A classification of instructions in drug prescriptions and pharmacist documents

Adrien Barton[a,b], Paul Fabry[b], Jean-François Ethier[b]

[a] *Institut de Recherche en Informatique de Toulouse (IRIT), CNRS, France*
[b] *Groupe de Recherche Interdisciplinaire en Informatique de la Santé (GRIIS), Université de Sherbrooke, Quebec, Canada*

Abstract

Drug prescriptions are often ambiguous or insufficiently formalized. The Prescription of DRugs Ontology, an OBO Foundry candidate, has so far analyzed the internal structure of instructions in drug prescriptions. This paper completes this investigation by analyzing the kinds of items containing such instructions that appear on drug prescriptions or pharmacists documents. This article distinguishes drug prescription items that initiate, continue, modify or stop a drug administration, and provides a few axioms for those classes. It also classifies items written by pharmacists, namely the record items, which typically specify further the original prescription; and the drug distribution reports, which state how much of a drug has been dispensed. Several medical scenarios clarify important distinctions between those items. Those distinctions have the potential to support a Learning Health System founded on an ontology, and raise theoretical questions about the nature of directive information entites, and synonymy between informational content entities.

Keywords:

Drug prescription; OBO Foundry; Information content entity; Directive information entity

Introduction

Decision support systems for drug prescription and drug administration could bring tremendous value to public health: as a matter of fact, adverse drug events cause about 5% of all hospital admissions (1,2) and are estimated to be the 4th to 6th leading cause of death in the US (2,3). However, the problem of insufficient data standardization among drug prescriptions is well-known and leads to inappropriate or ambiguous prescriptions (4).

A coherent and complete representation of prescriptions could be especially helpful in Learning Health Systems (LHS), in which health information generated from patients is continuously analyzed to improve knowledge that will be transferred to patient care through decision support systems (5). As a matter of fact, a LHS relies heavily on information exchange between hetereogeneous information systems.

For maximal coherence, LHS can be founded on ontologies (see (6) for an example). Indeed, ontologies could help to solve the "Tower of Babel problem" in medical informatics (7). The Prescription of DRugs Ontology (PDRO, read "Pedro") has been developed to address this issue in the context of drug prescriptions (8). It could be used to support health applications assisting prescribers in writing prescriptions, pharmacists in distributing the drugs and patients in taking their drugs.

The centerpiece entity of the PDRO ontology is the *Drug administration specification* (DAS), which specifies which drug should be taken by the patient, and according to which posology. Another important entity is the *Drug dispensing specification* (DDS), which specifies to the pharmacist how much of the drug he should dispense to the patient. For example, in 'metoprolol 100 mg PO BID, 28d × 13', 'metoprolol 100 mg PO BID' is the DAS, and '28d × 13' is the DDS, specifying to distribute 13 times enough Metoprolol for 28 days. The parts of a DAS have been investigated in details (8). For example, the DAS mentioned above has as parts 'metoprolol' (a *Drug product specification*), '100 mg' (a *Dose quantification specification*), 'PO' (for "per os", meaning "per mouth"), a *Route of administration specification*), 'BID' (meaning "twice a day", a *Dosing condition*; for a more thorough presentation of PDRO, see (8)).

However, the internal structure of a DAS is not the only relevant feature for an ontology of drug prescriptions. Another important question is the clarification of the kinds of items that can appear on drug prescriptions or pharmacists documents, which may contain such DAS and DDS (see figure 1). Indeed, a drug prescription can prescribe not only the initiation of a drug administration, but also the continuation, modification, or cessation of a drug administration.

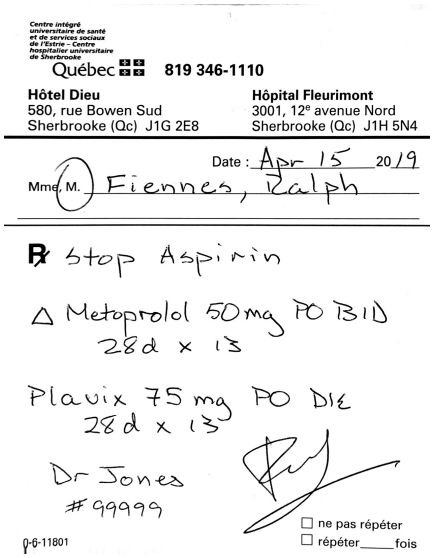

Figure 1 – Example of prescription with various drug prescription items

Moreover, DAS can be written not only by prescribers for therapeutic reasons, but also by pharmacists in order to guide the patient in the administration of the drug, as well as for archiving purposes. The latter items are especially important, are they are

often the main source of information on the drugs a patient is or has been taking, given that the original doctor's prescription is often not available outside the originating clinic. It is therefore important to clarify the ontological nature of the various items that can be written by prescribers and pharmacists on a drug prescription or a pharmacist record, in order to be able to classify them correctly in an ontology-based information system.

