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Regulatory affairs issues and legal ontologies in drug development

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1. ABSTRACT

It usually can take more than ten years from the time a new drug is discovered, until can be launched on the market. Regulatory requirements are part of the process of drug discovery and drug development. It acts at every developmental stage. Regulatory affairs works to establish an effective and uniform balance between voluntary and regulatory compliance and agency responsiveness to consumer needs. It evaluates and coordinates all proposed legal actions to ascertain compliance with regulatory policy. The ontology presented for regulatory affairs and drug research and development gives us the possibility to correlate information from different levels and to discover new relationships between the legal aspects. In addition, the transparency of the information is affected by the inability of existing integration strategies to organize and apply the available knowledge to the range of real scientific and business issue in critical safety and regulatory applications. Therefore, the semantic technologies based on ontologies make the knowledge reusable by several applications across business, from discovery to corporate affairs.

2. INTRODUCTION

The World Health Organization (WHO) defines a drug or pharmaceutical preparation as any substance or mixture of substances manufactured, sold, offered for sale, or represented for use in the diagnosis, treatment, mitigation, or prevention of disease, abnormal physical state or the symptoms present in man or animal. It can take over ten years from the time a drug is discovered to complete all the mandatory clinical phases and obtain regulatory approval for the new medicine to be launched on the market (1) (see Figure 1).

Regulatory requirements are part of the process of drug discovery and drug development. Regulatory affairs is a set of regulatory systems with several aims: set on regulations and compliance-oriented matters that have a significant impact on pharmaceutical industry development and performance. It coordinates, interprets and evaluates the government regulatory agency; establish compliance policy of government regulatory agency (2). Regulations are initiated based on laws and state what must be done, in

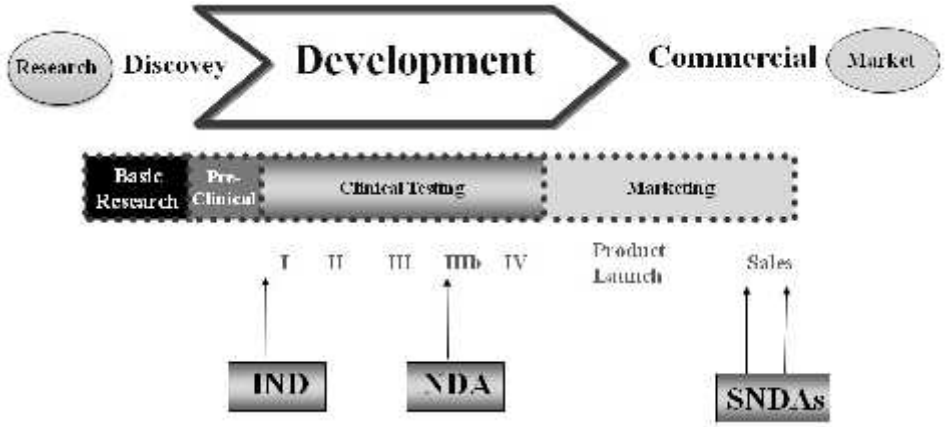

Figure 1. Drug development phases from research stage up to marketing; IND= Investigational New Drug, NDA= New Drug Application, SNDAs= Supplemental New Drug Application.

general. Regulations lead to guidelines which are documents issued by the regulatory agencies to clarify requirements and provide advice to accomplish. The guidelines are often specific to therapeutic areas or technical disciplines. Regulatory affairs works to establish an effective and uniform balance between voluntary and regulatory compliance and agency responsiveness to consumer needs. It evaluates and coordinates all proposed legal actions to ascertain compliance with regulatory policy. Pharmaceutical business is the highest regulated in the world.

Medicine regulation incorporates several mutually reinforcing activities, such as:

- licensing of the manufacture, import, export, distribution, promotion and advertising of medicines;

- assessing the safety, efficacy and quality of medicines, and issuing marketing authorization;

- inspecting and surveillance of manufacturers, importers, wholesalers and dispensers of medicines;

- controlling and monitoring the quality of medicines on the market;
- controlling promotion and advertising of medicines;

- monitoring adverse reactions to medicines;

- providing independent information on medicines to professionals and the public.

Regulatory strategy defines the plan for developing the product with the goal of obtaining regulatory approval in the markets of interest and life cycle management/maintenance, post approval. When an investigational new drug (IND) is in development, an efficient regulatory strategy will be designed, which should consider and evaluate:

- identification of similar drugs/treatment for specific indications;

- obtaining of regulatory approval documents;

- identification of relevant guidance documents, both regulatory and medical;

-identify and minimise regulatory assessment risk (increase predictability) (3).

Regulatory agency is an independent governmental commission established by legislative act in order to set standards in a specific field of activity, or operations, in the private sector of the economy, and to enforce those standards. Regulatory agencies function outside executive supervision. The agencies create regulations and guidance, based on released laws by the executive and legislative branches of the government. Regulations consist in the details to put statute into effect. The regulatory guidelines are not enforced by law.

Important regulatory bodies that govern pharmaceutical industry are the followings: European Medicine Agency (EMA) in Europe (4), Food and Drug Administration (FDA) in USA (5), Therapeutic Products Directorate (TPD) in Canada (6), Pharmaceutical and Medical Devices Evaluation Center (PMDA) in Japan (7). Global environment agency strategy focuses on some major trends, such as:

- improving the level of public health protection;

- strengthening the competition within the pharmaceutical market;

- increasing control of pharmaceutical aspects;

- increasing development pharmaceutics requirements;
- greater harmonisation via International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (8) and Mutual Recognition Agreements (MRA's) (9);

- increasing safety surveillance;

- increasing consumer awareness (2).

