Lister Hill National Center for
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Drug Terminology and Ontology
Integration, Dissemination, Quality Assurance and Applications

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1 Background

Biomedical terminologies and ontologies are enabling resources for clinical decision support systems and data integration systems for clinical and translational research [1, 2]. For the past decade, the National Library of Medicine (NLM) has been involved with the development of drug terminologies, such as RxNorm [3]. NLM also collaborates with other agencies on the development and distribution of drug information sources, including the National Drug File-Reference Terminology (NDF-RT) [4] (with the Department of Veterans Affairs), and DailyMed [5] (with Food and Drug Administration). Finally, through the Value Set Authority Center [6], NLM also serves as the reference for the value sets – including drug value sets – required for use in the Meaningful Use incentive program, in collaboration with the Office of the National Coordinator for Health Information Technology (ONC) and the Centers for Medicare and Medicaid Services (CMS).

As a research and development division of NLM, the Lister Hill National Center for Biomedical Communications (LHNCBC) supports the development and distribution of NLM products and services. For example, LHNCBC researchers have been closely associated with the development of the Unified Medical Language System (UMLS). The same is true for RxNorm and related resources. In addition to creating derivatives, such as RxTerms, LHNCBC researchers have integrated various external resources with RxNorm, facilitated its adoption by providing graphical and application programming interfaces, developed quality assurance processes for drug terminologies, and illustrated their use in applications.

In this report, we summarize 19 investigations related to drug terminology and ontology performed in our research group over the past decade [7-25], as well as 20 shorter communications in which we publicized our interfaces to drug ontologies and illustrated their applications [26-45]. As it is not possible or desirable to report each study in detail, we first present an overview of these investigations, organized along four dimensions (integration, dissemination, quality assurance and applications). Then, we selected one study representative of each dimension and present it in more detail.

2 Project Objectives

The overall objective of the *Medical Ontology Research* project is to develop methods whereby ontologies can be acquired from existing resources and validated against other knowledge sources, including the Unified Medical Language System (UMLS). Our work on drug terminologies and ontologies constitutes a specific part of this overall project. While fully consistent with these broad objectives, it also extends them in some important ways. In addition to developing methods for assessing the quality of drug terminologies and integrating them with other ontologies, we have also illustrated the use of drug information sources in applications. Moreover, our exploratory work on graphical and application programming interfaces for RxNorm has led us to take responsibility for production-grade applications and services, in addition to our research activities. These various aspects are reflected in this report.

3 Project Significance

This project is significant in many respects. Its production component is a direct contribution to the dissemination of RxNorm and other NLM terminology resources. We show later that our application programming interfaces have become a major distribution mechanism for RxNorm, and extend the terminology information in RxNorm with useful services (e.g., techniques for managing terminological variation

and navigating the complex RxNorm graph). By showcasing the use of RxNorm in applications, we also provide a proof of concept for some of its features, illustrating "RxNorm in action". Our research on integration helps extend the universe of RxNorm to other resources, such as ATC, and provide critical linkage to pharmacologic classes. By developing quality assurance methods, we contribute to assessing the quality of drug information sources, such as drug classifications. Finally, we work closely with the RxNorm development team, to which we provide advice on knowledge representation matters, as well as near-instant feedback.

4   Methods and Procedures

Four aspects of our research and development work on drug terminology can be distinguished, namely *integration* (e.g., alignment of drug entities, such as drug classes, across terminologies), *dissemination* (i.e., tooling to support the adoption NLM drug terminologies), *quality assurance* (i.e., evaluation of drug information sources) and *applications* (i.e., use of NLM drug terminologies for a specific purpose). We first present an overview of our research and development activities along these four dimensions. Then we present four studies in more detail, one for each dimension.

4.1   Overview

4.1.1   Integration

Integrating drug information sources encompasses various activities. In early work [24], we analyzed 23 drug information sources along 39 dimensions in four major domains (pharmacy, chemistry, biology and clinical practice) and showed that this framework was useful for selecting sources for specific use cases. We studied terminological variation in the names of drug entities, in order to support effective mapping to RxNorm through normalized matches [21] and approximate matches [16]. We contributed to the integration of the Anatomical Therapeutic Chemical (ATC) drug classification into RxNorm [31]. We have also developed methods to facilitate the interoperability (i.e., integration) of our application programming interfaces (APIs) across sources [10]. More recently, our investigations have focused on drug classes. Unlike drug names, the names of drug classes are much less standardized across sources, and lexical approaches to integrating drug classes are generally ineffective. We have developed methods for comparing drug classes based on the their drug members, and applied them to the comparison of two pairs of drug classifications, namely ATC and NDF-RT [13], and ATC and MeSH [12]. We later developed a framework for comparing drug classes across arbitrary sources [9], which we present in detail in section 4.2.1.