Methods

The OBO (Open Biomedical Ontologies) Foundry (9) consists in a repertoire of open source, applied ontologies in the biomedical domain. It is based on a set of best practices in the building of ontologies, structured upon the upper ontology BFO (Basic Formal Ontology). Each ontology aims at providing a logically coherent, scientifically accurate representation of its domain, promoting ontology re-use and maximal orthogonality of the various covered domains. The ontology of drug prescriptions PDRO has been developed as an OBO Foundry candidate (8) and can be found on the OBO Foundry website at http://www.obofoundry.org/ontology/pdro.html .

BFO classifies entities into *Independent continuant*, which encompasses e.g. *Material object* – like a metoprolol 50 mg tablet; *Dependent continuant*, which encompasses e.g. *Quality* – like the shape of a metoprolol 50 mg tablet; and *Occurrent,* which encompasses e.g. *Process* – like the process of Mr. Fiennes taking metoprolol 50 mg twice a day for a year. The OBO Foundry also encompass the Information Artifact Ontology IAO (10), which introduces *Information content entity* (abbreviated "ICE") as a subclass of *Generically dependent continuant*, whose instances can inhere in various bearers. For example, the same DAS, which is an ICE, can first inhere in the brain of a doctor, then in the hard drive of a computer, and finally in a printed paper. ICEs are characterized by being about something – for example, the ICE 'metoprolol' on a drug product monograph is about the class of metoprolol drug products.

Following (10), an ICE can be concretized by some quality; for example, a prescription can be concretized by the outline of a string of characters on a paper, by a configuration of a hard drive or even by some neuronal configuration inhering in a human. In the following, when we speak of e.g. the entity 'metoprolol' (using single quotes), we refer to an *ICE* that can be concretized by the string of characters "metoprolol" (whereas the class *Metoprolol* is a subclass of *Independent continuant*).

This article focuses on classifying the various kinds of prescriptions item that can appear on drug documents written by prescribers and pharmacists. The mereological (that is, parthood) structure of those items is described using the relations from BFO **has_part** and **part_of**. We use the OWL Manchester syntax to write the axiom in the ontology (11). Universals (or classes) are written in italic (e.g. "*DAS*"), and particulars are written in bold (e.g. "**DAS$_1$**" to refer to the DAS 'metoprolol 100 mg PO BID' written by Dr. Jones to Mr. Fiennes on 2018/01/01). When introduced for the first time, entity names will be prefixed by the ontology that introduce them; entity names written without prefix belong to the PDRO ontology.

IAO:Information content entity (ICE)
- *IAO:Document*
  - *Drug prescription*
  - *Pharmacist record*
- *IAO:Directive information entity*
  - *Drug prescription item* (DPI)
    - *Drug administration prescription item* (DAPI)
      - *Drug administration initiation prescription item* (DAIPI)
      - *Drug administration continuation prescription item* (DACoPI)
      - *Drug administration modification prescription item* (DAMPI)
    - *Drug cessation prescription item* (DCPI)
  - *Pharmacist record item* (PharRI)
  - *IAO:Action specification*
    - *Drug administration specification* (DAS)
    - *Drug dispensing specification* (DDS)
- *IAO:Data Item*
  - *Pharmacist drug dispensing report* (PharDDR)

Figure 2 – Taxonomy of relevant classes

2018/01/01 **DAIPI$_1$** = 'metoprolol 100 mg PO BID, 28d × 13'

2018/01/01 **PharRI$_{1.1}$** = 'Apo-Metoprolol 50 mg, 2 tab orally 8 am and 2 tab orally 8 pm every day. 112 tabs per distribution'

2018/01/01 **PharDDR$_{1.1.1}$**='2018/01/01, 112 tabs distributed'
2018/01/25 **PharDDR$_{1.1.2}$**='2018/01/25, 112 tabs distributed'
2018/02/22 **PharDDR$_{1.1.3}$**='2018/02/22, 112 tabs distributed'
2018/03/22 **PharDDR$_{1.1.4}$**='2018/03/22, 112 tabs distributed'
2018/04/19 **PharDDR$_{1.1.5}$**='2018/04/19, 112 tabs distributed'
2018/05/17 **PharDDR$_{1.1.6}$**='2018/05/17, 112 tabs distributed'
2018/06/14 **PharDDR$_{1.1.7}$**='2018/06/14, 112 tabs distributed'