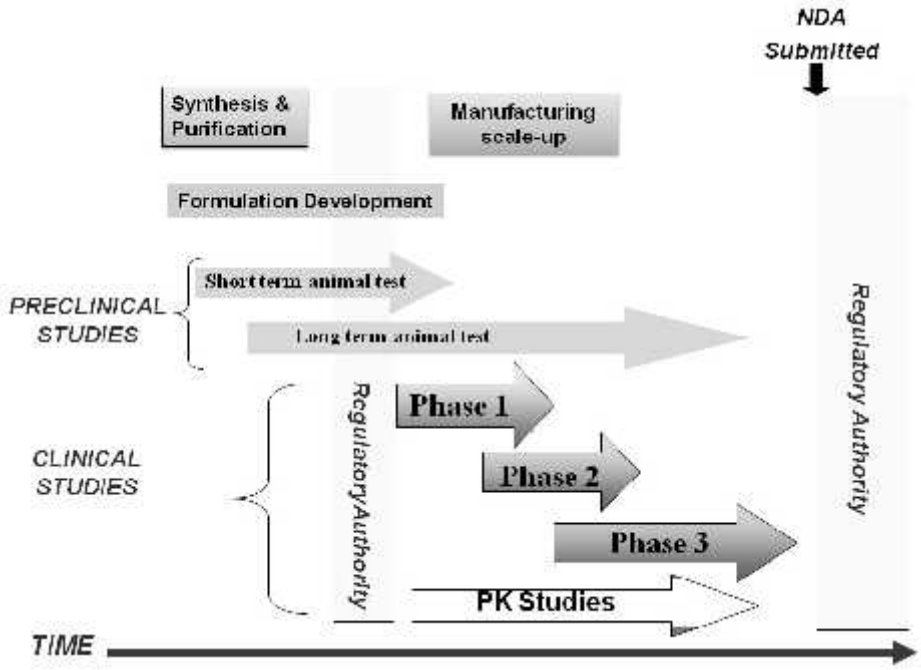

Figure 2. Description of drug development studies.

The pharmaceutical research and development (R&D) processes generate a huge amount of data and failed to generate the expected return in terms of enhanced productivity and pipelines. The transparency of the information is affected by the inability of existing integration strategies to organize and apply the available knowledge to the range of real scientific and business issue in critical safety and regulatory applications. Therefore, the semantic technologies based on ontologies make the knowledge reusable by several applications across business, from discovery to corporate affairs. In addition, the ontologies permit to the computers to use different lexical representations to refer to the same real world concepts (10) and can be automatically processed by machines, enabling automatic knowledge management, data integration and exchange, decision support and reasoning (11-13). This review presents the most important legal aspects and ontologies for regulatory affairs on drug development.

3. DRUG DEVELOPMENT

There is no standard path through which drug development should take place. New drug research starts with an understanding of how the organism functions, both normally and abnormally, at its most basic levels. The questions raised by this research help determine a concept of how a drug might be used to prevent, cure, or treat a disease or medical condition. This provides the researcher with a target (14). Therefore, a new drug development starts having the final product for intended use in mind.

Due to the complexity of drug development process, there are involved several different disciplines, such as: Pharmacology, Toxicology, Microbiology, Biopharmaceutics, Technologies, Chemistry, Regulatory Affairs, clinical study, etcetera. A new drug substance may be produced by chemical synthesis, recovery from a natural product, enzymatic reaction, recombinant DNA technology, fermentation, or a combination of these processes (1). As main steps in medicine development (Figure 2) should be considered the followings:

- Research, that is laboratory analysis of chemical compounds with action disease targets;

- Screening which evaluates positive leads;

- Optimization step to optimize drug chemistry and synthesize the drug to be used in the clinical testing;

- Preclinical phase in which laboratory and animal tests are performed to determine safety and biological efficacy of the drug;

- Clinical trials evaluate the safety and effectiveness of the compound in treating the human disease and characterise side effects. The highest international ethical research standards should be applied;

- Regulatory approval when prepare and submit clinical trials for review by international regulatory authorities;

- Manufacturing when transfer technology to manufacturing;

- Distribution to assure the supply of the medicine where needed, in compliance with the standards (15).

3.1. Synthesis, purification and characterization

Organic chemistry synthesizes new drug compounds, as well as isolates and characterizes natural products. In each case, the complex relationships between chemical structure and pharmacological action are of a particular interest. The pharmacological activity of a compound is an involved function of the structure, and very small changes like replacing one group with another, at a specific point in the molecule may significantly modify the pharmacological effect (16).

The first step in product characterization is to establish the precise chemical identity of the product. It is important to determine whether the material is a compound, for example a single chemical entity, a mixture of closely related compounds, mixture of isomers, or merely a loose molecular complex of readily dissociable components. Such information is fundamental to a proper evaluation of the biological properties of the material.

In the case of compounds of synthetic origin, identity is usually clearly defined in most of the cases by the synthetic route employed. However, it is essential not only that identity be confirmed by alternative means, but the different approaches should be capable of providing rapid verification whenever this may be required, at any stage of the development program. Modern spectroscopic techniques are sensitive tools for this purpose. The interpretation of spectroscopic data obtained from compounds, however, is dependent on the features of the material under study, whether is homogeneous or not (1).

Powerful separative techniques, particularly chromatography in all its forms, provide sensitive methods for purification. Liquid chromatography, which makes use of electronic recorders, is also eminently suitable and widely used for quantitative determination of the composition of mixtures of related compounds such as mixtures of isomers. The speed and high separative power of capillary gas chromatography can be particularly useful technique, if highly specialized, for the separation of complex mixtures during research phase of drug development.

Where the product consists of more than one isomer, the isomers must be capable of separate identification and measurement to establish means of ensuring batch-to-batch consistency of isomer composition. For optically active compounds, a polarimetric measurement of the specific optical rotation at the wavelength of the sodium D-line will be necessary. Occasionally, however, where the measured rotation is small, measurements on a more sensitive instrument at other wavelengths either directly or after derivatisation may be employed, to secure adequate control of the product. In exceptional cases, the identification of optical isomers differing in only one of several chiral centers may call for the use of optical rotatory dispersion or circular dichroism to provide a degree of sensitivity that cannot be obtained from simple measurements of optical rotation.