4.1.2   Dissemination

RxNorm has many similarities to the UMLS Metathesaurus (e.g., it integrates multiple drug vocabularies into a system of concepts and relations among them). It is therefore not surprising that RxNorm reused the UMLS Metathesaurus database schema for its representation. However, unlike the UMLS Metathesaurus, RxNorm imposes a structure over its source vocabularies, consisting of a small number of types of entities (e.g., ingredient, brand name, clinical drugs, etc.) and relations among them (e.g., the brand name Lipitor is the tradename of the ingredient atorvastatin). As a result, a given drug entity is related to other drug entities through a graph (e.g., the clinical drug atorvastatin 10 MG Oral Tablet is related to the ingredient atorvastatin and to the branded drug Lipitor 10 MG Oral Tablet, itself related to the brand name Lipitor).

Once represented in the storage format of the UMLS Metathesaurus relational schema, the logical structure of the RxNorm graph is no longer apparent. In 2004, we set out to create *RxNav*, a graphical browser for RxNorm, exposing the logical structure hidden in the relational format [45]. We rapidly realized that we needed an application programming interface (API) to support the functions of this browser (e.g., find a drug entity by name or by identifier, get the properties of a drug entity, and get the relations of a drug entity to other drug entities). We made this web services SOAP (Simple Object Access Protocol) API publicly available in 2006 [41], while adding features to the *RxNav* browser (e.g., links to external sources, such as DailyMed) [39]. In order to meet the requirements of our users, we started providing a RESTful version of our original SOAP API for RxNorm [36]. We created similar APIs for additional drug information sources (RxTerms and NDF-RT [33]). In the past few years, we created *RxMix*, a graphical interface allowing users to create complex queries against multiple drug information sources through functional composition [10]. Our latest development is *RxClass*, a browser (and companion API) for pharmacologic classes [26], presented in detail in section 4.2.2. *RxNav*, *RxClass*, *RxMix* and the APIs are available at http://rxnav.nlm.nih.gov/.

Usage of *RxNav* and the APIs for RxNorm, RxTerms and NDF-RT has been growing significantly over the past few years (Figure 1). The APIs have received about 100 million queries in 2013, and a similar amount of queries during the first semester of 2014. The majority of the queries are directed to the RxNorm API. Functions that resolve drug names and identifiers into RxNorm entities receive the most traffic. Our products have been cited in 16 publications [46-61], which only very partially reflects our 8500 monthly unique users on average (Figure 2). As shown by log analysis, our users include clinical and academic institutions, as well as pharmacy management companies, health insurance companies, EHR vendors, and drug information providers (including NLM's *MedlinePlusConnect* [53]). Developers of mobile apps have also started to integrate our APIs into their applications.

RxNav and the APIs serve the latest version of the drug information sources, including monthly updates for RxNorm, RxTerms and NDF-RT, weekly additions to RxNorm, and yearly updates of ATC and MeSH. Because the APIs are used in mission critical applications, we use multiple servers, including mirrors located at an independent location, in order to ensure high availability of our services.
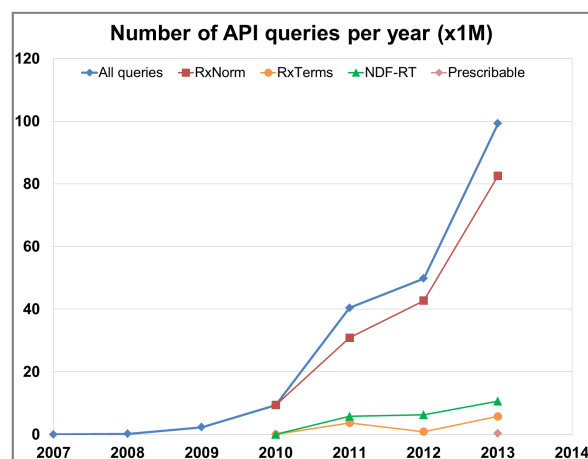