2018/07/12 **PharRI$_{1.2}$** = 'Vivo-Metoprolol 50 mg, 2 tab orally 8 am and 2 tab orally 8 pm every day'

2018/07/12 **PharDDR$_{1.2.1}$** = '2018/07/12, 112 tabs distributed'
2018/08/09 **PharDDR$_{1.2.3}$** = '2018/08/09, 112 tabs distributed'
2018/09/06 **PharDDR$_{1.2.4}$** = '2018/09/06, 112 tabs distributed'
2018/10/04 **PharDDR$_{1.2.4}$** = '2018/10/04, 112 tabs distributed'
2018/11/01 **PharDDR$_{1.2.5}$** = '2018/11/01, 112 tabs distributed'
2018/11/29 **PharDDR$_{1.2.6}$** = '2018/11/29, 112 tabs distributed'

2018/12/22 **DACoPI$_2$** = 'metoprolol 100 mg per mouth twice a day, 28 days × 13'

2018/12/27 **PharRI$_{2.1}$** = 'Vivo-Metoprolol 50 mg, 2 tab orally 8 am and 2 tab orally 8 pm every day. 112 tabs per distribution'

2018/12/27 **PharDDR$_{2.1.1}$** = '2019/01/01, 112 tabs distributed'
2019/01/24 **PharDDR$_{2.1.2}$** = '2019/01/25, 112 tabs distributed'

2019/02/21 **DAMPI$_3$** = 'metoprolol 50 mg PO BID, 28d × 13'

2019/02/21 **PharRI$_{3.1}$** = 'Vivo-Metoprolol 50 mg, 1 tab orally 8 am and 1 tab orally 8 pm every day. 56 tabs per distribution'

2019/02/21 **PharDDR$_{3.1.1}$** = '2019/03/15, 56 tabs distributed'
2019/03/21 **PharDDR$_{3.2.2}$** = '2019/04/12, 56 tabs distributed'

2019/04/15 **DCPI$_4$** = 'Stop metoprolol'

Figure 3 – Examples of relevant instances

Results

This section will introduce the new entities that are represented in PDRO (see Figure 2 for a taxonomy and a list of abbreviations of the relevant entities in this paper), illustrated by examples of instances that will be introduced progressively (see Figure 3, on which the informational entities created by the precriber are underlined, and those created by the pharmacist are not underlined).

Drug prescription item (DPI)

A drug prescription can prescribe the initiation a drug administration, but it can also prescribe the continuation, modification or cessation of a drug administration. Consider the following scenario $S_{METOPROLOL\_1}$, illustrated by Figure 3. On 2018/01/01, in Quebec, Dr. Jones deems that her patient Mr. Fiennes should take a drug with 100 mg of active ingredient metoprolol twice a day for hypertension control until further notice. She then writes **$DAIPI_1$**= 'metoprolol 100 mg PO BID, 12 × 1 month', where 'DAIPI' stands for "Drug administration initiation prescription item", abbreviated as "initiation item" (more details on this below). **$DAIPI_1$** aims at initiating a new drug administration of 100 mg of metoprolol per mouth twice a day every day. It has as parts **DAS_1** = 'metoprolol 100 mg PO BID' which directs this administration, and **DDS_1** = '28d × 13', which directs the pharmacist to distribute enough metoprolol to the patient for 28 days, 13 times. Note that the instruction "28d × 13" characterize the dispensing process, and not the time during which the drug is supposed to be taken: here, Mr. Fiennes is supposed to take metoprolol daily until further notice – probably more than one year; however, because the quantity of drugs dispensed to patient is strictly regimented, Mr. Fiennes can only buy the quantity necessary for 28 days, 13 times. Before he has taken his last metoprolol pill, Mr. Fiennes is supposed to meet again his doctor, who can order a distribution for another year (unless some medical complications have appeared or other clinical reasons).

Consequently, nearly one year later, on 2018/12/22, after Mr. Fiennes has obtained the last batch of metoprolol he could get with his first prescription, Dr. Jones writes to him a second prescription with the item **$DACoPI_2$** = 'metoprolol 100 mg per mouth twice a day, 28 days × 13', where "DACoPI" stands for "Drug administration continuation prescription item", abbreviated as "continuation item". Here, **$DACoPI_2$** has two parts: **DAS_2** = 'metoprolol 100 mg per mouth twice a day', which is synonymous with **DAS_1**, and indicates to take the same drug in the same way; and **DDS_2** = '28 days × 13' that indicates the pharmacist to distribute enough metoprolol for 28 days to Mr. Fiennes 13 more times.

