

A Multilevel Model of Pharmaceuticals

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Abstract. Pharmaceuticals, i.e., medical drugs, are of pivotal importance in medical care delivery: they are part of hospital processes starting from clinical pathways, through financial accounting, to, e.g., inventory management. Therefore, it seems reasonable to account for medical drugs and integrate them into models of hospitals' processes. As pharmaceuticals, among others, exhibit multiple classification levels and there is a need to treat types as instances, in this paper we apply a relatively new language paradigm and design a multilevel model of medical drugs. We evaluate the proposed model threefold: against requirements, by prototypical application and with the help of domain experts.

Keywords: multilevel modeling, pharmaceutical, FMML^x

1 Introduction

Health-care organizations in general, and hospitals in particular, perceive investing in information technology (IT) as an opportunity to improve the quality of care delivery and reduce costs [1-3]. A pre-requisite for efficient and effective IT application is having a deep understanding of hospital and its processes [4]. Therefore, various researchers proposed the application of domain-specific modeling languages (DSMLs) to support sense-making of a hospital [5-7], with the aim to provide foundations for implementation of hospital information systems (HISs) [4]. However, up till now the focus has been mainly assigned to modeling the flow of clinical pathways, i.e., hospitals' medical processes [5] and not on the involved resources. As pharmaceuticals are of pivotal importance in medical care delivery, it seems however reasonable to account for and integrate them into models of hospitals' processes.

Modeling of pharmaceuticals is nonetheless quite challenging [8]. Firstly, a pharmaceutical product itself is quite complex: it has a rich set of features [9-11], comes in multiple hierarchies (Fig. 1) [9,10], and its characteristics may differ between countries (e.g., reimbursement schema) [9]. Secondly, various processes consider it at different classification levels, e.g., inventory management on the level of packs with serial numbers, drug dispensing on the level of branded product, and drug prescription on the level of type of product, its dosage and pack-size [9].

Although various attempts have been undertaken to model pharmaceuticals and capture their characteristics, e.g., as ontologies [11] or via schemes [12], none of the

existing initiatives, to the best of our knowledge, models pharmaceutical products in their entirety and accounts for their variability in a way that would satisfy information needs of all hospital stakeholders. Therefore, in this paper we focus on modeling of pharmaceuticals in the realm of hospital modeling [5] and tackle the question how a pharmaceutical product should be modeled in order to provide relevant information depending on the underlying modeling purpose resp. modelled process.

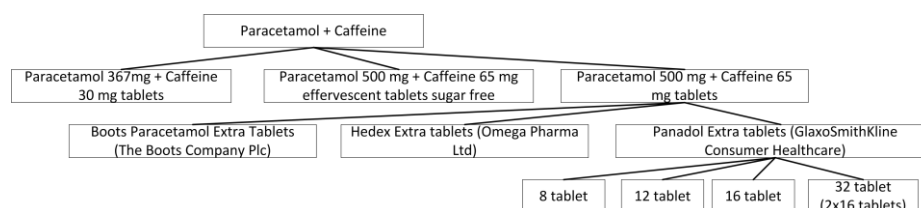


Figure 1. Exemplary hierarchy of pharmaceuticals, NHS database [12]

We follow a design-oriented research path and model pharmaceuticals in collaboration with domain experts. To reach our goal, first, we investigate the concept of pharmaceutical and relevant hospital processes. Then, we identify the main goals that the modeling language should meet. Considering the identified requirements, among others, a need to support numerous classification levels, treat types as instances and equip modeling elements with behavior, we apply a multilevel modeling approach [13]. We evaluate the proposed model threefold: against the requirements, by prototypical implementation, and with the help of domain experts.

The paper is structured as follows. First, the main concepts connected with pharmaceuticals are explained and the main processes using information on pharmaceuticals are mentioned. Then, the goals and resulting requirements towards the approach used to model pharmaceuticals are discussed and a multilevel model of pharmaceuticals is proposed. The paper concludes with final remarks.