Figure 1. Total number of queries per year to the drug APIs (in million)
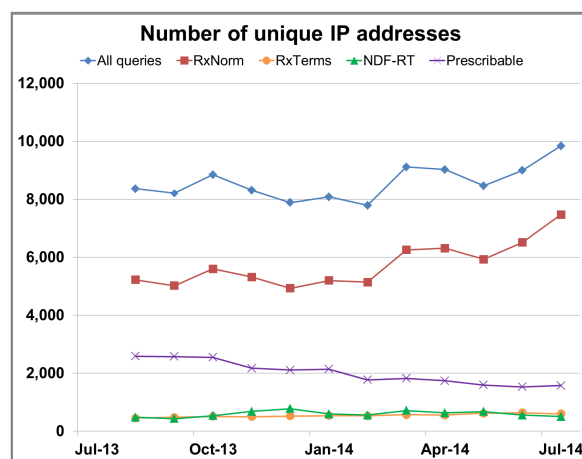

Figure 2. Number of unique users per month to the drug APIs

4.1.3 Quality assurance

Our work on quality assurance of drug terminologies and ontologies is consistent with our research activities on quality assurance of ontologies, which were reviewed by the Board of Scientific Counselors in the past [62]. We leveraged the RxNorm API to assess the consistency of RxNorm [22, 23]. Our auditing method proved effective in identifying a limited number of errors (e.g., missing links) that had defeated the quality assurance mechanisms in the RxNorm production system. Recent activities have focused on the evaluation of drug classes. We showed that there were few classes with exactly the same members between NDF-RT and SNOMED CT [19]. In contrast, we found that the ATC classes, although developed for pharmacoepidemiology, were generally consistent with clinical classes in NDF-RT [11]. We investigated the coverage of drug classes in standard terminologies [17] and found that, among the terminologies in the UMLS, SNOMED CT was the source that provided the best coverage (75%) of the 223 reference class names. We also noted that classes reflecting drug metabolism by the Cytochrome P450 enzyme family (e.g., CYP2C8 inhibitors) had poor coverage across sources. More recently, we investigated the consistency of inferred drug-class membership relations in NDF-RT [8], which we present in detail in section 4.2.3.

4.1.4 Applications

We contributed to the design of *MyMedicationList*, an early proof-of-concept application that allowed patients to manage medication lists, leveraging the RxNorm API [25, 37, 38]. The functions of this web-based and mobile application – now discontinued – are now integrated in virtually any patient portal. We showcased the use of RxNorm for identifying and normalizing drugs in several information extraction investigations, including for pharmacogenomics [14, 34], drug-drug interactions [28], clinical research [27], as well as for the validation of drug value sets [15]. We also investigated the use of drug information sources in clinical applications, such as cohort selection based on drug classes from NDF-RT [18] and analysis of prescribed daily doses with ATC [7], which we present in detail in section 4.2.4.

4.2 Four examples

In this section, we present four investigations to illustrate the dimensions of our work on drug terminologies introduced earlier, namely integration, dissemination, quality assurance and applications.

4.2.1 Integration – A framework for assessing the consistency of pharmacological classes across sources [9]

The objective of this study is to develop a framework for assessing the consistency of drug classes between MeSH and ATC. Our framework integrates and contrasts lexical and instance-based ontology alignment techniques. For example, as illustrated in Figure 3, by comparing class names in the two sources, we find a lexical match between Fluoroquinolones in MeSH and Fluoroquinolones in ATC (2 classes with this name in ATC). Moreover, by comparing the drug members (i.e., instances) shared by these classes, we identify a similarity between Fluoroquinolones in ATC and not only Fluoroquinolones, but also Anti-Bacterial Agents in MeSH. Moreover, we propose metrics for assessing both equivalence relations and inclusion relations among drug classes.

We identified 226 equivalence relations between MeSH and ATC classes through the lexical alignment, and 223 through the instance-based alignment, with limited overlap between the two approaches (36). We

also identified 6,257 inclusion relations. We analyzed the reasons for discrepancies between lexical and instance-based alignments. Many erroneous lexical mapping come from underspecified class names in ATC (e.g., Fluoroquinolones for "Ophthalmic fluoroquinolones"). Missing lexical mappings usually result from lexical variation and missing synonyms (e.g., Potassium-sparing agents in ATC vs. Diuretics, Potassium Sparing in MeSH). Finally, failure to identify instance-based mappings often comes from missing drug-class membership relations in one of the classifications.