On 2019/02/21, the medical condition of Mr. Fiennes worsens (he develops bradycardia), and Dr. Jones deems that his patient now needs to take a lower dose of metoprolol every day. Dr. Jones writes then **$DAMPI_3$** = 'metoprolol 50 mg PO BID, 28d × 13', where "DAMPI" stands for "Drug administration modification prescription item", abbreviated as "modification item". **$DAMPI_3$** has as part **DAS_3** = 'metoprolol 50 mg PO BID', which halves the dose to be taken on each administration, comparatively to the dose specified by **DAS_1** and **DAS_2**.

Finally, on 2019/04/15, Dr. Jones realizes that Mr. Fiennes has been developing an intolerance to metoprolol (heart block) and should not take this medication anymore. She then writes a prescription specifying **$DCPI_4$** = 'Stop metoprolol', where "DCPI" stands for "drug cessation prescription item", abbreviated as "cessation item".

To account for the various kinds of information content entities (ICE) that are illustrated above, we introduce a taxonomy of categories presented in figure 3, as subclasses of IAO:*Directive information entity* (with abbreviated names mentioned after). We provide the following Aristotelian definitions (7):

- *Drug prescription item* (DPI, abbreviated as "prescription item"): "A directive information entity that is a part of a drug prescription and specifies some action(s) related to one or several drugs. It is typically intended to direct some actions to be performed by a patient and pharmacist(s). It may also specify a healthcare objective."

- *Drug administration prescription item* (DAPI): "A drug prescription item that specifies the administration of a drug. It may also specify the dispensing of a drug, and it typically gives pharmacists the permission to dispense the drug product to a patient. It may also specify a healthcare objective."

- *Drug administration initiation prescription item* (DAIPI): "A drug administration prescription item that specifies the initiation of the administration of a drug. It may also specify the dispensing of a drug."

- *Drug administration continuation prescription item* (DACoPI): "A drug administration prescription item that specifies the continuation of the administration of a drug whose initiation was specified by a former drug prescription. The DAS contained in the drug administration continuation item is synonymous with the DAS contained in the drug administration prescription item of this former drug prescription. The drug administration continuation item may also specify the dispensing of a drug."

- *Drug administration modification prescription item* (DAMPI): "A drug administration prescription item that specifies the modification of the administration of a drug product. It may also specify the dispensing of a drug."

- *Drug cessation prescription item* (DCPI): "A drug prescription item that specifies the cessation of the administration of a drug."

Those considerations show that all drug prescriptions do not contain a DAS: some drug prescriptions specify only a cessation of drug administration, and many cessation items do not have a DAS as part – consider e.g. **$DCPI_0$**: 'Stop acetaminophen' or **$DCPI_1$**: 'Stop oral medication' (however, some cessation items have a DAS as part, such as **$DCPI_2$**: 'Stop metoprolol 50 mg PO BID'). All drug prescriptions contain a prescription item though:

Drug prescription SubClassOf **has_part** some *DPI*

Drug Administration Prescription Item (DAPI)

A Drug Administration Prescription Item (DAPI) specifies the administration of a drug. Therefore, it contains a DAS:

DAPI SubClassOf **has_part** some *DAS*

However, a particular administration item might not explicitly states whether it intends to initiate a drug administration (in which case it is an initiation item), to continue a drug administration (in which case it is a continuation item), or to modify a drug administration (in which case it is a modification item). For example, without information about the context, it would not be

clear whether **DAS1**='metoprolol 100 mg PO BID', **DAS2**='metoprolol 100 mg per mouth twice a day' or **DAS3**='metoprolol 100 mg PO BID' mentioned above are supposed to initiate (in which case they are part of an initiation item), continue (in which case they are part of a continuation item) or modify (in which case they are part of a modification item) a drug administration.

Consider another ambiguous example with the following scenario SNOVORAPID. Suppose that on 2018/02/01, Dr. Livingstone writes on a prescription for Mr. McMurphy, who is diabetic, **DPI5** = 'NovoRapid 10u S/C before breakfast, 28d × 13' (where "10u" stands for 10 units", and "S/C" stands for "sub-cutaneous"); and on 2018/03/01, he writes to him **DPI6** = 'NovoRapid 10u S/C before lunch, 28d × 13'. Without more specification, it is not clear whether **DPI6** is a modification item intended to modify the time of administration of NovoRapid from before breakfast to before lunch, or whether it is an initiation item intended to add to the morning administration of NovoRapid another administration at lunch time. In such a case, it is of utmost importance to know whether **DPI6** is a modification item or an initiation item. Some notations may be used to clarify this: in Quebec, for example, a triangle symbol "Δ", as in Figure 1, (or the word "modifier") is sometimes added in a drug prescription next to an item in order to clarify that it is a modification item, and not an initiation item.