2 Pharmaceuticals – Basic Terminology

The European Union (EU) defines pharmaceuticals as “medicinal products”, i.e., “(a) any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or (b) any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis” [14, p. 36]. A pharmaceutical is thus a drug that is used in medicine as a diagnostic, preventive, or therapeutic product [9,10]. Each drug consists of some active moieties/active ingredients (i.e., substances causing a biological effect in living organisms [10]), which can be differentiated into active pharmaceutical ingredients (i.e., ingredients which can serve for prevention, relief, healing or detection of diseases [10, p. 3]) and toxins (i.e., ingredients causing harmful effects) [9].

A medicinal product encompasses at least one active ingredient (e.g., prednisolone) and additional, inactive ingredients (i.e., excipients, e.g., flavors). Each substance has some potency/dosage strength (i.e., “a measure for the dosage respectively concentration, which is required to reach a certain effect: the higher the potency, the lower the necessary dosage” [10, p. 3]). Each drug can be characterized by some therapeutic effect, possible side-effects, and drug-drug-interactions [11].

A medicinal product comes in different dosage forms (e.g., tablets, capsules, syrups). The pharmaceutical’s dosage form is chosen based on the route of administration (i.e., the way it is absorbed into the body, e.g., non-invasive per oral (through mouth), topical (through skin), or inhalation), respectively defines it [9].

Finally, drugs with the same active ingredients come not only with different potencies, routes of administration and dosage forms, but also with different branded/trade names and in different packs, whose sizes and forms are regulated by corresponding, often country-specific, norms and rules [1,9]. Indeed, there are differences between various countries regarding packs allowed (e.g., blister packs for solid drugs) taking into account, e.g., their character, classification and therapeutic effect or allowed sizes. For instance, for drugs with a short duration of use, packs will be usually designed to provide one course of medicine, for drugs with a longer period of use, packs will be for 28/30-days supply [9,10].

Taking into account the availability of many traded products, the notion of pharmaceutical equivalence has been coined for the products that contain the same active ingredient(s), are of the same dosage form and route of administration and are identical in strength/concentration. However, the products may differ in characteristics such as producer, shape, excipients (e.g., flavors) etc. [9].

The differences between various countries do not relate only to the forms and sizes of packs, but significant differences may be spotted when it comes to, among others, regulation and prescribing practices affecting drug information requirements, drug management and administration [1]. Different countries not only permit the use of different medicinal ingredients, but also have different legal classifications of some drugs, available/allowed ranges of forms/strengths, or different licensed indications.

In addition to that, drug names are quite often different for the same drug in different countries. Indeed, the national naming schemes are quite often country-specific. That is, they refer to ingredients used in the particular country with names intended to be meaningful to its citizens. This lack of standardization hampers the analysis and gathering of information. Therefore, to foster comparability and data exchange on pharmaceuticals, but also to identify drugs that are based on the same active moiety, but have, e.g., country-specific names, the World Health Organization (WHO) introduced in the 1950ies the concept of International Nonproprietary Names (INN) [15]. INNs provide unique names allowing to uniquely identify medical substances. This not only facilitates flow of scientific information and communication among health professionals, but INNs are also used, e.g., by national drug registration authorities and by health assurance bodies defining reimbursement schemes [16].

Being unique and widely recognizable, INNs also serve to classify pharmaceuticals based on the active moiety they contain. In addition, medicinal products are classified taking into account (1) active moieties and the affected organ or system, using the

international Anatomical Therapeutic Chemical Classification System (ATC system) [17], (2) the mode of action, i.e., the way the pharmaceutical works, its therapeutic effect, or the part of the biological system it affects, or (3) the level of control of the drug availability (on prescription, in pharmacies, and over-the-counter [9]).

Motivated by the lack of standardisation in describing drugs, in addition to the standard terminology and classifications mentioned above, numerous (drug) vocabularies have been proposed, which form the foundation of information content in electronic health records, e.g., SNOMED-CT (<http://www.snomed.org/>) or compatible with it the National Health Service (NHS) Dictionary of Medicine and Devices (dm+d) [12]. NHS dm+d captures the variability of drugs by using four key components [12]: *Virtual Medicinal Product* (virtual therapeutic moiety including the form and strength, e.g., Prednisolone 20mg tablets), *Virtual Medicinal Product Pack* (a generic title for a generic or proprietary product pack), *Actual Medicinal Product* (an actual product linked to the name of a particular supplier), and finally *Actual Medicinal Product Pack* (an actual product linked to the supplier and pack size).