This investigation is the first attempt to align drug classes with sophisticated instance-based techniques, while also distinguishing between equivalence and inclusion relations. Additionally, it is the first alignment of drug classes between ATC and MeSH. By providing a detailed account of similarities and differences between drug classes across sources, our framework has the prospect of effectively supporting the creation of a mapping of drug classes between ATC and MeSH by domain experts.
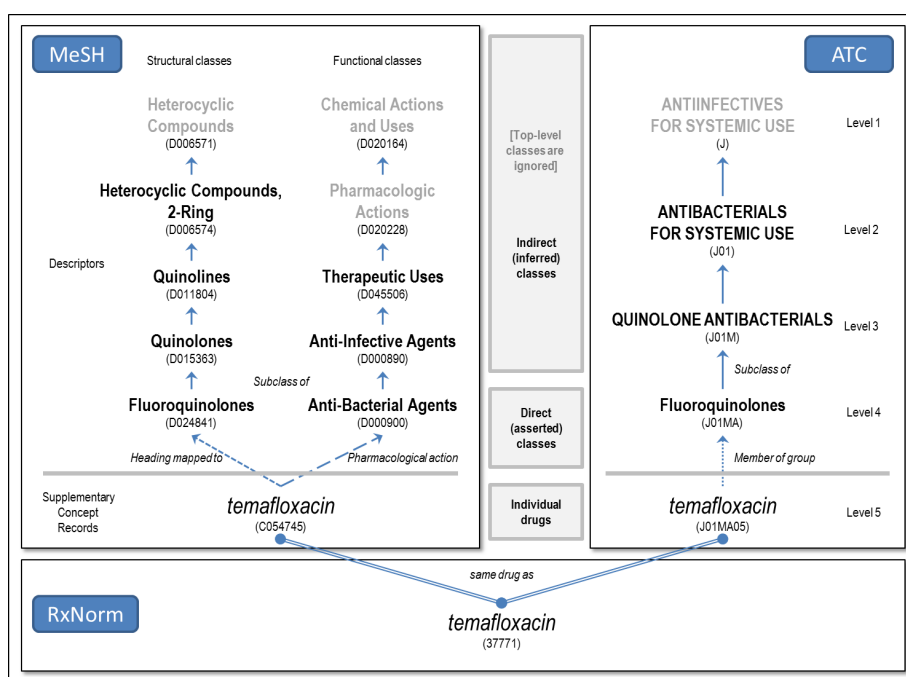

Figure 3. Individual drugs and drug classes in RxNorm, MeSH and ATC

4.2.2   *Dissemination – RxClass - Navigating between drug classes and RxNorm drugs [26]*

Drug classes constitute important information about the drugs and are critical to important use cases, such as clinical decision support (e.g., for allergy checking). *RxNav*, our RxNorm browser, already displays the classes for RxNorm drugs, but its drug-centric perspective does not accommodate the exploration of drug classes. This is the reason why we developed a web-based companion browser, *RxClass*, which supports navigation between RxNorm drugs and drug classes from several sources, including ATC, MeSH, NDF-RT and Structured Product Labels from the Food and Drug Administration (FDA). *RxClass* was first released in July 2014 and is available at http://mor.nlm.nih.gov/RxClass/.

Three sources of drug classes are integrated in *RxClass*. The Anatomical Therapeutic Chemical drug classification (*ATC*) is a resource developed for pharmacoepidemiology purposes by the World Health Organization Collaborating Centre for Drug Statistics Methodology. The Medical Subject Headings

(**MeSH**), developed by the National Library of Medicine (NLM), provides a rich description of pharmacological actions for the purpose of indexing and retrieval of biomedical articles. The National Drug File-Reference Terminology (**NDF-RT**), developed by the Department of Veterans Affairs, provides clinical information about drugs and contains the FDA Established Pharmacologic Classification (EPC), as well as Disease, Chemical Structure (Chem), Mechanism of Action (MOA), Physiologic Effect (PE) and Pharmacokinetics (PK) class types.

ATC and MeSH provide both the vocabulary for drug classes and the drug-class membership relations. In contrast, several sources (DailyMed, FDASPL and NDF-RT) provide drug-class membership relations in reference to the NDF-RT vocabulary for classes. All drugs are normalized to RxNorm.

Like *RxNav, RxClass* is supported by functions from an application programming interface (API), which can be used independently for integrating drug class information in programs. The API serves the latest information available from the drug information sources.

Figure 4. Drugs from the ATC class *Beta blocking agents, selective*, **with the ATC hierarchy of classes on the left navigation pane and the list of RxNorm drug members on the right**

As shown in Figure 4, *RxClass* provides a graphical interface to explore the hierarchical class structures of each source and examine the corresponding RxNorm drug members for each class. *RxClass* provides the following features. The user can navigate through the drug classes via the hierarchical menu, or use the search feature to identify a drug class or RxNorm drug. *RxClass* supports the exploration of all classes for a given drug across multiple classifications. *RxClass* provides an autocomplete function which will

help identify class or drug names in search mode, as well as spelling suggestions for misspelled drug and class names during search.