In some cases, prescribers do not make the effort of clarifying whether a particular DPI is an initiation item or a modification item because it does not have any clinical importance. For example, a doctor prescribing 'Aspirin 81 mg PO once a day' may not specify whether this is an initiation item or a modification item, as Aspirin 81 mg would typically be administered only once a day (note, however, that the patient may not be aware of this, and therefore, even in such cases it might be useful to clarify to the patient whether the DPI is an initiation item or a modification item).

Because of this ambiguity, we need the catch-all class *DAPI* to encompass the classes *DAIPI*, *DACoPI* and *DAMPI*: when we don't know whether a DAS intends to initiate or modify a drug administration, we can classify it as being a part of an administration item, without specifying whether this administration item is an initiation item, a continuation item or a modification item.

To clarify whether a administration item is a modification item or not, a modification item will often not only specify an addition to the former drug administration, but recapitulate how the whole administration of the drug should now be done. For example, if Dr. Livingstone wants to add a NovoRapid administration before lunch to the one before breakfast, instead of writing **DPI6**, he might write **DPI7**: 'NovoRapid 10 u S/C twice a day before breakfast and before lunch, 12 × 1 month'. The two next subparts will now elaborate on continuation items and modification items.

Drug Administration Continuation Prescription Item (DA-CoPI)

A continuation item specifies the continuation of an ongoing drug administration. A continuation item includes a DAS synonymous to a formerly prescribed DAS, as well as a DDS that will direct a new dispensing of the drugs to the patient. Therefore, we introduce the following axiom:

DACoPI SubClassOf **has_part** some *DDS*

(the axiom "SubClassOf **has_part** some *DAS*" is inherited by *DACoPI*, as it is a subclass of *DAPI*) For example, in SMETOPROLOL_1, **DACoPI2** has as part **DAS2** that is synonymous with **DAS1**, as well as **DDS2**.

Drug Administration Modification Prescription Item (DAMPI)

A modification item specifies the modification of the administration of a specific drug product (note that the term "modification" should be understood here in an informal way, as in BFO, processes cannot change, contrarily to continuants (12)). This means that a modification item can modify the posology or the medical strength of a drug administration, but not the active ingredient, excipient or drug product. There is indeed a significant medical difference between changing the posology or the strength of a drug on one hand, and changing the drug product on the other hand.

After this overview of the items that can be written on a drug prescription by prescribers, we can now turn to analyze the items written on pharmacists documents by pharmacists, and how they articulate with the items written by prescribers.

Pharmacist record item (PharRI)

An important source of knowledge about the drugs taken by patients are items written by pharmacists that we call *Pharmacist record item* (PharRI). We define a a pharmacist record item as "A directive information entity written by a pharmacist and containing one DAS and one DDS. This DAS is similar to or provides further specifications about the related DAS formerly written by a prescriber. The DDS mentions how much of the drugs should be dispensed at each dispensing "

To illustrate this, consider again the scenario SMETOPROLOL_1. The drug prescription containing **DAIPI1** will be entered in an electronic health record and sent to Mr. Fiennes' pharmacy. While dispensing the medication according to the prescription on 2018/01/01, the pharmacist Mr. White writes the following pharmacist record item in his records: **PharRI1.1** = 'Apo-Metoprolol 50 mg, 2 tab orally 8 am and 2 tab orally 8 pm every day. 112 tabs per distribution'. **PharRI1.1** is composed by two parts: the drug administration specification **DAS1.1** = 'Apo-Metoprolol 50 mg, 2 tab orally 8 am and 2 tab orally 8 pm every day', and the drug distribution specification **DDS1.1** = '112 tabs per distribution'. Whereas **DAS1** (written by Dr. Jones) only instructed Mr. Fiennes to take 100 mg of any drug product containing the active ingredient metoprolol twice a day, **DAS1.1** (written by the pharmacist Mr. White) instructs him more specifically to take 2 tabs of 50 mg of Apo-Metoprolol at 8 am, and 2 tabs at 8 pm, every day.

In cases where the DAS written by a prescriber is already very specific, the pharmacist might write a similar DAS. Note also that a pharmacist might write several different pharmacist record items based on the same DAS, e.g. if he runs out of one specific drug. For example, on 2018/07/12, Mr. White has run out of Apo-Metoprolol. Therefore, he decides to dispense to Mr. Fiennes Vivo-Metoprolol, another drug that contains the same active ingredient metoprolol. Thus, he writes **DAS1.2** = 'Vivo-Metoprolol 50 mg, 2 tab orally 8 am and 2 tab orally 8 pm every day'. In this case, both **DAS1.1** and **DAS1.2** provide additional instructions by the pharmcist to the patients compared to what was specified by the prescriber in **DAS1**.

