The Major Role of Clinicians in the Discovery of Off-Label Drug Therapies

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Abstract:

Objective: To determine, through a review of the medical literature and author contact, the role of clinicians in the discovery of off label use of Food and Drug Administration approved prescription drugs

Data Sources: The literature was accessed through MEDLINE (1999–December 2003). Additional sources accessed included the U.S. Patent Office and Micromedex, Thompson Scientific and Healthcare, Inc.

Data Synthesis: A survey of new therapeutic uses for "New Molecular Entity" drugs approved in 1998 was conducted for the subsequent 5 years of commercial availability. During that time period, a total of 144 new applications were identified in a computerized search of the literature for the 29 new drugs approved in 1998. Literature and patent searches were conducted to identify the first report of each new application. Authors of the seminal articles were contacted via survey and telephone interview to determine whether they were in fact the originators of the new applications. If they were, examinations of article contents and author surveys were used to explore whether each new application was discovered via clinical practice that was independent of pharmaceutical company or university research ("field discovery") or whether the discovery was made by or with the involvement of pharmaceutical firm or university researchers ("central discovery").

Conclusions: Post-NDA discoveries of new, off-label uses for new drugs were present in 22 of the 29 drugs in our sample. We found that 59% (85/144) of the drug therapy innovations in our sample were discovered by practicing clinicians via field discovery. The major role of clinicians in the discovery of new, off-label drug therapies has not been previously documented or explored. We propose that this finding has important regulatory and health policy implications.

Introduction

In this paper, we explore how new, off-label applications for existing drugs are discovered. Clinicians' use of FDA-approved drugs in "off-label" applications is a very important part of medical practice. Data suggests that in some fields such as chemotherapy and prescriptions for children, off-label use of drugs accounts for as much as 85% of total prescriptions. (1) Indeed, for some diseases such as non-small cell lung cancer and cystic fibrosis, off-label uses of existing drugs are either the only drug therapies available or are therapies of choice. (2)

Research on innovation processes in other fields has documented that both product users (medical clinicians in the case of this study) and product manufacturers (pharmaceutical manufacturers in the case of this study) play important and distinct roles in the development of new products and new product applications. Users, it has been found, tend to develop products and applications involving functional novelty. In contrast, manufacturers tend to develop products and applications that address well-understood needs. (3, 4) Both users and manufacturers use similar scientific methods – theory and observation–based trials and learning. Both have levels of quality that range from high to low.

The importance of clinicians as innovators has not been explored in pharmacotherapy to our knowledge. Yet, as we will show, they are responsible for discovering over half of off-label applications for existing drugs. If clinicians are indeed important in this field of innovation, there are important regulatory and clinical implications. Our rationale is simple. Clinical practitioners carry out a much higher volume of formal and informal experiments than do manufacturers and universities. In the case of laboratories and formal clinical trials, the total volume of experiments going on in humans per new molecular entity probably only numbers in the hundreds or thousands of subject exposures for each new indication or use. In the case of clinical practice, the total volume of formal and informal experiments going on is equivalent to the number of prescriptions generated for the product. In essence, each use of the drug represents a new clinical experiment. Since, as we will explain, "volume matters" in the discovery of new off-label applications of existing drugs, it becomes very important to efficiently capture important findings generated during the course of clinical practice. Improvements to regulatory and information-collection practices must be made to achieve this. For example, many of the

potentially valuable observations arising in the course of clinical practice are currently lost because of inadequate means and incentives provided to clinicians to report anomalous and potentially interesting findings regarding novel off-label applications of drugs.

In this paper we will first review literature on the sources of innovation. Next, we will present our methods and then our findings. Finally, we will discuss the implications of our findings for drug discovery practice and policy, and offer suggestions for further research.