3 Selected Hospital Processes Using Pharmaceutical Data

Pharmaceuticals (or information on those) are used in numerous hospital processes.

Clinical pathways (CPs): a CP is based on a defined clinical guideline and aims to manage institution-specific medical care of “a well-defined group of patients during a well-defined period of time” [19, p. 562] that contributes to improving the quality of care processes, reducing risks, increasing the efficiency of the resource usage, and increasing the patient satisfaction [19,20]. CPs come with different abstraction levels and use the information on drugs as follows. On the level of institution-independent clinical guidelines we deal with a specific class of drugs with some therapeutic effect and/or some active moiety. On the level of some CP, we may either use a specific class of drugs or point to a specific brand of a drug (possibly also with information on the manufacturer, depending on the innovativeness of a product). On the level of patient-specific CP, we point to some specific branded drug with a specific pack size (however, not to a specific pack with some serial number).

Prescription of drugs: the process in which a health-care professional prescribes a drug based on a given indication. Prescribers, depending on the country-specific rules, can opt for the prescription of active substances or brand-name products. A prescribed pharmaceutical has the following properties [4]: brand name or generic name, manufacturer (optional), national/regional drug code(s), active substance(s) denomination(s) (e.g., INN), form, unit dosage, packaging, type of container, number of units. If applicable, additional information, e.g., on the reimbursement level is captured.

Dispense of drugs: the process in which a health-care professional (usually a pharmacist) takes in the prescription and validates it against pharmaceutical knowledge and regulations. If the outcome of the validation is positive, the pharmacist decides on the specific drug, and makes it available to the patient. A record is kept of the dispensed drug (brand, type, form, quantity, etc.). In many cases

the dispenser is entitled to make changes to the prescription (e.g., change the brand of the drug, cf. discussed pharmaceutical equivalence), or reject the prescription. Differences here can exist among different health-care systems.

Administration of drugs: the process in which the medication is actually administered to the patient. The following information is kept, e.g., in the (electronic) health record: specific branded product name, batch number and expiration date, time of administration as well as quantity administered, cf. [4].

Inventory management: the process within which the actual products are being stored (in specific conditions), inventoried, and ordered based on predefined stock levels. Different usage analysis and predictions are used in order to identify the optimal stock size and level, as the lack of availability of a drug may have severe consequences to patients' clinical outcome [4]. Therefore, information on available pack sizes, delivery time, as well as recording dispensed items is required. In hospitals, inventory management applies to both point of care and pharmacy [4].

Decision support: it encompasses such activities as manually or electronically checking for drug interactions, drug allergies/intolerances, correct dosage taking into account patient's age and lab results, duplication of active ingredients in different drugs, identification of equivalent products [4]. In addition, an access is provided to information on therapeutic recommendations, drug contraindications and known side-effects [4,18,21,22].

Epidemiology studies and reporting: Health-care stakeholders are obliged (quite often by law) to conduct various types of reporting, e.g., use of drug categories and the achieved health outcome, adverse drug reaction, usage data (e.g., antibiotics utilization patterns [23]). This reporting is performed on the level of active moiety with its dosage strength and dosage form (e.g., Ibuprofen, 200 mg, capsule), i.e., usually no branded trade name or proprietary names are provided. It may require integrated patient and pharmaceutical data, e.g., number of patients on some active moiety with/without dosage strength and form.

4 Modeling of Pharmaceuticals

Goals and Requirements: The modeling of pharmaceuticals should first and foremost foster availability of information on drugs within relevant (models of) hospital processes, with the aim to: (1) raise the transparency of medical drugs, their characteristics, applications and adverse interactions, (2) raise patient-safety by minimizing the possibility of clinical errors [24], (3) meet regulatory requirements (e.g., reporting), (4) increase the efficiency and effectiveness of relevant processes (e.g., reuse data among different processes: updating medication plan, computerized physician order entry, discharge letters) and (5) contribute to an optimal drug therapy [24]. Based on the conducted literature analysis, analysis of hospital processes and conversations with domain experts, the following requirements have been identified.

R1: Accounting for different hierarchy levels. Rationale: The processes require information on drugs on different levels of abstraction, e.g., while dispensing is recorded on the level of some specific drug, the inventory goes down to some specific

packs with serial numbers. Thus, the approach should provide information on drugs spanning different levels, e.g., generic types, branded products, specific instances.

