'_1$**, are not the same entity.

The specific form of an ICE can also matter to its identity. For example, both a physical formula $x(t) = \alpha \cdot t^2$ and its graphical representation may be about the same trajectory of an object along one spatial axis, but they represent this trajectory in different fashions, and are therefore different kinds of ICEs: typically, the first one would be an instance of (a group of) IAO:*Symbol* and the latter an instance of IAO:*Figure* (which are both subclasses of IAO:*ICE*).

This raises the question of what kind of variations are tolerated between IQEs that would concretize the same ICE. More specifically, consider the nine instances of *IQE* in Table 1, which mention the universal *Cognitive representation*, the relation **is_conformant_to** and the relation **is_about** as defined by Smith & Ceusters (2015).

Let us consider the instances **IQE$_i$** concretized by **ICE$_i$** ($2 \leqslant i \leqslant 10$), without presuming which of those particular **IQE$_i$** are the same. According to Smith & Ceusters (2015), when an IQE is conformant to a cognitive representation, both concretize the same ICE.[7] Therefore, **ICE$_2$** and **ICE$_3$** are the same

[7]The identification of **ICE$_2$** and **ICE$_3$** might fit with the "language of thought hypothesis" (Fodor, 1975), although this would require more thorough investigations. However, it also seems to raise some theoretical difficulties. Consider the strings "taiyō", "たいよう" and "太陽", which are three different spellings (in three different writing systems: romaji, hiragana and kanji) of

entity, and **ICE$_4$** and **ICE$_5$** are also the same entity. Moreover, **IQE$_3$** is conformant to **ICE$_4$**, and thus **ICE$_4$** and **ICE$_3$** are both the same entity. This implies that **ICE$_3$** is identical to **ICE$_5$**, showing that details such as the color, specific shape, or kind of location of a concretization does not change its informational content. If hard drive configurations are treated similarly to brain configurations, **ICE$_6$** should be considered as the same entity as **ICE$_5$**. Thus, **ICE$_2$**, **ICE$_3$**, **ICE$_4$**, **ICE$_5$** and **ICE$_6$** would be the same entity.

Arguably, even **ICE$_{10}$** is the same entity as **ICE$_2$**–**ICE$_6$** – despite Dr. Smith having had no contact with Dr. Jones and Dr. Williams. As a matter of fact, it has been decided at some point in history that a string "Metoprolol" would refer to the active ingredient Metoprolol, which led to the creation of an ICE referring to this active ingredient. This ICE was communicated from person to person by language (through medical books, oral communication, etc.), leading to the same ICE being copied and concretized as a cognitive representation of many persons, including Dr. Smith and Dr. Jones (or Dr. Williams).

On the other hand, **ICE$_7$**, **IQE$_8$** and **ICE$_9$** are different from each other, and also different from **ICE$_2$**–**ICE$_6$**. As a matter of fact, **ICE$_9$**'s nature differs fundamentally from others: it is a chain of numbers, where the others are chains of letters. But **ICE$_7$** and **IQE$_8$** are also different from **ICE$_5$**, as they are not composed by the same string: the identity of an ICE does not only depend on its reference, but also on how it refers to it.

Finally, Smith & Ceusters (2015) and Hogan & Ceusters (2016) argue that the provenance of ICEs – namely who created them, when, and with which intention – also matters to their identity. This implies that if Dr. Jones creates **DAS$_a$** 'Acetaminophen 650 mg q4h PRN' as a part of a prescription for Mr. Hubbard, and Dr. Williams creates **DAS$_z$** 'Acetaminophen 650 mg q4h PRN' as a part of a prescription for Mr. Smith, then **DAS$_a$** and **DAS$_z$** would not be the same entity.

This plurality of ICEs may seem like a hindrance to deal with synonymy in OBO Foundry ontologies. However, there is a simple way to represent the fact that all **IQE$_i$** ($2 \leqslant i \leqslant 10$) mentioned above are synonyms: a class *ICE referring to the active ingredient metoprolol* may be introduced, such that every **IQE$_i$** ($2 \leqslant i \leqslant 10$) is an instance of this class. Such a class should be enough to fulfill practical purposes related to synonymy when using PDRO.