In summary, *RxClass* extends the drug-centric *RxNav* graphical application by providing a class-centric view on RxNorm drugs. Similarly, the new class API supports functions that were not available with previous APIs and unifies queries across drug classifications. Future developments will include support for comparing drug classes.

4.2.3 Quality assurance – Evaluating the consistency of inferred drug-class membership relations in NDF-RT [8]

The National Drug File Reference Terminology (NDF-RT) contains both drugs and drug classes, including FDA's Established Pharmacological Classes (EPCs). Moreover, in addition to providing a description of both the drugs and the EPCs in terms of properties, such as chemical ingredient, mechanism of action and physiologic effect, NDF-RT also associates the drugs with the EPCs directly (through asserted relations extracted from Structured Product Labels). For example, as illustrated in Figure 5, the drug albuterol and the class beta2-adrenergic agonist are both characterized by the mechanism of action adrenergic beta2-agnoists. The drug-class relation between albuterol and beta2- adrenergic agonist can be inferred from NDF-RT and compared to drug-class relation asserted in the Structured Product Labels. The objective of this investigation is to evaluate the consistency of inferred drug-class membership relations in NDF-RT with asserted drug-class relations from the Structured Product Labels.
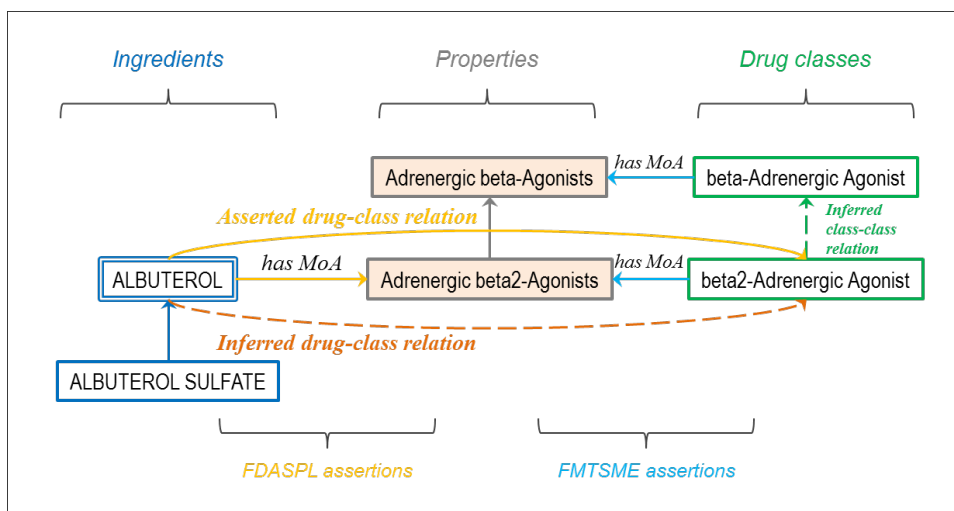
Figure 5. Characterization of the drug *albuterol* and the class *beta2-Adrenergic Agonist*, in terms of the mechanism of action (MoA) property *Adrenergic beta2-Agonist*, with inferred and asserted drug-class relations

We use a reasoner for the Web Ontology Language (OWL) to infer the drug-class membership relations from the class definitions and the descriptions of drugs and compare them to asserted relations. There are 1,787 asserted and 1,047 inferred direct drug-class relations, of which 872 are in common. When also considering drug-class relations between a drug and the ancestors of the class of which it is a member, we obtain 4,169 asserted and 2,378 inferred drug-class relations, of which 2,310 are in common. Our failure analysis reveals several types of issues. Missing inferences reflect missing associations between a drug

and its properties or between a class and its properties (i.e., incomplete drug or class descriptions), preventing the inference from happening. Inferences with no corresponding asserted relations are generally caused by missing drug-class relations in the reference set extracted from the Structured Product Labels, of which we found few cases. Finally, inconsistent inferred and asserted drug-class relations are generally attributable to granularity differences. For example, the antibiotic amikacin is associated with Aminoglycoside Antibacterial [EPC] (through asserted relations), but with the less specific Aminoglycoside [EPC] (through inferred relations).

In summary, this investigation quantifies and categorizes the inconsistencies between asserted and inferred drug classes and illustrates issues with class definitions and drug descriptions.