R2: *Semantically rich description.* Rationale: Discussed processes require rich information on drugs (e.g., starting from a therapeutic effect to reimbursement schema), therefore the approach should allow to create semantically rich models that would provide the desired information.

R3: *Support for both modelling productivity and language reusability.* Rationale: On the one hand, the modeling approach should foster reusability by providing rather generic concepts accounting for product-independent aspects common to all drugs in order to be applicable in a wide range of scenarios. However, on the other hand, it should foster the productivity of modeling by providing a set of semantically rich concepts already in the language specification.

R4: *Support for finding the optimal drug therapy.* Rationale: The modeling approach should contribute to reducing clinical errors and to optimal drug therapy. Therefore, it should support practitioners by, e.g., making them aware of unsafe measurement of drugs, prescribed overdoses, potential drugs interactions. Therefore, the relevant information (domain-specific constraints) should be incorporated already in the language specification and used while applying the language.

R5: *Support for calculations and reporting.* Rationale: To support the discussed processes, a modeling approach should support processing of information defined within the models/language, e.g., identifying overdoses and contra-indications, as well as calculating usage patterns and other statistics for the needs of internal and external epidemiological reporting. It follows that the modeling approach, on the one hand, should account for the required information, e.g., on the adverse reactions (cf. R4). On the other hand, it should provide relevant operations that would perform required computations on different levels of abstraction (cf. R1).

R6: *Integration with external data sources.* Rationale: As, e.g., new ingredients are invented, new branded drugs offered, or the stock-level in the hospital pharmacy changes dynamically, the created models should be dynamic in the sense that it should be possible to link language or model elements to external data sources/operational-level systems, e.g., drug databases, and include relevant abstractions within models. This is to ensure that the models are up-to-date and can indeed support the decision making process (cf. R4).

Discussion: Due to the space limitations, the evaluation of existing approaches to represent pharmaceuticals cannot be presented here in details. Instead two main conclusions from the conducted evaluation are mentioned: not only the desired scope of the representation is not supported, but also the existing approaches neither offer the required expressiveness nor the desired mechanisms. We argue that whereas the scope is the matter of goals pursued by an approach, there is a need to investigate the application of alternative language architecture to fulfill other requirements.

In the conventional meta modeling, one describes domain concepts and their relations using a meta model (M_2), which is then instantiated on the type level (M_1). The conventional modeling comes with a couple of rules, e.g., (1) a type/instance dichotomy, implying, among others, that types cannot have a state; (2) a strict separation between different levels (i.e. between language specification, i.e., M_2 , and

language application, i.e., M_1); and (3) no possibility to account on M_2 for information applicable on M_0 [13]. However, to address the identified requirements we need a language architecture that deviates from those rules. Firstly, drugs exist in a remarkable variety of types, each of them possessing a variety of type-specific attributes and further hierarchies (cf. Fig. 1) and the refinement relation between different hierarchy levels is partly specialization and partly instantiation (e.g., on the one hand Prednisolone 500 mg orally is an instance of Prednisolone, on the other hand, it is its specialization, which comes with an additional set of attributes). If we follow the traditional modeling paradigm, we need to decide which of those we want to account for. Considering the identified requirements and with the aim to avoid conceptual redundancy and support modeling productivity, we would be interested in making this hierarchy part of a language specification (M_2) and thus, decide for the specialization relation. Thus, we would model a meta type *Pharmaceutical* and specialize it in, e.g., *PrednisoloneProduct* which in turn may be specialized into specific products *PrednisoloneOrally*. However, by deciding to represent the refinement relations as specializations, we would be dealing with a so called level mismatch problem [27] as various hierarchy levels are mapped onto exactly the same model level (i.e., M_2). Although it is certainly *technically* possible to overload the level, by relying on specialization, this would constitute a *workaround inducing an accidental complexity of created models*, cf. [27]. Next, we would want to incorporate information (e.g., on therapeutic effect) already in the language specification, however, we would not be able to do that as meta types cannot have a state (e.g., we cannot assign values to their attributes). In addition, we would like to link concepts defined as part of language specification with concepts being part of language application (e.g., state that *Prednisolone* (M_2) is produced by some specific company (M_1)). This however is also not possible as the only relation allowed between levels is the instantiation relation. Further, as we want to support both productivity and reusability, we also want to be able to define on higher levels (e.g., M_2) what we know would be relevant on lower levels only (e.g., defining that a pharmaceutical has some expiration date known on the instance level only) and in this way increase the concepts' reusability. This requires however support for deferred instantiation (i.e., allowing to define on each level of abstraction what is relevant for our purposes and deferring its instantiation to some not directly preceding level), which is not supported by traditional approaches. Finally, R4-R6 expect us to link models to external data sources and provide support for analyses and reporting. Fulfilling those requirements would require an integrated programming and modeling environment, i.e., a common representation of model and code. However, as the mainstream object-oriented programming languages feature only one classification level, therefore types and/or meta types are represented as objects by overloading the M_0 level of a programming language. Thus a common representation of code and model is not possible and model-code synchronization is needed [13,25].