Literature review: the sources of innovation

Traditionally, it has been assumed by innovation process scholars, that product manufacturers would be the developers of all or most new products. After all, they seem to be the ones best positioned to reap related financial gains. However, empirical research during the past two decades has now shown that product users rather than manufacturers are the actual developers of many of the commercially important new products in fields studied to date. This stream of research has also shown that user-developed products tend to differ from manufacturer-developed products in an important way: they tend to be "functionally novel."

In the field of scientific instruments, for example, previous research has found that users tended to develop innovations that enabled the instruments to do qualitatively new types of things for the first time. (3) In contrast, manufacturers tended to develop innovations that enabled users to do the same things they had been doing, but to do them more conveniently or reliably (Table 1) For example, users were the first to modify electron microscopes to enable them to image and analyze magnetic domains at sub-microscopic dimensions. In contrast, manufacturers were the first to computerize electron microscope adjustments to improve ease of operation. Improvements in sensitivity, resolution, and accuracy fall somewhere in the middle, as the data show. These types of improvements can be driven by users seeking to do specific new things, or by manufacturers applying their technical expertise to improve the products along known general dimensions of merit, such as accuracy.

The source of this difference has been traced back to information asymmetries between users and manufacturers. Users tend to know more about their needs and about their contexts of use than do manufacturers. This information tends to be held locally and hence it is "sticky." Stickiness of information has previously been shown to alter the sources of innovation (3-5)

We argue that similar information asymmetries exist in the case of discovery of new applications for existing drugs. As a consequence, many of the potential applications of an approved drug cannot be predicted on the basis of data available to laboratory researchers. Instead, it seems reasonable that many will only be discovered via "learning by doing" during widespread testing and use in the field.

Our reasoning echoes that offered by Eric Raymond regarding "Linus' Law" in software debugging (6). In software, the discovery and repair of subtle code errors or "bugs" can be a very costly matter. (7) However, Raymond argued, the same task can be greatly reduced in cost and also made faster and more effective when it is opened up to a large community of software users. Under these conditions, he said, "Given a large enough beta tester and co-developer base, almost every problem will be characterized quickly and the fix obvious to someone. Or, less formally, 'given enough eyeballs, all bugs are shallow." (6) He then goes on to explain. "More users find more bugs because adding more users adds more ways of stressing the program…. Each [user] approaches the task of bug characterization with a slightly different perceptual set and analytical toolkit, a different angle on the problem….." So adding more beta-testers … increases the probability that someone's toolkit will be matched to the problem in such a way that the bug is shallow to that person." More simply put, the more sets of eyes devoted to a problem, the more likely it will be solved.

The analogy to the field discovery or distributed drug-testing process that we are exploring is, of course, that each clinician has a different set of patients to whom they prescribe a given drug during normal clinical practice. A patient(s) of some clinician will then serendipitously have the right combination of disease and other characteristics to manifest a valuable new application (or negative side effect) for that drug.

The FDA process of drug discovery and new drug approval, although costly and time consuming, is not as clinically robust as is use in the field. Depending on the drug class, as few as several hundred humans may have been exposed to the test drug during clinical trials. This paucity in numbers is made even more problematic by homogeneity of test subjects. Clinical trials rarely provide a full understanding of the true value of drugs as a result of these factors. Recent revelations of the risks associated with Vioxx after years of commercial use and Tysarbi after only several months of use highlight the inherent deficiencies in controlled clinical trials to

identify the risks and benefits of prescription drugs. Widespread use in the marketplace can in principle provide much better data.

Studies on other types of innovation and in a range of fields supports the probability that clinicians in regular medical practice will be the source of many and diverse innovations, such as innovations in the off-label use of drugs. Just as there is heterogeneity among patients, users of consumer and industrial products also are highly heterogeneous, often needing to apply a given type of product to different purposes under different conditions. As a result, many users innovate in the field by discovering new product uses or actually developing new products to better serve their own needs. Table 2 summarizes empirical research findings on this matter.

