Identification and Analysis of Sources Relative to the Characteristics of Pharmaceutical Innovation

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***Abstract* - Every year new drugs appear on the market. Information about the therapeutic innovation is contained in many heterogeneous sources. A physician needs to identify easily and fast the whole of the drug innovations relative to his sphere of activity, to understand the nature of these innovations and their potential impacts on the practice. We analyzed the available sources and the nature of this information which can be found after the marketing drug. We explored the American, European including French sources. We identified the sources that constitute the base in identification of pharmaceutical innovation. We explored its structure and format to know if they could be used in the development of therapeutic monitoring tool. We selected the sources that help to characterize pharmaceutical innovation concerning to type of innovation and according to impact of the new drug. We proposed a tool which identifies the drugs prescribed for pathology "type 2 of diabetes" using DailyMed source. The tool allows finding the type of innovation and its impact. This work has identified the main sources of information available at the moment of drug marketing. Each of the described sources in this paper is important, but insufficient to characterize the pharmaceutical innovation.**

***Index Terms* — drug sources, information seeking, medical informatics, information resources, databases.**

I. INTRODUCTION

When a drug is marketed, the physician needs to position it in the therapeutic arsenal for deciding the pertinence of its prescription in terms of benefit/risk. To generate this opinion about the new drug, he has several sources which reveal all the properties of the drug (monographs), or which offer a comparison with other drugs of the same indication. Finally, the use of new drug recommendation is completely formalized via clinical guidelines. The time of these documents production is variable: the monograph dates since the date of the drug marketing, the report of evaluation is later and retrospective, the clinical guidelines are updated very infrequently. These documents, being fixed in time, provide information at a given time.

Each country has its specific standards to evaluate the drug impact.

Food and Drug Administration of US provides standardized information relative to the new drugs after their marketing authorization. The information specifies if it is a new molecular entity, a new salt or ester, a new formulation, a new combination of drugs already marketed in the United States, a new manufacturer, a new indication for a product already marketed or it is another innovation. The therapeutic benefit for the patient is classified as P (Priority review drug), S (Standard review drug) or O (Orphan drug) [1]. This manner of characterizing the innovation has the disadvantage of not indicating analytically to the physician, the real interest of this one.

From Europe, Austria is the country that presents the most detailed characterizations of the pharmaceutical innovations, described in pharmacological and therapeutic terms [2].

In France, the French Agency for Sanitary Health of the Health Products (Afssaps) quantifies the actual benefit (SMR) of each innovation. This one summarizes the benefit (disease severity, efficacy, therapeutic alternatives) and the risks related to use of the new drug. The ASMR measures the improvement that the drug is likely to bring compared to already available drugs [2]. These indicators represent a summary of what a drug brings to certain moment and moves in time depending on the data on which they were founded. To appreciate fully the value of these indicators, the physician always need to refer to the textual document of evaluation which is long.

In these approaches, the innovation is seen mainly in terms of efficacy [3, 4, 5] which is restrictive. An important innovation can lead to an identical efficacy associated with less frequent side effects or less severe effects.

To build objectively its judgment on a new drug is a task that requires time, capacities of critical analysis, familiarity with the multitude of the available documents, capacity to identify them and reach it. For example, to form an opinion about the Pradaxa TM, an oral anticoagulant used in the prevention of venous thrombosis after the hip surgery, the doctor can read the clinical guidelines on the anticoagulation postoperatively. The document dating from 2005 does not contain this new drug. He may read the evaluation report of medical department rendered issued in July 2008 and he is able to position this new molecule compared to the heparin of low molecular weight, but he must also be vigilant to the output of more contemporary drugs having similar characteristics (Xarelto TM whose opinion is published in January 2009 and who is not compared to the previous molecule). Finally, he must connect to the site of clinical trial to identify posterior clinical tests to these 2 opinions which could inform more.

If the clinical guideline gives the relevant information for the physician, the other available documents do not provide exhaustive searched information and it is necessary to cross several sources to have an opinion.

Methods of Knowledge Engineering in Medicine provide a base that can lead to the automated extraction of information available on the Web, their synthesis and a summary for their quick apprehension by the physician.

The objective of this work is to identify sources for characterizing pharmaceutical innovation, to study the feasibility of developing automated tools that could assist the physician in his scientific monitoring. This paper presents an analysis of the sources which can be queried and their treatment modalities.