Moreover, whatever theory of ICE is chosen, one could introduce classes of IQEs to capture similarities between concretizations. For example, one could introduce the class of concretizations that are written in English, or in French, or with blue ink, or on a computer screen. As a matter of fact, some classes of concretizations may be more likely to lead to errors than others. This could be relevant for retrospective annotations of data not initially structured according to the ontology.

4.2. The social ontology underlying PDRO

As mentioned earlier, a drug prescription may interact with the social reality (Öhlund & Goldkuhl, 2008). This subpart will first discuss several social functions of prescriptions: permitting the buying of a drug, permitting insurance reimbursement, informing that a drug can be administered (or taken), recommending it, and socially prescribing its administration; and how the distinction between the informative and recommendative dimensions can clarify the nature of some DAS. Second, it will specify a proposal

the Japanese word referring to the sun. Since they are written in different writing systems, they should presumably concretize three different ICEs, which are synonyms. However, it is unclear which of those ICEs would be concretized by the cognitive representation of a Japanese speaker: arguably, one may think about a word without thinking about it in a specific alphabet – an illiterate person could certainly do so.

on how those permissions and social prescriptions can be seen as socio-legal *specifically* dependent continuants. Finally, the last subsection will present how some deontic entities can contradict or imply the existence of other deontic entities.

4.2.1. The social functions of prescriptions

In modern health care systems, there is a background prohibition to buy or sell any prescription drug unless explicitly permitted by a prescription. A drug prescription brings about permissions overriding this background prohibition. The first function of a drug prescription is thus to permit the patient to buy drugs from a pharmacist, and the pharmacist to sell it to the patient (in many jurisdictions, it even obliges the pharmacist to do so, when required by the patient).

A drug prescription is not restricted to this function though: indeed, a doctor may write a DAS for an over-the-counter drug, which the patient is already allowed to buy. In many social systems, an additional role of drug prescriptions is to authorize insurance reimbursement: this is the second function of drug prescriptions. But a doctor may also write a drug prescription for an over-the-counter drug that would not be reimbursed. This shows that there are other important additional functions of drug prescriptions, that will now be analyzed: informing, recommending, and socially prescribing.

Given the medical condition of a patient, a doctor can do two things: inform him that he could take a specific drug in his situation (that's the third function), or recommend him to take this drug (that's the fourth function). Most of the times, the doctor not only wants to inform his patient, but also to recommend him to take the drug. This is not always the case though: in some cases, a doctor may only inform him that he could take this drug given his situation, without recommending it. For example, he could consider that the balance between side-effects and benefits is not clearly in favor of the patient, without being able to exclude the possibility that the patient would have the benefits without the side-effects; and thus, if properly informed, the patient may be allowed to take the medication based on his own evaluation of his situation (consider the case of Ativan mentioned earlier). More generally, the doctor may not want to (or cannot) deny the right of the patient to take this drug. He could also want to let the patient decide whether his condition is impacting his well-being enough to justify taking the medication. In all those cases, the doctor could inform the patient about the possibility to take this medication without recommending it. In most cases, however, a doctor arguably recommends the patient to take the drug he prescribes to him. The act of recommending could be defined as the act of evaluating this course of action as desirable. More specifically, if P_1 recommends P_2 to do A, then P_1 judge that it would be desirable (or adequate, or good) that P_2 would do A, given his knowledge of A's consequences, P_2's own values and P_1's own ethical commitments (e.g. deontological commitments such as beneficence, non-maleficence, etc. – cf. Beauchamp & Childress, 2001).

In a society where doctors would have totally non-paternalist roles, doctors would only inform – and possibly recommend – patients about the drugs they can take. But in a society in which doctors have more paternalist roles, a doctor also prescribes in a stronger sense his patient to take some drugs: the informational drug prescription brings about a social prescription to administer the drug to the patient (or for the patient to take it himself), as specified in the DAS. This social prescription is a normative entity that can be seen as a mild obligation, whose intensity depends on the strength of the paternalistic dimension of the doctor role in his society.