Note that in some areas such as California (13) or Québec (cf. law 41 (14)), pharmacists can prescribe medications for problems for which the patient has not visited a doctor – such as urinary infections. In this case, the pharmacist acts as a prescriber before acting as a dispenser. Therefore, he would write first an administration item in his prescriber role, before writing a pharmacist record item in his regular drug dispenser role (in such cases, the DAS contained in the pharmacist record item would generally be similar to the DAS contained in the administration item).

As we have seen, a DDS can be part of an administration item or of a pharmacist record item. In the former case, it specifies the total quantity of drug that is to be dispensed on the basis of this prescription (e.g. '28d × 13' in **DAIPI$_1$**); and in the latter case, it specifies the quantity of drug that is to be dispensed each time the pharmacist dispenses the drug to the patient (e.g. '112 tabs per distribution' in **PharRI$_{1.1}$**).

Finally, we define a *Pharmacist record* as "A document containing all the pharmacist record items pertaining to one patient and related to a given time period." A typical pharmacist record will include all pharmacist record items that were written in the last year for the patient.

Pharmacist drug dispensing report (PharDDR)

Another important entity is the *Pharmacist drug dispensing report* (PharDDR), that states how much of a given drug has been dispensed on one occasion. A pharmacist drug dispensing report does not instruct to realize some instruction (such as a drug dispensing), but instead specifies how much of a given drug has been dispensed. For example, on figure 2 above, **PharDDR$_{1.1.1}$**='2018/01/01, 112 tabs distributed' states that 112 tabs of the drug specified in **PharRI$_{1.1}$** have been dispensed on 2018/01/01. Therefore, we classified *Pharmacist drug dispensing report* as a subclass of IAO:*Data Item*, which is defined by IAO as a "an information content entity that is intended to be a truthful statement about something (modulo, e.g., measurement precision or other systematic errors) and is constructed/acquired by a method which reliably tends to produce (approximately) truthful statements". We define a pharmacist drug dispensing report as "A data item that is part of a pharmacist information system and specifies how much of a given drug product has been dispensed to a patient."

Discussion

We will now clarify a few subtle but important distinctions between some of the information content entities mentioned above. In particular, we will show that although it is possible to write a modification item to stop a drug administration, modification items cannot always replace cessation items. Similarly, although it is possible to write a modification item to continue a drug administration, it is not equivalent to writing a continuation item to do so. Presenting the distinction between so-called "continuing drug administration conditions" and DDS will be essential for explaining the latter point.

Writing a modification item to stop a drug administration

We defined a modification item as prescribing the modification of the administration of a drug product. As we are going to see, by modifying the ending date condition of a prescription, it is possible for a modification item to have the effect of ceasing prematurely a drug administration; however, modification items cannot replace all kinds of cessation items.

Consider the following scenario S$_{AMOXICILIN}$. On 2019/01/01, Dr. Livingstone writes **DAIPI$_8$** = 'Amoxicilin 500 mg PO TID 1-14 January' for Mr. McMurphy, which initiates the administration of Amoxicilin 500 mg per mouth three times a day for 14 days. Suppose that 5 days later, the bacteria infecting Mr. McMurphy has been identified, and it was found that the infection could be treated efficiently with only 7 days of antibiotics. Two options could be pursued. First, Dr. Livingstone could write on 2019/01/07, after the third administration of Amoxicilin to Mr. McMurphy, the **DCPI$_9$** = 'Stop Amoxicilin', which specifies an immediate cessation of administration of Amoxicilin. But alternatively, he could write **DAMPI$_{10}$** = ' Δ Amoxicilin 500 mg PO TID after the third dose on January 7th 2019' at any time before or on the 2019/01/07: it is not a cessation item, but a modification item, as it modifies the duration of administration of Amoxicilin from 1-14 January (as specified in **DAIPI$_8$**) to 1-7 January. Therefore, a modification item can be used to cease the administration of a drug.

In general, however, modification items or cessation items would be used in different circumstances. For example, a cessation item would be written in case of an allergy, whereas a modification item would typically be used in cases like the one we just mentioned. Moreover, it is not always practically possible to use one or several modification items instead of a cessation item: for example, a doctor could write the cessation item "Stop all PO medications" even if he does not have access to the full list of medications that the patient is currently taking.