Considering the above discussion, although modeling of drugs using traditional two-level modeling is *technically* possible, it would not allow us to deliver a satisfactory solution, i.e., a solution without workarounds, model redundancy and accidental complexity. Therefore, the alternative paradigm is considered.

5 Multilevel Model of Pharmaceuticals

Multilevel modeling covers any approach to modeling that aims to provide systematic support for representing multiple classification levels within a single body of model content [26]. A few multilevel modeling approaches have been proposed, among them, potency-based multilevel modeling/deep instantiation [27], multilevel object (m-object) [28] as well as the Flexible Meta-Modeling and Execution Language (FMML^x) [13]. As FMML^x exhibits distinctive features compared to other approaches [13,29] and as the only one offers a common representation of model and code [13], it becomes our language of choice for modeling pharmaceuticals.

A detailed description of FMML^x can be found in [13]. FMML^x is based on the extension of XCore [30], which is the meta model of an executable meta modeling facility (XMF) [31]. XCore allows for an arbitrary number of classification levels. This is accomplished through a recursive and reflexive language architecture [30]. In XCore a meta class Class inherits from Object. At the same time, objects (instances of Object) are instantiated from Class. As a result, every (meta) class is an object and may have a state [25]. The recursive language architecture allows also for a common representation of code and model. Thus, model elements are classes that allow for the definition of attributes and operations, but at the same time, as they are also objects, we can assign values and execute operations [13]. The definition of attributes, operations and relations has been equipped with intrinsicness [13] (i.e., the deferred instantiation mechanism). It is represented by an integer value that indicates the level on which a given attribute, relation or operation is to be instantiated (cf. the white number in the black box next to the definition of the element in question, Fig. 2). If no intrinsic level is indicated, the element is to be instantiated one level below the current one. FMML^x is supported by the meta modeling and programming environment XModeler [13]. Being a programming environment, XModeler offers mechanisms to, e.g., obtain information from other sources as well as trigger some actions.

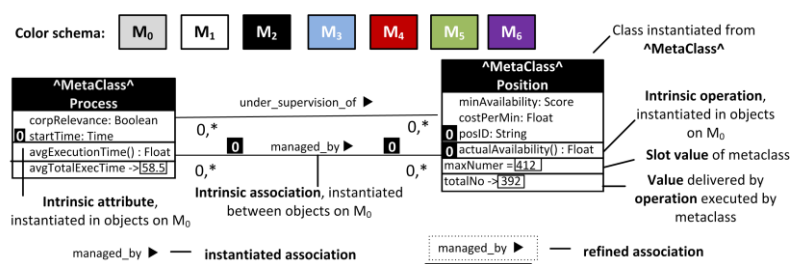


Figure 2. FMML^x – Concrete Syntax based on [13]

Multilevel model: Figure 3 presents an excerpt from the multilevel model of pharmaceutical products. Due to space limitations only selected concepts and selected properties are shown and discussed. On the highest level of abstraction, we define a class Pharmaceutical (M₇). Already at this level, we define everything we know, e.g., that it has a batch number, some expiration date, some producer, some dosage and pack size; although most of those aspects will be known only on the lower levels of

classification (cf. assigned intrinsicness). Here, we take advantage of various auxiliary classes (e.g., RouteOfAdministration, DosageStrength). On M_6 , we assign the active pharmaceutical ingredient (M_0) to the product, by instantiating the level-crossing relation `has_active_ingredient`. Among others, the basic dosage strength, route of administration and dosage form are considered on M_5 , M_4 and M_3 , respectively.