NMR technique is particularly valuable in distinguishing geometrical isomers (1). Very important in drug development process, at an early stage, is to identify and quantify potential impurities present. These impurities relate to the source materials (i.e. the substance itself if it is a natural product, starting materials for synthesis, or intermediates), the manufacturing process and the stability of the product (i.e degradation products) (17). Inorganic impurities that might interfere with the assessment of toxicological profiles are confined to residues from toxic elements arising from catalysts and reagents used in synthesis. Detection, profiling and control of impurities are matters of particular importance in drug development, their limits during shelf life are subject of compliance, as described in the respective regulatory guideline(s). The data generated must be used in accordance with the principles detailed in the ICH guideline. Safety aspects should be taken into consideration and evaluated. The methods employed for compound characterization, also for identification and quantification of its impurities need validation, to prove they are suitable for intended purpose (16).

Further on, pharmaceutical development aims to design the final pharmaceutical product and its manufacturing process to consistently deliver the product, conforming to the intended performance. Product quality and performance linked to clinical safety and efficacy (14).

3.2. Pre-clinical study

Once a compound shows potential for clinical development, extensive pre-clinical studies on its pharmacology and toxicology are undertaken, on live cells and animals, as model studies. Animal tests, “preclinical investigations,” or “non-clinical studies”, as they are also termed, are designed with particular regard to possible future testing of the drug in humans, or “clinical investigation” (18).

The task of evaluating the beneficial effects against the possible harmful effects of any medicine is complex. Evaluation takes into account the nature of the active ingredients, the dosage form (for example, tablet or liquid), the nature of the disease or condition to be treated, the effective dose that needs to be given, the type of patient (for example, age, sex) and the duration of treatment. A high risk to benefit ratio may be acceptable in the treatment of terminally ill patients, where the quality of life might be enhanced, whereas a very low risk to benefit ratio is expected in the treatment of patients with self-limiting diseases, for the purpose of prophylaxis (for example, vaccines) and for those requiring life-long treatment for their illnesses (19).

In order to be certain that a new drug is safe, detailed studies are performed on the effects of varying doses and prolonged administration of that drug. Pharmacology studies provide acute toxicity data. The toxicologist then must refine the acute toxicity measurement in laboratory animals and begin subacute and chronic studies. The latter are conducted in a variety of species, at several dosage levels of the drug, and over periods of time ranging up to 30 months. During the test period, animals are observed carefully for all adverse symptoms. Pharmacodynamics (study of interactions

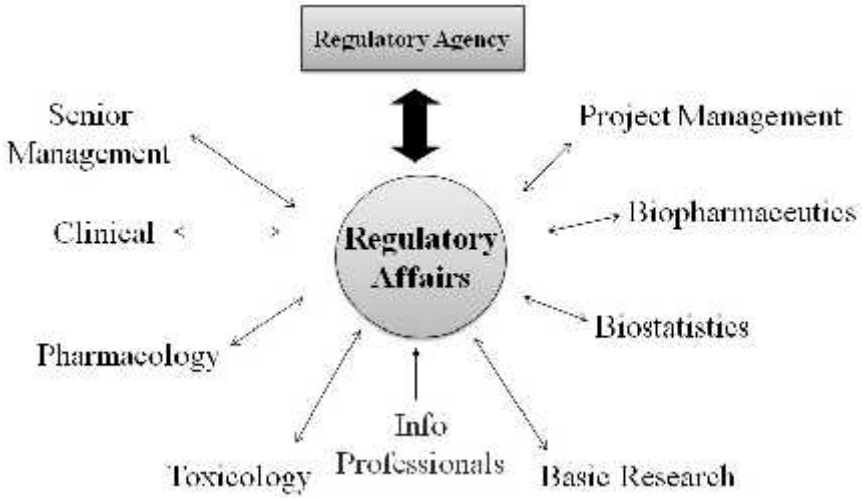

Figure 3. Illustrating regulatory affairs role within drug development context.

between the drug and living structures) and pharmacokinetics (study of the process of bodily absorption, distribution, metabolism and excretion of the medicine and its compounds) studies are performed and the obtained results evaluated. At the end of this period, and occasionally during its progress, animals are sacrificed, and their vital tissues, such as liver, heart, kidney, intestine, brain, etc, are removed and studied grossly and microscopically by a pathologist. In addition to gross and microscopic pathology, biochemical and physiological responses are measured as an indication of liver function, kidney function, endocrine function, etc. (15). Laboratory and animal tests are designed to determine:

- The relative toxicity of the new chemical. These tests would include acute toxicity and LD50 tests to determine toxic dosage, as well as median and long-term toxicity tests for harmful effects on the animal and on various specific organs, such as the eyes, liver, and brain;

- The probable or possible side effects of the drug;

- Proposed route of administration;

- Safety of the compound;
- The highest dose that could be tolerated;

- Proposed highest dosage for use.

The knowledge gained in pre-clinical phase, are used further for clinical studies, in humans (20).

3.3. Clinical study

Clinical research is the bridge between the basic research in laboratory and the patient. The priority during clinical trials is the patient safety, and, therefore, the subjects are closely monitored. Clinical trials are closely supervised by appropriate regulatory authorities. All studies that involve a medical or therapeutic intervention on patients must be approved by a supervising ethics committee before permission is granted to run the trial. An Institutional Review Board (IRB) reviews and approves the trial protocol before the trial can even begin. It assesses the informed consent process, benefits and risks, and how volunteers will be selected in the process (21). Regulatory affairs ensure compliance to obtain authorizations for clinical trial, the legal and ethical documentation required by the competent authorities. The local ethics committee has discretion on how it will supervise non-interventional studies (observational studies or those using already collected data) (22).

Each phase of a clinical trial is based on a clinical protocol that attempts to answer questions that will enhance and improve treatment and therapies. These trials are conducted to determine drug permeability and absorption, by studying drug's bioavailability and bioequivalence, as well as toxicity limits. The clinical investigation of experimental drugs in humans is normally done in three phases (Phase I, II, and III), with more and more people included in each subsequent phase. Phase IV is carried out after product licence has been granted (23). Post-marketing clinical trials begin to test the long-term effects of the newly-approved drug. Usually, a new drug is scrutinized closely for one to two years after approval but, in effect, all drugs are continuously monitored by the competent authorities for many years (24). If a clinical trial concerns a new regulated drug or medical device (or an existing drug for a new purpose), the appropriate regulatory agency for each country where the sponsor wishes to sell the drug or device is supposed to review all study data before allowing the drug/device to proceed to the next phase, or to be marketed (25). Regulatory affairs acts at all developmental stages. It plays an important role also in assessing results from the different activities and disciplines involved in the drug development (Figure 3).