II. MATERIAL AND METHODS

Prior we constituted the preliminary list of sources that are used to characterize pharmaceutical innovation from knowledge of experts. These experts included a Doctor of Medicine / Doctor of Philosophy ("MD / PhD) and a Doctor of Pharmacy / Doctor of Philosophy (" Pharm. D / Ph. D ") From The Department of Medical Information Of The Avicenna Hospital.

The sources chosen by experts correspond to those used in their research activities and in their daily work. Subsequently, we expanded the exploration of resources. Our research strategy included an Internet research of various medical web sites, such as BioMed Central, Medscape, First DataBank, the sites of drug agencies in Europe and America. Similarly, we researched about pharmaceutical innovation via PubMed.

We explored the American sources, European including French.

Among the sources analyzed we selected those that help us to characterize pharmaceutical innovation about the type of innovation (new molecule, new association, new strength, new formulations, etc.) and relative to the impact of new drug in terms of efficacy and safety.

We performed a detailed analysis of the content of retained sources. Then, we explored the format to see if they can be used in the construction of the computerized tool of therapeutic monitoring.

III. RESULTS

Illustrations and tables should be progressively numbered, following the order cited in the text; they may be organized in one or two columns. Tables must be accompanied by a caption placed at the top. Figures (abbreviated Fig.) must be accompanied by a caption placed underneath. References made to tables in text will not be abbreviated e.g. “in Table I, TN Roman means Times New Roman”.

Each formula should occupy one line. Consecutive numbers should be marked in brackets.

1. Analysis of sources on the characteristics of therapeutic innovation

We defined the basic set of sources that provide information on pharmaceutical innovation. We have identified two types of information sources that characterize innovation: those which compare and which does not compare the new drug treatment to other existing treatments.

1.1 Sources on drug therapy without comparison to other

The drug monographs

From the marketing of manufactured product, his monograph (or Summary of Product Characteristics) is available by health authorities. This monograph is divided into chapters (composition, indications, contraindications, etc.); the content of these chapters is in free text with a requirement of structuring and coding variable from one country to another.

The U.S., for example, impose a detailed description as an XML structure and a certain number of terminologies to describe the contents of Chapters [6] (eg, clinical conditions are coded using the list of problems VA / KP (Veterans Health Administration and Kaiser Permanente), which is a subset of SNOMED). The monograph is structured to be returned to the user in XML formalism via the website DailyMed [7].

The codification of some elements of the monograph is often performed by the editors of banks drugs, such as in France [8] indications and contraindications are coded in CIM10.

These editors often provide enhancements of the drug information with data from the literature [9, 10] and with monographs structuring models to feed the system functionality of assistant to the prescription. This information is available into the drug banks which are an important source for documenting therapeutic innovation.

Current clinical trials

The banks of clinical trials contain current or completed trials. Trials may include drugs that are already available on the market or in process of the development, as well as protocols of drug combinations (eg in cancer or in treatment of HIV infection).

The *meta*Register of the bank Current Controlled Trials [11] provides access to major registers making it one of the largest controlled trials resources in the world. Although its primary aim is to include information about ongoing controlled trials, the *meta*Register does include information about some completed trials. Research is makes by International Standard Randomised Controlled Trial Number or by keyword. The clinical trial is described in free text topics in which drugs or combinations tested appear in the title, hypotheses and interventions. The target pathology of the trial is in free text in the title and in the inclusion criteria. When a drug not yet marketed is tested, it appears as a code name. The «Study hypothesis" provides explanation for its mechanism of action. But it should be noted that trial results are not recorded in the bank. Its content does not provide answers to the question posed in this paper but rather information about the existence or not of an ongoing clinical research for a given disease.

The information from pharmacovigilance

When the drug is marketed, monographs include already the side effects observed during the completed trial. But the side effects are gradually supplemented by those that occur during the using of drug and by those that reported in the pharmacovigilance databases [12], but unfortunately this information are not public.

The new side effects are often described in the “case-reports” form published in journal indexed with MeSH keywords in Medline. They can next found via bibliographical engines like PubMed.

Drug classification

Drug Classifications allow classify drugs according to their chemical, pharmacological, therapeutic properties. Examples are the ATC (Anatomical Therapeutic Chemical Classification System), the supplementary concepts of MeSH and chemical and pharmacological classifications of MeSH.

These sources can help to qualify the novelty of a molecule, of a mechanism of action or chemical class. However, it should consider the updating time of these sources and how they are structured. Indeed, the introduction of a new class that could to call into question the structure of the resource. There is a risk to find innovations in classes like "not elsewhere classified", which will not be very useful.