There are at least two ways to understand "mild" in this context. In the first construal, social prescription would follow the logic of obligation (McNamara, 2014), but the penalty or blame in case of violation of a recommendation would generally be milder than the penalty or blame in case of violation of a full-blown obligation. For example, in a society where doctors have weak paternalist roles, the

penalty that a patient would incur if he does not take his drug as prescribed would be a verbal reprimand from his doctor, and maybe some mild social disapprobation from society (as well as possibly some insurance-related consequences). A second construal of the notion of mild obligation would use so-called "fuzzy deontics" introduced by Sadegh-Zadeh (2012). He suggests to "fuzzify" the concept of obligation: obligation can have various degrees. This leads to a ranking of norms according to the degree of obligatoriness of what they prescribe. Thus, a doctor-patient social prescription may be interpreted as a fuzzy obligation with a degree lower than 1; and various social prescriptions could have different degrees of obligatoriness.

Note that those five functions of prescriptions do not always concern the patient, but may concern e.g. some relatives in charge of deciding whether the patient will take the drug, in case the patient is incapacitated in some way. Moreover, there may be a sixth social function of drug prescriptions in some circumstances, namely to command other health care professionals (such as nurses) who are in charge to administer the drug to the patient. This command is generally a stronger obligation than the mild obligation that bears on the patient: it should generally be followed by the health care professional, although it might be objected to – in case e.g. of mistake in the prescription, or conscientious objection (such as helping a patient to die, in some jurisdictions).

This distinction between information and recommendation could also be useful to formalize important distinctions between DAS, clarifying the two possible meanings of "PRN" mentioned earlier in Section 1. This distinction could be implemented in the future in PDRO by distinguishing "informative DAS" (DAS that are parts of a prescription informing the patient that he can take a given drug at a given dosing) from "recommendative DAS" (DAS that are parts of a prescription recommending the patient to take a given drug at a given dosing).

Finally, note that some permissions or recommendations created by some informational prescriptions might imply external obligations for the patient. For example, in some countries, it is compulsory to be treated for tuberculosis. Also, it might be ethically required to continue an antibiotic treatment once started, to avoid antimicrobial resistance at a societal level. However, it is not the informational prescription itself which specifies such legal or ethical obligations: the obligation is specified by laws or ethical norms that are external to the prescription.

4.2.2. Social prescriptions as socio-legal specifically dependent continuants

Drug prescriptions have been analyzed as bringing about a permission, and sometimes a mild form of obligation, which raises the question of what are such so-called "deontic" entities.

The permission of an individual to buy a medication M, and his social prescription to take it, share some commonalities with a socio-legal generically dependent continuant; namely, they come into existence through a social act of prescribing M, and are concretized by specific roles: the role of patient allowed to buy M, and the role of patient prescribed to take M. Using terms introduced by Brochhausen et al. (2013), the patient who gets the permission to receive M would be called the "declaration target" of this permission; he is the bearer of the relevant permission and social prescription brought about by the writing of the prescription, which is a document act. As for the doctor issuing the permission, he is the bearer of a "declaration performer role": he bears a role that is realized by him being the agent in a declaration, namely signing the prescription of M.

The introduction of socio-legal generically dependent continuants has been motivated by the transferability of claims and obligations: "What makes claims and obligations different from the color of my shirt is that they are transferable" (Brochhausen et al., 2013) However, the permission to buy a medication differs from a socio-legal generically dependent continuant as it cannot be transferred from one individual to another individual: if Mr. Hubbard has the same condition as Mr. Wilson, and is allowed

to buy the same medication under the same modalities, then two different instances of permissions will exist (one inhering in Mr. Hubbard, and another one inhering in Mr. Wilson), but the permission given to Mr. Hubbard cannot be transferred to Mr. Wilson. This is sometimes made very clear by drug notices that specify explicitly that the drug has been prescribed for one specific person, and should not be taken by anyone else, even if they have the same symptoms.