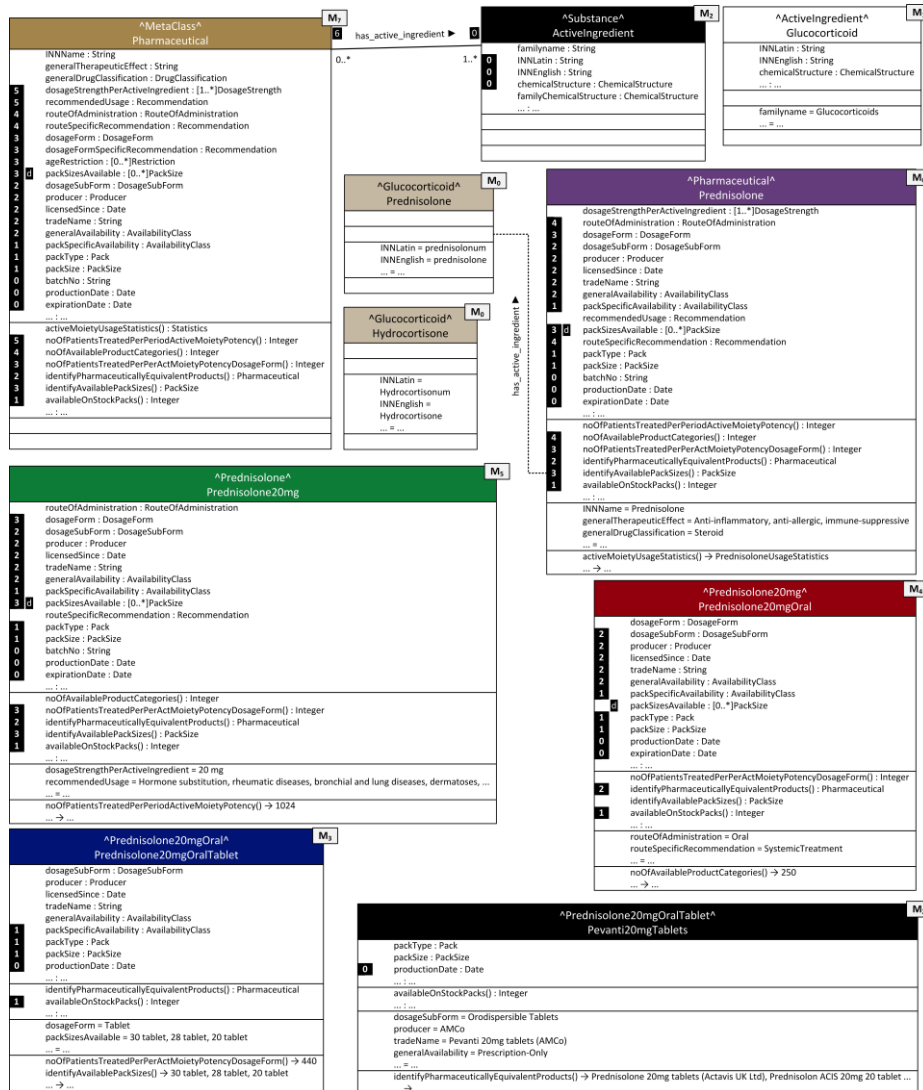


Figure 3. Excerpt from the multilevel model of pharmaceuticals

On each level we benefit from the relaxed type/instance dichotomy and thus, we state relevant information on, e.g., the recommended application specific to the active ingredient or therapeutic effect of some specific dosage strength. The products offered

by different producers are situated at M_2 . There we also define additional inactive ingredients as well as subtypes of a dosage form (e.g., chewable tablets). In addition, by using XOCL [30] we define relevant operations, e.g., for the needs of reporting or inventory management (cf., `identifyPharmaceuticallyEquivalentProducts()`), which may be executed (e.g., `noOfAvailableProductCategories=250` on M_4).