1.2 Sources on the comparisons of drug treatments

Results of clinical trials

For all sources already mentioned joins articles indexed in PubMed. The summary of completed clinical trials can be obtained from the BioMed Central database [13]. The information is structured into 4 sections: a description of the trial, results, interpretation of results and conclusion.

Meta-analysis

The results of the meta-analysis and synthesis of literature are available in the Cochrane database [14]. But they were made later after the placing on the market the new drug. The content is presented in free text.

Clinical guidelines

The clinical guidelines are developed to help the physician in the care of the patient. They are written by the expert groups of scientific societies or national agencies. The clinical guidelines contain the results of clinical research that are graded according to level of evidence prepared by the experts. The clinical guidelines are based on the facts and their content is explicit. However, as the interval between publications is several years, the physician is confronted with the problem of obsolescence of information. Their structure evolves over time and differs much from a disease to another. In France, for example, they are available in PDF format, a fact which makes information extraction impossible at present.

Summary

This analysis has led to identify the main existing sources and nature of information that we can find (Table 1). Just after the marketing of the drug, the main sources are drug monographs published by the agencies and already structured in drug databases. At these resources are in addition the publication of clinical trial results and any publications which can be accessed from Pubmed.

Unfortunately, all sources are not exploited in the construction of the characterization tool of innovation. The information contained within sources on comparisons of drug treatments is not structured. Its use in the computerized tool of monitoring therapeutic becomes impossible.

The research of information for most of these sources is made from the name of the drug.

2. Example of tool developing for extracting information from the source DailyMed

As it was mentioned the most of sources provide information on the drug from its name. Nevertheless, the practitioner needs to find information about medicines from the health problem.

TABLE I. THE NATURE OF INFORMATION SOURCES

Source	**Nature of information**	**Comparative information**	**Information structured**
Drug monographs	Molecule, combination, form, route of administration, pharmaco-therapeutic class, mechanism of action, efficacy, safety	no	yes
Current clinical trials	Molecule, combination, mechanism of action, efficacy, safety	no	yes
Pharmacovigilance	safety	no	no
Drug classifications	Molecule, combination, pharmaco-therapeutic class, mechanism of action,	no	yes
Results of clinical trials	Efficacy, safety	yes	yes
Meta-analysis	Efficacy, safety	yes	no
Clinical guidelines	Molecule, combination, route of administration, efficacy, safety	yes	no

Our goal was to build a program that allows the extraction of information about a health problem to show that the contribution of each new drug.

We selected the site DailyMed to extract the maximum information about medicines. It is a source that contains monographs for all marketed drugs in the U.S. The files are in XML format. We used .Net technologies to extract information about the pathology "type 2 diabetes".

The created application can extract the brand name drug of the product marketed, the name of active ingredient, the mechanism of action and the number NDA / ANDA (New Drug Application / (Generic) Drug Approvals).

For pathology "type 2 diabetes" program identifies 129 products, because the file structure is quite heterogeneous and evolves over time. We took into consideration the structures used from 1999 because we focus on pharmaceutical innovation. The NDA may even appear many times, the fact that is linked to the existence of several presentations of the same product. The made program allows the user to find from the indication (diabetes type 2) the drugs that are marketed in the U.S. Using the Drugs@FDA Database, the NDA leads us to the type of pharmaceutical innovation and the importance of this innovation. For example, we find that the product Actos TM with the NDA 021073 has a new molecule (pioglitazone) as the type of innovation and this treatment is classified as a priority (P).

This example shows the limited nature of the classification proposed by the FDA, because the concept of pharmaceutical innovation is much larger and not limited only to characteristics specified by FDA. Similarly, it is difficult for the practitioner to understand the reduction of information about the therapeutic benefit only to priority treatment, standard treatment or orphan.

IV. CONCLUSION

This work has identified the main sources of information available at the time of marketing of the drug, which should allow to instantiate the model for each innovation. We have shown that these sources are heterogeneous relative to the type of information, structure and format. We created a program that shows the possibility to get information about the type of innovation and its impact using the data and the

classification proposed by the FDA starting the health problem.

To create a pertinent tool for characterization of pharmaceutical innovation is necessary to use several sources of information. Each described sources in this paper is important, but insufficient to characterize the drug at a time T, hence the interest for creating computerized tool that will judge the contribution of the latter.

At present our team is working on modeling of pharmaceutical innovation to provide its full description. For further we plan to use multiple sources of information with purpose to judge the drug as objectively as possible via computerized tool of monitoring therapeutic, which will allow the practitioner to deliver quality medical care in short time.

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