3.4. Perspectives in regulatory affairs

Once all the steps in drug development are successfully accomplished and all information and results starting from early research stage, up to end of clinical trial are available, the Common Technical Document (CTD)

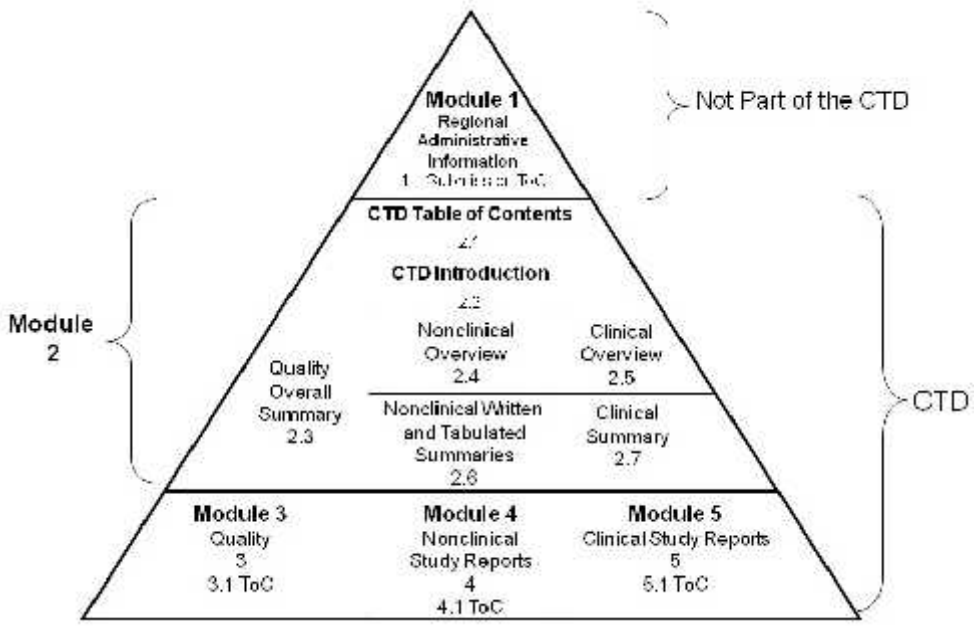

Figure 4. CTD structure.

(26), which actually represents the product dossier is prepared and subsequently submitted to the competent authorities for evaluation and approval.

The CTD is a prescribed organization of the information (chemical, pharmaceutical, non-clinical and clinical) required to be submitted. It provides an appropriate format to transfer the product information that have been acquired, to the regulatory authority for assessment (23). Based on CTD document, the regulatory review and communication with the applicant will be facilitated by the standard document of common elements. CTD comprises 5 modules in total (Figure 4), organized as it follows:

- Module 1: Regional Information (contains the administrative and prescribing information according each regional regulatory agency);

- Module 2: Quality overall summary:

- Nonclinical overview;

- Clinical overview;
- Nonclinical written summaries;

- Clinical summaries;

- Module 3: Quality;

- Module 4: Safety (Nonclinical);

- Module 5: Efficacy (Clinical).

Once the evaluation is complete and dossier approved, a marketing authorization is released.

4. ONTOLOGIES

The lack of the whole-process productivity in drug development can be attributed to the inefficient use of information and to the difficulties in making knowledge held in distributed databases visible inside large multidisciplinary organization. Many knowledge management (KM) (27) and data-integration strategies have had limited success because of patchy implementation, incomplete rollout and their technological constraints. The data integration (28, 29) is usually performed using distributed warehouses and static repositories, the information rarely being reusable between projects. In pharmaceutical R&D there are at least four large-scale integration ways: rule-based links such as SRS from Lion Bioscience (30), data warehouse such as Atlas (31), ad hoc query optimizers such as Discovery Link (32) and federated middleware frameworks such as GRIDS (33). In most cases, the semantic integration is static and new questions and contexts cannot be accommodated easily. Therefore, a more effective approach is to focus explicitly on the representation of knowledge rather than just its management.

The key to being able to integrate information in a reusable way is the use of semantics, which describe the meaning of a word or concept by using ontology (34). This semantic representation of knowledge is more scalable, flexible and able to support multiple existing and future business applications. Ontology is a discipline founded in philosophy (35) and computer science (36) that is the central part of the new wave of semantic technologies such as Semantic Web (37). In Philosophy, Ontology is defined as “the science of what is, of the kinds and structures of objects, properties, events, processes and relations in every area of reality” (34). The central goal in philosophical

ontology is a definitive and exhaustive classification of all entities (38). In Computer Science, the ontologies are considered as graph-theoretic structures consisting of "terms", which represent real world entities and constitute the nodes of the graphs, linked by "relations", which form the edges between the nodes (39). The most accurate and complete definition of ontology was proposed by Studer, Benjamins, and Fensel in 1998: “a formal, explicit specification of a shared conceptualization" (40).

The most important ontology languages are the Resource Description Framework (RDF) (41) and the Web Ontology Language (OWL) (42), both proposed by the World Wide Web Consortium (W3C) and based on the Extensible Markup Language (XML) (43). RDF uses a graph-based model to represent information in triplets of the form <subject><predicate><object>. Each triple can be graphically represented as a directed graph where the "predicate" is an edge from the "subject" node to the "object" node. In addition, RDF Schema (44) extends the capabilities of RDF and makes the ontology much more useful to domain specialists. OWL (OWL-Lite, OWL-DL and OWL-Full) is the recommended knowledge representation language for building ontologies for the Semantic Web and provides computational reasoning capabilities across ontologies in order to infer new knowledge from existing information. OWL is based on a subset of description logics (DLs) (45) that facilitates the description of concepts with an emphasis on decidability of reasoning tasks, which can be executed by an automatic reasoned.