4.2.4 Applications – Analyzing U.S. prescription lists with RxNorm and the ATC/DDD Index [7]

In addition to being a drug classification system, the ATC/DDD Index (Anatomical Therapeutic Chemical (ATC) Classification System/Defined Daily Dose) also list a defined daily dose for most drugs. For example, ATC lists "1 g" as the daily dose for amoxicillin, when administered orally. The objective of this investigation is to evaluate the suitability of ATC, developed in Europe, for analyzing prescription lists in the U.S., in terms of drug classification and daily doses.

We mapped RxNorm clinical drugs to ATC. As shown in Figure 6, two elements were required for the mapping. On the one hand, the ingredient of the RxNorm drug has to map an ingredient in ATC (e.g., amoxicillin in RxNorm to amoxicillin in ATC). Additionally, we require that the dose form of the RxNorm drug be compatible with the administration route in ATC (as is the case between Oral Product in RxNorm and "O" in ATC). We used this mapping to classify a large set of prescription drugs (from Surescripts) with ATC and compared the prescribed daily dose to the defined daily dose (DDD) in ATC.
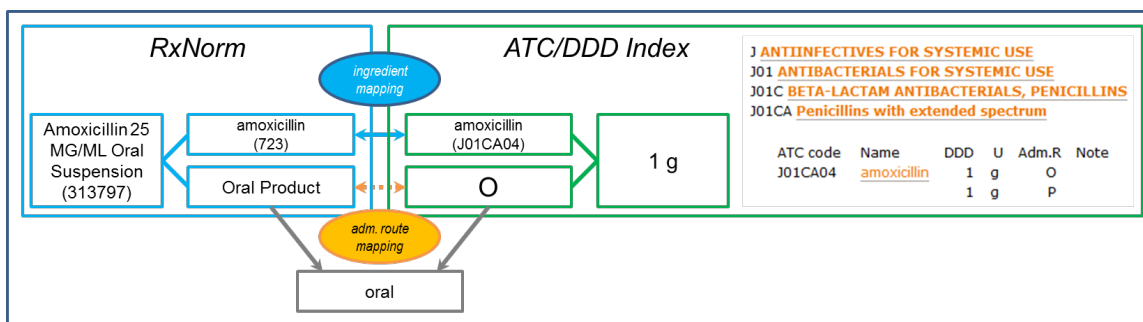

Figure 6. Mapping between RxNorm and ATC through both the ingredient and the route of administration

We found that 64% of the 11,422 clinical drugs could be precisely mapped to ATC. 97% of the 87,001 RxNorm codes from the prescription dataset could be classified with ATC, and 97% of the prescribed daily doses could be assessed. More specifically, as illustrated in Figure 7 (using a logarithmic scale, because of the amplitude of the variation among the ratios), the prescribed daily dose (PDD) exactly matches ATC's defined daily dose (DDD) in 28.6% of the prescriptions. The PPD/DDD ratio is in a 66%-150% range for 49.5% of the prescriptions (i.e., between 2/3rds of the DDD and 1.5 times the DDD). It is in a 50%-200% range for 76.1% (i.e., between half and twice the DDD), and in a 33%-300% range for 86.1%

(i.e., between 1/3rd of the DDD and 3 times the DDD). Only 3.4% of the PDDs are beyond 300% of the DDD and 10.4% below 33% of the DDD.