Continuing drug administration condition and DDS

It will be important here to stress the difference between two prescription items that might seem superficially similar. For this, consider the following scenario S$_{METOPROLOL_2}$. On 2018/01/01, Dr. Livingstone prescribes to Mr. McMurphy **DAIPI$_{11}$** = 'Metoprolol 100 mg PO BID until 2018/12/30'. We will see that this differs from the scenario S$_{METOPROLOL_1}$, in which Dr. Jones wrotes to Mr. Fiennes on 2018/01/01 **DAIPI$_1$** = 'metoprolol 100 mg PO BID, 28d × 13'. As a matter of fact, 'until 2018/12/30' is an instance of what was called in (8) a *Continuing drug administration condition* for the administration of the drug: that is, it specifies that Mr. McMurphy should take 100 mg of metoprolol per mouth twice a day until 2018/12/30. On the other hand, '28d × 13' is an instance of DDS: it prescribes to the pharmacist to dispense 13 times enough metoprolol for 28 days. Therefore, **DAIPI$_1$** specifies to Mr. Fiennes to take metoprolol 100 mg per mouth twice a day until further notice, and specifies to pharmacists to dispense to Mr. Fiennes 13 total doses for 28 days; on the other hand, **DAIPI$_8$** specifies to Mr. McMurphy to take metoprolol 100 mg per mouth twice a day until 2018/12/30, and does not specify anything explicitly to the pharmacist – who would however know, when reading **DAIPI$_{11}$**, how much of metoprolol he is authorized to dispense to Mr. McMurphy in total. This means that in regular circumstances, **DAIS$_1$** and **DAIPI$_{11}$** would have the same practical effect of enabling the patient to buy metoprolol and take it for about a year, from 2018/01/01 to 2018/12/30.

$DAIPI_1$ and **$DAIPI_{11}$** are not equivalent though. In Quebec (and many other jurisdictions), a prescription is valid for 24 months. This means that Mr. Fiennes can use his prescription to buy a 28-days-long dose of metoprolol as long as he has not bought 13 such doses, and until 2020/01/01 (that is, 24 months after the prescription was written). Suppose for example that Mr. Fiennes leaves for Florida during the month of February 2018, and forgets to bring his medication with him during this trip; as a result, he does not take any metoprolol for the whole month of February. Because he has bought 12 × 28 daily doses of metoprolol on 2018/12/30, he can still buy a quantity for 28 days of metoprolol in January 2019, as the prescription is valid until 2020/01/01. On the other hand, if this would happen to Mr. McMurphy, he could not use his prescription to buy metoprolol in January 2019, as **$DAIPI_{11}$** explicitly specifies to stop taking metoprolol after 2018/12/30 (maybe he is scheduled for a specific test on January 2019 that would be incompatible with him taking metoprolol).

Note that using instructions such as **$DAIPI_1$** instead of **$DAIPI_{11}$** can have unfortunate consequences if done improperly. Consider the scenario S_{PLAVIX}, in which Dr. Jones wants to prescribe anti-coagulation drug Plavix to Mr. Fiennes for one year (but not more, as he has significant bleeding risk factors) because he has just been implanted a cardiac stent. Incorrectly, she writes 'Plavix 75 mg PO DIE 28d × 13' on 2018/01/01 instead of 'Plavix 75 mg PO DIE until 2018/12/31' (where "DIE" means "once a day"). Dr. Zhivago, a family doctor who is less familiar with cardiac stent, interprets this as specifying to take Plavix until further notice, and '28d × 13' as a DDS that only limits the quantity of Plavix that can be dispensed with this prescription. Thus, one year later on 2018/12/22, Dr. Zhivago writes a continuation item 'Plavix 75 mg PO DIE 28d × 13' to continue the Plavix administration to Mr. Fiennes for one more year, although it was not the intention of Dr. Jones, and it is not medically advisable.

To avoid such mistakes, a system of prescription support could suggest explicitly when a drug should be taken until further notice, by specifying it explicitly – with e.g. instructions such as 'Metoprolol 100 mg PO BID *until further notice*, 12 × 1 month'.

Writing a modification item to continue a drug administration

Because of what we just saw, some modification items might also seem to have a practical effect similar to a continuation item, namely continuating the administration of a drug. We saw earlier in $S_{METOPROLOL\_1}$ that to continue the administration of metoprolol to Mr. Fiennes, Dr. Jones could write **$DACoPI_2$** on 2019/01/01, which authorizes the pharmacist to dispense 13 doses of 28 days of metoprolol to Mr. Fiennes. Alternatively, in $S_{METOPROLOL\_2}$, Dr. Livingstone could write **$DAMPI_9$** = 'metoprolol 100 mg PO BID until 2019/12/29' on 2018/01/30 to authorize Mr. McMurphy to buy enough metoprolol for one more year. Note that **$DAMPI_9$** is a modification item that modifies the continuing condition specified by **$DAIPI_8$** from 'until 2018/12/30' to 'until 2019/12/29', rather than a continuation item. However, as we saw earlier, it is not equivalent to write **$DACoPI_2$** or **$DAMPI_9$**, as a DDS is not equivalent to a continuing drug administration condition.