In bio-related fields ontologies are entitled "bio-ontologies" (10, 46) and used by researchers to annotate primary data or to associate terms from ontologies to the existing data (47). Therefore these data can be understood and managed, both by humans and computers, allowing a large-scale data search (48) and analysis (49) at different levels, from gene to phenotype and disease (28, 29, 50-52). The largest repository of bio-ontologies is the Open Biomedical Ontologies (OBO) resource (53), supported by the NIH National Center for Biomedical Ontology (NCBO), and available through the BioPortal Website (54). OBO contains more than 60 bio-ontologies, which are being evolved and extended through the OBO Foundry collaborative endeavor and used a new ontology language entitled OBO-format that provides human readability, ease of parsing and extensibility with minimal redundancy (55, 56).

4.1. Ontologies in drug development

DrugBank (57) and PharmGKB (58) are the most famous pharmacological resources and are using ontologies to structure their information about drugs, drug discovery and design. RxNorm ontology (59) involves an effort from NLM to provide standard names for clinical drugs and for dose forms as administered to a patient by providing links from clinical drugs to their active ingredients, drug components and related brand names. Medical Subject Headings (MeSH) (60) is an ontology that facilitates searches in many biomedical resources such as MedLine (e.g. PubMed). Veterans Health Administration (VHA) National Drug File (NDF) (61) supports VHA clinical applications and includes information about drug costs, ingredients, and inventory management, and also complete taxonomy of diseases.

Potential drug - drug interactions are supported by the Drug Interaction Ontology (DIO) (62), which provides a formal definition of molecular events and the relations among them based on drug metabolic pathways, dynamically generated by molecular events triggered after the administration of certain drugs (63). The European Bioinformatics Institute (EBI) maintains an ontology of drugs as well, which is called Chemical Entities of Biological Interest (ChEBI) (64). The drug target strategies are supported by several ontologies such as Protein Ontology (PRO) (65, 66), Protein Ontology (PO) (67), Proteomics Process Ontology (ProPreO) (68) and Protein Modification (PSI-MOD).

SuperTarget (69) is a Web application that integrates drug-related information about medical indication areas, adverse drug effects, drug metabolization pathways and Gene Ontology terms of the target proteins. The drugs are classified using the Anatomical Therapeutic Chemical (ATC) ontology (70), controlled by the WHO. Pharmacovigilance is another drug-related ontology focused on the early detection of unwanted or adverse effects of drugs and safety surveillance after in launching on the market (71). Ontologies used for coding adverse drug reactions are MedDRA (Medical Dictionary for Regulatory Activities) (72), which classifies adverse event information associated with the use of biopharmaceuticals and other medical products (73), COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) (74) and World Health Organization - Adverse Reaction Terminology (WHO-ART) (75). In the area of Pharmacogenomics (76), the Suggested Ontology for Pharmacogenomics (SO-Pharm) (77) is designed for genotype, drug, phenotype and trial representations and enables the support to the knowledge about pharmacogenomic hypothesis, case study, and investigations.

The huge volumes of chemical, genomic, physiological and disease data make that drug discovery scientists often feel incapable of facing the existing huge sets of unstructured pharmacological data to extract the knowledge they require in order to make complex decisions that are really beneficial. This fact constitutes an important barrier to the development of systematic studies (69). Therefore, ontologies become a solution to overcome heterogeneity problems in the business pharmaceutical environment (78-80), allowing to reduce the time and cost of developing useful pharmacological agents.

As an application of the Ontology for Biomedical Investigations (OBI) (81), the Drug Discovery (DDI) Investigations ontology (82) is defining the main entities and relations in the research and development phase of the drug discovery pipeline and provides a standard to facilitate the exchange of drug discovery information between different companies and to obtain high research reporting