Although the mapping of RxNorm ingredients to ATC appears to be largely incomplete, the most frequently prescribed drugs in the prescription dataset we analyzed were covered. This study demonstrates the feasibility of using ATC in conjunction with RxNorm for analyzing U.S. prescription datasets for drug classification and assessment of the prescribed daily doses.
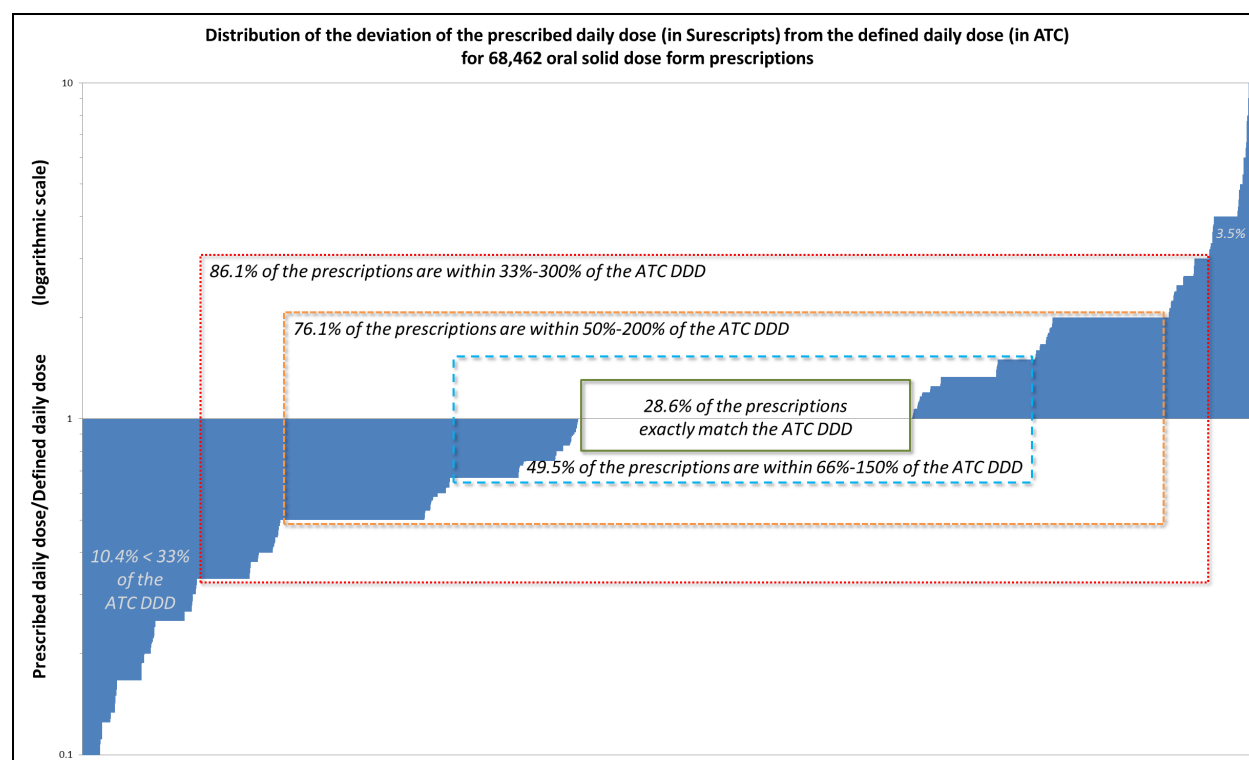

Figure 7. Distribution of the deviation of the prescribed daily dose from the defined daily dose

5   Project Status

Our work on drug terminology and ontology is ongoing, under the umbrella of the *Medical Ontology Research* project. As shown in Figure 8, our contribution to research and development on drug terminologies and ontologies has been sustained over the past decade. The 39 studies listed in this report represent 21% of our 183 publications since 2004. Not surprisingly, we primarily used short communications for reporting progress on our dissemination activities (graphical and application programming interfaces), while reporting research results (integration and quality assurance) in journal articles and conference proceedings (Figure 9). Our Google Scholar citation profile, shown in Figure 10, offers a proxy for the impact of our work (3398 citations since 2009).

Our focus on drug terminology research has intensified in the past few years, with 26 (38%) of 68 publications since 2010. Other research efforts in our project include the use of Semantic Web technologies in biomedicine, the extraction of adverse drug events from MEDLINE, and quality assurance of ontologies (beyond drug ontologies) and value sets.
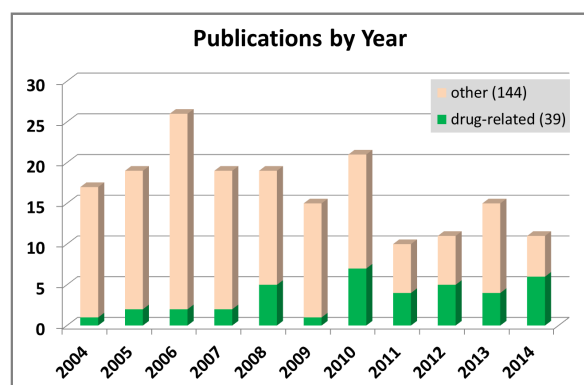
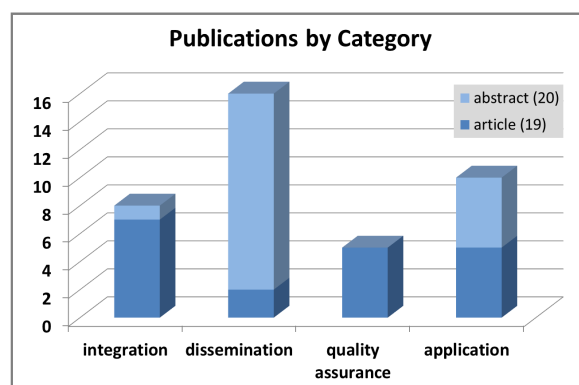**Figure 8. Proportion of publications from our group devoted to drug terminology**