Limitations

The entities introduced above provide interesting use cases to advance further several theoretical investigations concerning BFO and mid-level OBO Foundry ontologies such as OBI and IAO. First, what is the connection between a directive information entity such as an administration item and the process it directs? Does an administration item direct a class of processes, or only the process that will indeed be realized?

Second, what is the connection between directive information entities that direct compatible processes (such as **DAS_1** and **$DAS_{1.1}$**, or **DAS_1** and **$DAS_{1.2}$**), and those that direct incompatible processes (such as **$DAMPI_3$** and **$DCPI_4$**)?

Third, what is the nature of a synonym relation between ICE? How can we represent the fact that **DAS_1** and **DAS_2** are synonyms?

Finally, drug prescriptions can give rise to normative and social entities such as permissions, recommendations or obligations (8,15,16). How do conflicting prescription items interact in such matter? After a prescription item gave rise to a first permission, can another prescription item make this permission disappear? Or does it just give rise to a conflicting normative entity? And what does it mean for normative entities to conflict?

Conclusions

This article has distinguished several kinds of prescription items, illustrated by the scenario $S_{METOPROLOL\_1}$: first, administration items, which are divided among initiation items, continuation items, and modification items; as well as cessation items. This has been completed by an account of some items written by pharmacists, namely pharmacist record items, which typically specify further the DAS written by the prescriber; and pharmacist drug dispensing reports, which state how much of a drug has been dispensed. A few axioms have been specified: a *Drug prescription* has a prescription item as part, a *DAPI* has a *DAS* as part, and a continuation item has a *DDS* as part. The scenario $S_{AMOXICILIN}$ has shown that although a modification item can be written to direct the cessation of a drug administration, modification items cannot always replace cessation items. Similarly, the scenario $S_{METOPROLOL\_2}$ has shown that although a modification item can be written to direct the continuation of a drug administration, using a modification item is not equivalent to using a continuation item for this goal.

Those distinctions are essential for supporting a LHS, and have the potential to clarify several ambiguities. Decision support systems could force the prescriber to specify, when he writes an administration item, whether this is an initiation item, a continuation item or a modification item, to avoid problems such as the one presented in $S_{NOVORAPID}$; and force him to separate clearly the instructions to the patient (which are expressed by a DAS) and the instructions to the pharmacist (which are expressed by a DDS), to avoid problems such as the one presented in S_{PLAVIX}.

Some prescribing systems are problematic. Many of them can only represent the pharmacist record items with the exact commercial drug product that was dispensed, but do not represent the DAS written by the prescriber. For example, in $S_{METOPROLOL\_1}$, such a prescribing system would represent **$DAS_{1.1}$** and **$DAS_{1.2}$**, which fully specifies the drug to be administered, but not **DAS_1**, which only specifies the active ingredient. In such a system, it is not possible to determine whether the pharmacist wrote **$DAS_{1.2}$** because he ran out of Apo-Metoprolol and decided to prescribe Vivo-Metoprolol instead, or because Dr. Jones found out that Mr. Fiennes had an allergy to the excipient in Apo-Metoprolol, and

therefore decided that Mr. Fiennes had to take Vivo-Metoprolol instead. Such distinctions, however, are highly relevant from a clinical point of view.

Those ontological distinctions could also support, for quality control, the automatic checking of the congruence between the DAS written by the pharmacist and the DAS written by the prescriber; the automatic writing of well-formed DAS by the pharmacist, that give totally unambiguous instruction to the patients; or automatic support to drug administration, such as smartphone apps reminding the patient which medication he should take, and when.

Actually, the conceptual clarification that was presented can be useful to all kind of information systems beyond those directly based on ontologies; for example, for the creation of a database schema representing drug prescriptions.

More fundamentally, those distinctions raise theoretical questions about how a directive information entity is related to a process, the relations between directive information entities that direct compatible or incompatible processes, and how to define a synonymy relation between ICE[1].

Address for correspondence

Jean-François Ethier, JF.Ethier@usherbrooke.ca

Adrien Barton, adrien.barton@irit.fr

Acknowledgments

We thank three reviewers for their helpful suggestions.

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[1] In this spirit, Ceusters et al. (17) define a "co-referential-with" relation as holding between two ICEs when they describe exactly the same portion of reality.