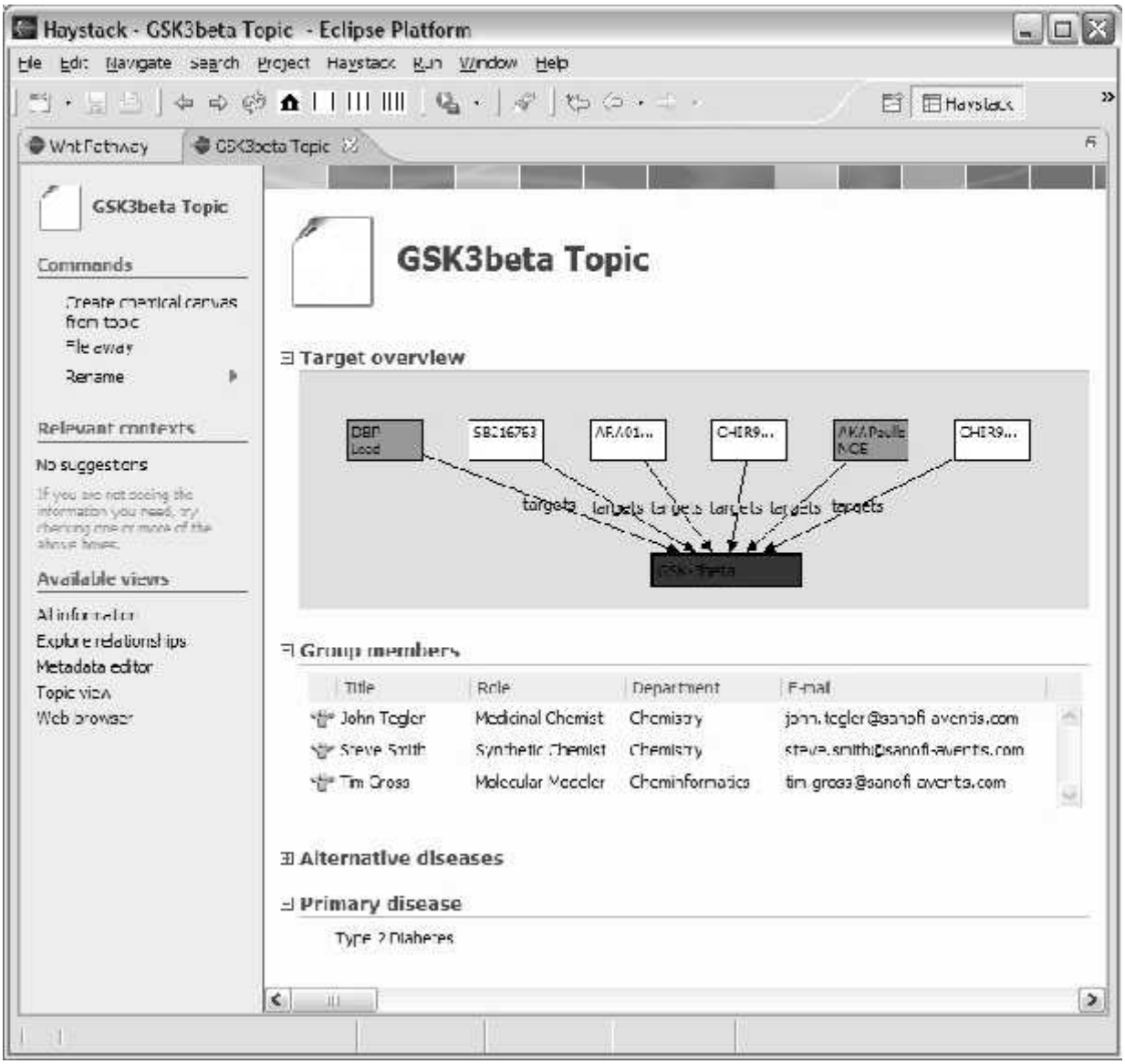

Figure 5. Haystack - BioDASH demonstration with Glycogen Synthase Kinase 3 beta as the target.

quality (83). DDI is based on EXPO (84), an ontology of scientific experiments, and LABORS (85), which is a customized version of EXPO expressed in OWL-DL. DDI follows the OBO Foundry principles (53) so that it can be easily integrated with other existing ontology resources. One of the main applications of DDI is the support for the Robot Scientist Eve (86), which is designed to run automatic drug discovery investigations. BioDash (87) represents a semantic web dashboard for drug development which attempts to aggregate heterogeneous yet related facts and statements (using an RDF model) into an intuitive, visually descriptive and interactive display. The key idea behind RDF is enabling a number of important capabilities by introducing some syntactical simplifications on XML: (1) personal or domain-specific annotations, classifications, and other forms of knowledge can be added to any application's data without interfering with its normal function; (2) information retrieval is made easier, because RDF-enabled Web browsers and search engines can index and extract classification metadata from any RDF file; (3) arbitrary RDF data files, containing pieces of knowledge from multiple applications, can be easily merged to form a larger whole (information integration); (4) automated, rules-based processing is possible e using off-the-shelf RDF inference engines. The BioDASH demonstration from Figure 5 is built on Haystack, which is an extensible Semantic Web Browser developed by the Haystack research group at the MIT Computer Science and Artificial Intelligence Laboratory, a plug-in for the Eclipse platform and runs on Windows, Linux, and Mac OS X. The demonstration focuses on an investigation into the therapeutic value of GSK3beta (glycogen synthase kinase 3 beta), a regulatory enzyme associated with multiple diseases, including diabetes type 2 as well as Alzheimer's.

Over the past years numerous initiatives, roadmaps and emerging standards have seen an increasingly rapid development. One example is Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) (88), a systematically organized computer processable collection of medical terminology covering most areas of clinical information such as diseases, findings, procedures, microorganisms, pharmaceuticals etc. that allows a consistent way to index, store, retrieve, and aggregate clinical data across specialties and sites of care. It also helps organizing the content of medical records, reducing the variability in the way data is captured, encoded and used for clinical care of patients and research (89).

The World Wide Web Consortium (W3C) created in 2008 the Semantic Web Health Care and Life Sciences (HCLS) Interest Group (90). The European Commission financed the SemanticHEALTH Sixth Framework Programme (FP6) project (91) with the objective of delivering a Semantic Interoperability roadmap for Europe. NeOn (92) is a project involving 14 European partners and co-funded by the EU's FP6 under grant number IST-2005-027595 and has the aim to advance the state of the art in using ontologies for large-scale semantic applications in the distributed organizations. Its infrastructure is based on the notion of networked ontologies and defines four main ontology assumptions: Dynamic (ontologies will evolve), Networking (ontologies are interconnected via mappings, alignments or by means of reuse), Shared (ontologies are shared by people and applications), and Contextualized (ontologies are dependent of the context in which are built or are used) (93).

4.2. Legal ontologies

The 80's legal knowledge formalization was mainly based on the choice of the best paradigm of representation (declarative versus deductive approach, rule-based, logic based). In 90's, the Artificial Intelligence (AI) & Law community focused on the features of legal reasoning and of the dialectic dimension of law (deontic modalities, defeasible reasoning, argument construction). The legal expert systems never came out of the level of prototypical applications, since they were lacking a solid methodology for knowledge modeling: formalizing legislative knowledge was a subjective process, time- (and cost-) consuming, relatively unreliable from the user perspective, and not easily re-usable by different applications (94).

Therefore the AI & Law community becomes interested in ontology-based approach that permits the formal definition of the components of legal knowledge. The first intuitive argument for the adoption of ontologies as a description model for comparing norms is that they will provide a common (even if not neutral) language to express them, since only homogeneous entities can be compared. A further practical consideration is that most initiatives in the field of legal standard definition (LeXML, Metalex, NIR) consider legal ontologies strictly connected with the structuring of normative text. Ontology is therefore both a description model and a source of metadata for semantic tagging, providing at the same time a tool for conceptual retrieval and a model of content which maintains references to legal texts.

The norm comparison may be conceived in several ways (95): as a diachronic process where the norms from the same system and regulating the same domain may be compared in order to detect differences related to changes in time, or specializations of the situations (amendment, exception, extension) or as a synchronic process where the norms of different systems, regulating the same situation, can be compared in order to assess differences in national or local. First step in the comparison process is the text structuring "pre-processes" the normative information in order to identify the entities involved in the regulation (definition, constitutive norms) and to enable the comparison of similar classes of norms (prescription, sanctions, administrative or financial regulations) and to exclude rules dealing with the management and updating of the legal systems (amendments, crosslinks). When comparing the normative structure of EC and national texts, it is likely to assume that most EC regulations include prescriptive rules directed to the national legislative bodies of the Member States, which should be implemented, at the national level, as prescriptions, constitutive rules, and procedures. The ontology library for EC Directives has the following characteristics: the EC Directives and national laws are represented in separate ontologies, which both inherit the Core Legal Ontology and the Foundational Ontology used to build the Core, the ontology of the content domain (social world) addressed by the directives is also based on the Foundational Ontology, the national implementation of directives should inherit both from EC directives and from the national laws, without being inconsistent, the rules of conduct and codes of practice in the Directive's domain inherit from the national implementation of the Directive and any compliant application ontology will inherit from all those ontologies, besides the basic service and task ontologies addressed by the application.