Thus, social permissions to buy or sell a medication and social prescriptions to take it seem to be socio-legal *specifically* dependent continuants. Indeed, suppose that Mr. Hubbard is allowed to buy Metoprolol and is socially prescribed to take it; if he disappears, then both his permission and social prescription disappear with him – which is the mark of specifically dependent continuants. That is, the same way that the existence of transferable claims and obligations motivate the introduction of socio-legal generically dependent continuants, the existence of non-transferable claims and obligations motivate the introduction of socio-legal *specifically* dependent continuants.

4.3. Conclusion

By formalizing the informational parts of a prescription, PDRO enables the annotation of real-world prescriptions at various mereological levels. It supports, for example, the specification of a drug product based on its active ingredient(s), its branded name, its strength(s) or its form, avoiding the ambiguities and overspecificities often encountered in e-prescribing systems. Complex dosing instructions can be represented in a coherent manner, as illustrated by the example of Amoxicillin for bronchitis. This is achieved by dissociating the instructions for an entire drug administration from the instructions for a single dose administration. In addition, the conditions determining those specifications have been distinguished, and illustrate how synonymous statements can play the role of these conditions to cover the variety of expressions found on prescriptions.

We discussed the nature of ICEs and suggested that classes of synonymous ICEs – that is, ICEs that are about the same thing – can fulfill several applied purposes. We also distinguished five social functions of drug prescriptions: permitting the buying of a prescription drug, enabling insurance reimbursement, informing that a drug can be administered to a specific patient, recommending its administration, and giving rise to a mild obligation to administer it. Additionally, the ontological analysis of social entities involved in drug prescriptions can contribute to a more general and encompassing theory of social entities in the OBO Foundry framework. In particular, we suggest that socio-legal generically dependent continuants should be completed by socio-legal specifically dependent continuants such as the permission to buy a specific drug, or the recommendation or mild obligation to take it at a given dosage.

PDRO could both improve the semantics of electronic prescriptions and prospectively enable the interoperability of prescription data. Used in conjunction with other OBO Foundry ontologies, it can be used to express complex decision-support rules to identify potentially inappropriate prescriptions among hospitalized elderly patients (Cossette et al., 2017). With the introduction of action specifications and conditions, we can also envision, for example, smartphone applications that guide patients with polypharmacy in safely taking their medication as directed, and thereby reduce adverse drug events. In particular, as touched on earlier, dosing instructions by doctors are often incompletely specified. For example, the string “bid” specifies taking two doses during a day, without specifying when those doses should be taken. While having a patient taking a pill at 8 am followed by one at 9 am would theoretically fulfill the instruction, this is clearly not the intent of the physician and could lead to important adverse drug events. To address this ambiguity in local electronic prescriptions, we are developing statements in an additional ontological layer that can be used as additional dosing conditions, such as the minimum and maximum

time elapsed since the previous dose before the next one is taken. On top of potentially reducing adverse drug events due to administration mistakes, the use of explicit, temporally constrained conditions is essential to enable the creation of smartphone applications to help patients take their medication at the right time and in a safe manner.

Future research will investigate how to formalize relations of aboutness in PDRO, which introduces special challenges for an OWL representation. For example, an instance of ICE such as 'amoxicillin' is not about a specific instance, but about a whole class of *Amoxicillin* drugs; and OWL does not allow representing relations between an instance and a class (except instantiation). Therefore, alternative forms of representation – for example following the referent tracking model (Ceusters & Smith, 2006) – could be preferred to adequately represent such aboutness relations. Upcoming work will also deal with developing application ontologies that complete the reference ontology that is PDRO with a formalization of local norms. To this goal, we are developing additional application ontology layers which describe electronic drug prescriptions that conform fully to local norms in the Canadian province of Québec. Alternative application ontologies can be built to express the norms in jurisdictions other than Quebec. On a practical level, such ontologies could be used to guide an exchange format or annotate and structure an existing format like the Fast Healthcare Interoperability Resources (FHIR; Bender & Sartipi, 2013) for communicating standardized electronic prescription data.

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