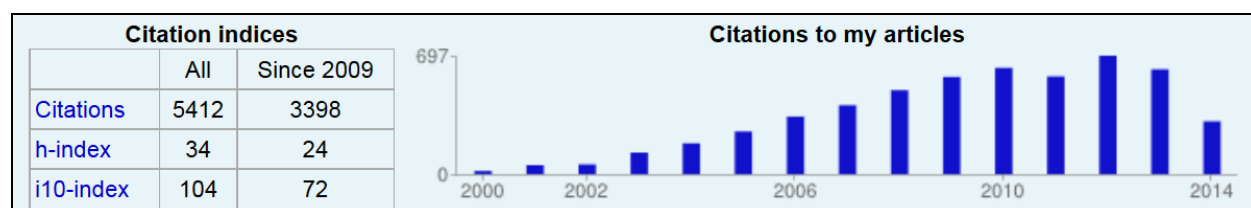**Figure 9. Proportion of drug-related publications by category**

Figure 10. Google Scholar citations for Olivier Bodenreider

6   Evaluation Plan

There is no single evaluation plan for this project, but rather a variety of evaluation strategies for its multiple components. We use a rich set of analytics for the evaluation of *RxNav*, *RxClass*, *RxMix* and the APIs to drug information sources, with special focus on total number of queries and unique users. When a gold standard is available for integration studies, we use the usual precision and recall evaluation framework (e.g., for approximate matching [33]), unless there is a more appropriate approach (e.g., ambiguity and variability metrics for normalization [21]). In many cases, however, no gold standard is available for a particular dataset or use case and we sometimes have to resort to purely descriptive studies (e.g., our framework for comparing drug classes [9] and our assessment of daily prescribed doses against ATC [7]).

7   Project Schedule and Resources

Some of these research and development activities have involved exclusively *Medical Ontology Research* personnel. (Two contractors provide programming support.) This is the case of our work on graphical and application programming interfaces for drug information sources [22-24, 26, 29, 30, 32, 33, 35, 36, 39-45]. A large number of projects have been carried out by summer students [10, 14, 19] and post-doctoral students [8, 9, 11, 12, 14, 15, 28, 31, 34], reflecting our sustained contribution to the NLM training program. Finally, a significant part of our work is done in collaboration with other groups at NLM [7, 17, 25, 27, 37, 38] and outside NIH [13, 16, 18, 20, 21]. In addition to Lister Hill colleagues, our collaborators have included colleagues from other federal agencies (e.g., from FDA), industry researchers (e.g., from First Databank), as well as academic groups in the U.S. (e.g., Mayo Clinic) and France (e.g., University of Bordeaux).

8   Summary and Future Plans

As part of the *Medical Ontology Research* project, we have explored drug terminologies and ontologies along multiple dimensions, including integration, dissemination, quality assurance and applications. These activities align with the research and development missions of the Lister Hill Center and effectively support NLM's drug terminology activities, especially RxNorm, for which our application programming interfaces (APIs) have become a major distribution mechanism. In addition to the development of highly used, production-grade applications and services, we have made significant contributions to research on drug ontologies. More specifically, we have contributed to integrate RxNorm with other drug information sources, and have extended its realm to pharmacologic classes. We have developed methods to assess the quality of drug ontologies, including RxNorm, and we have also illustrated their use through various applications.

In the future, we want to pursue our work on drug information sources along the same four dimensions. We plan to integrate RxNorm with resources used in basic research (e.g. DrugBank, KEGG, ChEBI, PubChem, and DrON, the drug ontology from the Open Biomedical Ontology family). We also plan to test our integration framework for pharmacologic classes to other drug classifications (e.g., SNOMED CT classes and FDA's Established Pharmacological Classes), in collaboration with domain experts. We want to extend our RxNorm API with text mining functions to support the identification of RxNorm drug entities in text. We have started to assess the quality of drug-drug interaction repositories. Finally we would like to leverage drug ontologies in clinical applications, such as allergy checking, medication dose checking and medication reconciliation. Future developments will also take into account the feedback we are about to receive from a survey of our users performed over the summer.

9   Acknowledgments

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