In ontology field, several core ontologies have been developed in order to formalize the legal concepts from a high level of abstraction and shared across legal domains. Some examples include the Functional Ontology for Law (FOLaw) (96), the Frame-Based Ontology (97), the LRI-Core ontology (98), DOLCE+CLO (Core Legal Ontology) (99), the LKIF-Core Ontology (100), and the Ontology of Fundamental Concepts (101).

Core Legal Ontology (CLO) is based on foundational ontologies (102) and proposals in the field of legal ontologies (103). CLO organizes juridical concepts and relations on the basis of formal (meta) properties defined in the Descriptive Ontology for Linguistic and Cognitive Engineering (DOLCE) foundational ontology [4], the first module of the WonderWeb Foundational Ontologies Library (WFOL). The basic types of entities that populate the domain of Law are assumed to be clearly identifiable and reasonably intersubjective, and, as such, they are pointed out through a minimal set of properties and relations from DOLCE and some of its recent extensions,

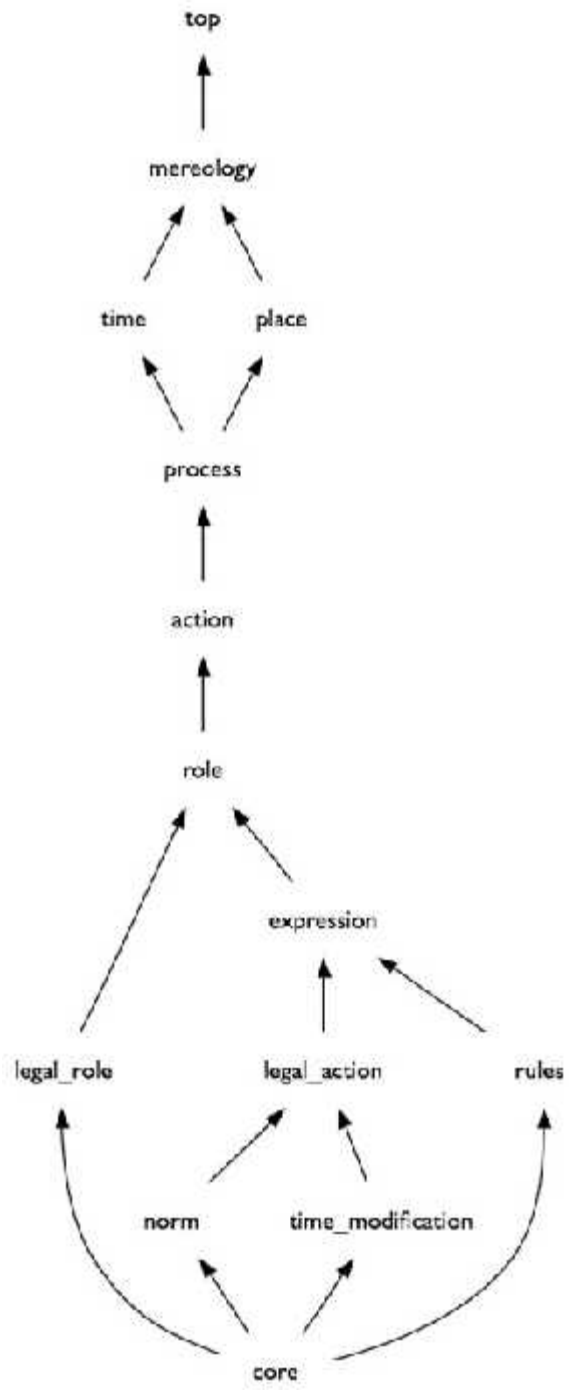

Figure 6. LKIF-core modules in Estrella.

notably the "Descriptions and Situations" ontology (D&S) [9]. The methodological choices, as well as the exploitation of properties suitable for the legal domain, are based upon the approach of legal theory and philosophy of Law. For example, the most common definition of norm shared by legal theoreticians is based on the schema "fact-norm-effect": properties (in some case the existence itself) and events inherent in the entities of the legal world depend on norms, whose role is that of describing generic facts (situations), and ascribing to them generic effects (legal qualifications). Jurwordnet is an extension to the legal domain of the Italian version of EuroWordNet (104) and contains description model for legal information and a lexical resource for accessing multilingual and heterogeneous information sources.

European project for Standardized Transparent Representations in order to Extend Legal Accessibility (Estrella, IST-2004-027655) was a European project coordinated by the Leibniz Center for Law, Faculty of Law of the University of Amsterdam, a part of the Information Society Technologies (IST) in the Sixth Framework Programme for Research (FP6) of the European Commission (January 1, 2006–June 30, 2008). The platform provides the LKIF language, the Legal Knowledge Interchange Format (LKIF) core ontology, the HARNESS architecture, the eXistrella content management system and the Carneades argumentation engine. LKIF is a Semantic Web based language designed for legal applications built upon emerging XML-standards, amongst them Resource Description Framework (RDF) and Web Ontology Language (OWL), and Application Programming Interfaces (APIs) for interacting with the inherent legal knowledge systems. The format was tested on tax legislation and regulations but is designed to be applicable in all legal areas. It aims at a standard vocabulary allocating approximately 200 abstract as well as concrete concepts and their definitions classified into 15 modules. Five abstract concepts refer to top, place, mereology, time and spacetime and four basic-level concepts are added with process, role, action and expression. The legal ontology contains three modules: legal action, legal role and norm. Two frameworks are provided by modification and rules (see Figure 6). The details about the legal sources and rules & epistemic roles in LKIF are presented in Figures 7 and Figures 8. These examples show the importance of integration of knowledge by legal ontologies in regulatory affairs in drug development.