Evaluation: We have conducted a threefold evaluation: against the identified requirements, by prototypical application in the XModeler tool (cf. Fig. 4) and with the help of domain experts. Regarding the latter, domain experts working in the pharmacy as well as responsible for HIS conducted the sanity check of the requirements as well as of the proposed multilevel model. When it comes to the requirements, it may be clearly seen that the application of the selected language and the supporting tool opened new possibilities for modeling of drugs. The expressiveness of the approach used allows to (1) account for the specificity of pharmaceuticals without a need to overload layers and apply workarounds, as well as (2) define mechanisms that provide support for desired functions (e.g., reporting).

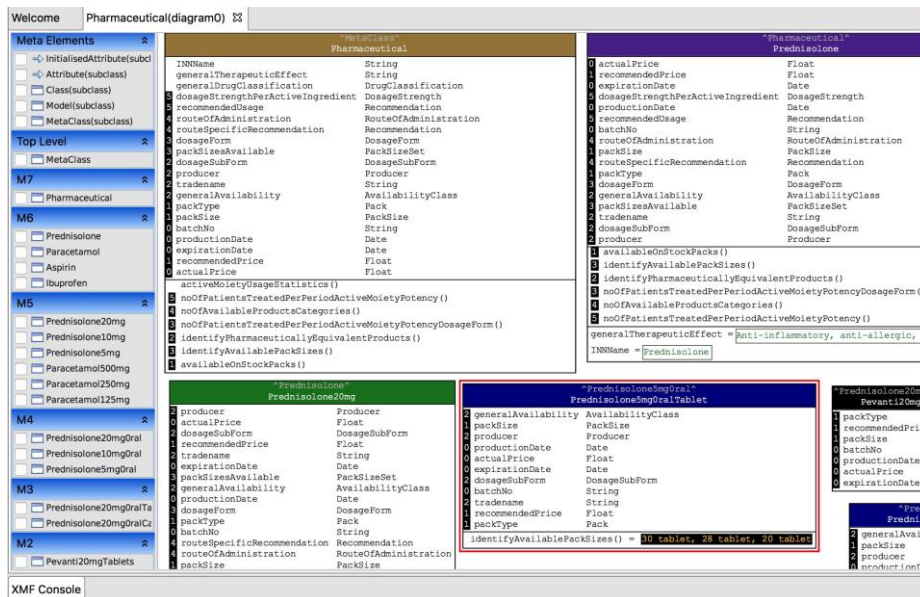


Figure 4. XModeler Screenshot

By allowing defining multiple classification levels, FMML^x makes it possible to define and use concepts that correspond directly with the desired level of details. Thus, we have a possibility to account for the fact that pharmaceutical products span multiple levels of classification, with instances, brands/traded types and generic products being part of the domain of inquiry and related to each other. At each classification level we have the possibility to express relevant information, making the model semantically rich and also facilitating its reuse. At the same time, we have the possibility to freely choose the level we want to deal with within various

processes and thus, information needs of different stakeholders may be satisfied and different views on pharmaceutical products are accounted for. A common representation of model and code allows avoiding the model-code synchronization problem, and treating classes as objects allows defining relevant operations. In addition, thanks to the integrated modeling and programming solution the required epidemiology information can be retrieved. Once the model will be integrated with the electronic CP and electronic health record, one can execute further operations supporting required reporting, e.g., regarding no. of patients treated with Prednisolone (M₆), Prednisolone orally (M₄), Prednisolone oral tablet (M₃), or information on the observed adverse reactions may be automatically tracked. It also becomes possible to link the model elements with external data sources (e.g., drug databases).

6 Conclusions and Outlook on Future Research

In this paper based on the literature study as well as interactions with domain experts, we have proposed a multilevel model of pharmaceuticals. We have designed the model using the integrated modeling and programming approach FMML^x, which allowed designing models that express the objects of consideration directly without the need for overloading. Nevertheless, we consider the proposed multilevel model as the first step only, as a few aspects connected with the pharmaceutical domain are accounted for in a rather superficial manner. This applies to, e.g., accounting mainly for EU-specific rules and regulations, superficial definitions of supporting concepts, e.g., dosage instruction. Regarding the latter, although we have accounted for it as a textual description, e.g., “Take two tablets three times a day”, it seems reasonable to consider a more structured representation that would allow calculating a dose or quantity and thus, improving the patient safety by standardizing the way that dosage instructions are communicated. All of the above aspects are part of our future work.

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