5. SUMMARY AND PERSPECTIVE

The regulations work to protect patients of harmful medical products and to facilitate the availability of beneficial medical products to patients. As a result, no drug can be marketed until substantial evidence of its quality, safety and effectiveness has been provided for evaluation to the competent authorities. Substantial evidence is obtained by testing the product in animals and humans, to see how it works and if it causes any harm. The tests are performed under controlled conditions to eliminate wrong results or interpretation of results. Rigorous scientific, regulatory and medical standards are applied throughout.

Many pharmacological resources are using ontologies to structure their information about drugs,

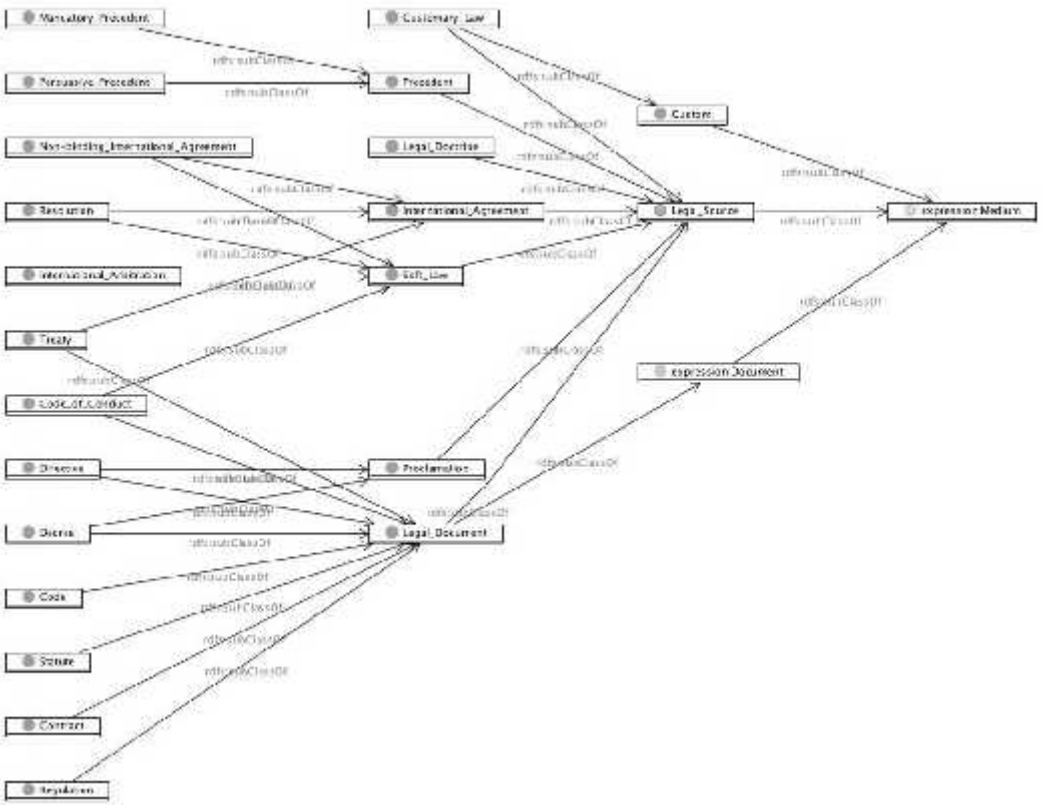

Figure 7. LKIF legal sources.

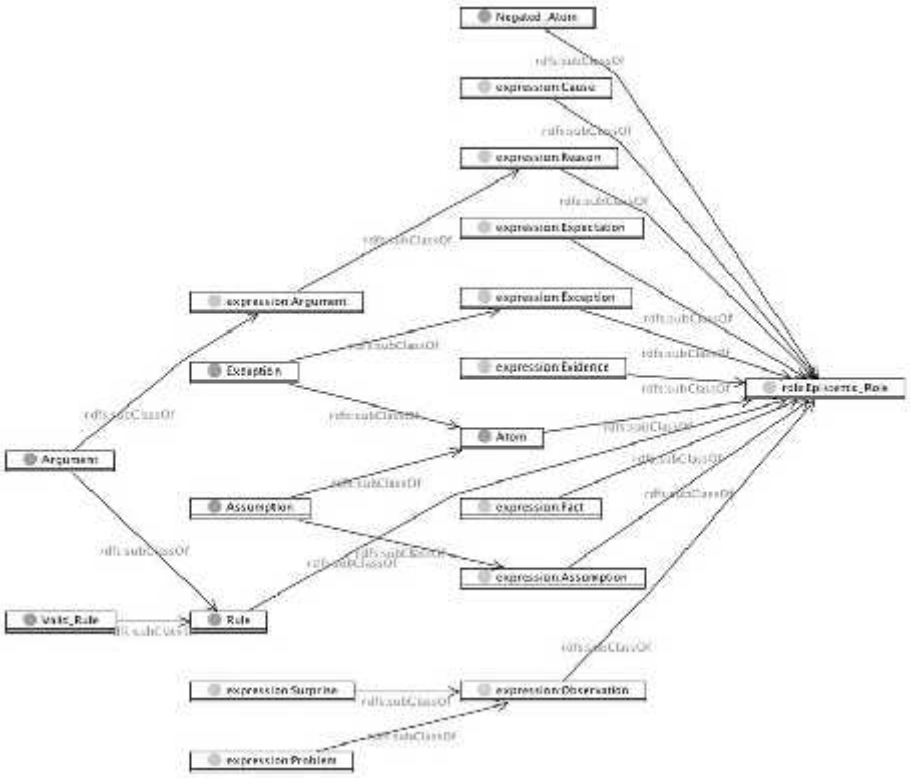

Figure 8. Rules & epistemic roles in LKIF.

drug discovery and design. Moreover, ontology-based approach permits the formal definition of the components of legal knowledge. Ontology is also a description model and a source of metadata for semantic tagging, providing at the same time a tool for conceptual retrieval and a model of content which maintains references to legal texts.

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