Available data from diverse fields supports the observation that a significant number of users develop, build or modify existing products in their fields of regular activity. If field discovery is a significant factor in the process of defining new drug indications, examples should be readily apparent. In our preliminary studies we did found this to be the case. Two examples of field discovery are provided below:

Botox Cosmetic (Botulinum Toxin A)

Botulinum Toxin A (Botox, Allergan, Inc) was originally approved in 1989 as an orphan drug for the treatment of strabismus, hemifacial spasms, and blepharospasm. The indications for use increased so that by 2002 botulinum toxin A was approved for the treatment of cervical dystonia in adults to reduce the abnormal head position and neck pain associated with cervical dystonia and the treatment of strabismus and blapharospasm associated with dystonia. In April 2002, the Food and Drug Administration approved Botox Cosmetic for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients age 65 years and older. (16) The financial impact of this change in FDA approval was substantial. According to the Allergan annual report, domestic and international sales of Botox rose from $239.5 Million in 2001 to $439.7 Million by year-end 2003. This 83% increase in sales volume for Botox Cosmetic was well in excess of the 20.9% increase in sales for the company's eye care products and 31.2% increase in sales of skin care products. (17)

The first reported use of botulinum toxin A for cosmetic purposes, was published by an ophthalmologist in 1992. (18) We contacted the first author and confirmed that the first reported use of botulinum toxin A for cosmetic purpose was the result of observations made in using the drug for its FDA approved indications. According to the author, the manufacturer did not play any role in the development of the clinical trial.

Propofol as an antipruritic

Propofol (Diprivan, was approved by the Food and Drug Administration for use as an in 1989. (19) It is used as a sedative hypnotic drug in the induction of anesthesia.

> Although it is now a mainstay in the early phases of anesthesia having replaced thiopenthal, the mechanism by which propofol works is not understood.
>
> The practice of anesthesia has evolved over the years with greater attention to post operative management, a key concern prior to surgery. To that end, many anesthesiologists will routinely provide for pain control using an epidural drug administration technique. Drugs such as narcotics like morphine or local anesthetics such as lidocaine, can be injected into this space or given by continuous infusion into the space. Many patients suffer from intense itching initially when morphine or another narcotic is administered this way. This intense itching can be very troublesome and is difficult to treat with the usual drugs.
>
> In 1992, anesthesiologists published the results of the first use of propofol for the relief of itching due to epidurally administered narcotics. (20) The first author was contacted to determine the events leading up to the use of propofol in this rather novel fashion. Indeed, on questioning, he noted that the initial observation was serendipitous. They noticed a patient complaint of intense itching, nausea and vomiting related to epidural morphine was treated with the coincident administration of subtherapeutic doses of propofol. This use of propofol, although not approved by the Food and Drug Administration is employed commonly in hospitals across the United States today.

Note that neither of these two discoveries emanated from a centralized or planned investigation. Both were made in the field by observant clinicians who then chose to report their findings.

Source of off-label applications – methods and findings

We propose that there are two distinct and simultaneous processes of innovation in pharmacotherapy. Some new applications for FDA-approved drugs will be identified in a centralized process by pharmaceutical firms in laboratory settings and in clinical trials; others will be discovered by the non-centralized observations and experimentation of clinicians in the field.

Methods

Each year a number of new drug applications for new chemical entities are approved by the Food and Drug Administration. In the years following first commercial introduction, a number of new, "off-label" applications for the new drugs are typically identified. In order to explore this phenomenon, we decided to review all new indications for a cohort of "new chemical entity" new drug applications that had been approved in 1998. We then analyzed the introduction of new clinical uses for these newly approved drugs over a period of five years –

from 1999 through 2003. This period of time was chosen to allow sufficient product maturity for widespread clinical use as well as time for reporting of findings in the literature. Because the definition of a new use may be considered arbitrary we chose to utilize a presumably objective abstracting subscription (Micromedex, Thompson Scientific and Healthcare, Inc.) to initially identify new published uses for the 29 new chemical entity drugs in our sample. A total of 144 new and effective uses for these new drugs were identified within Micromedex. New potential but ineffective uses were not included.

The discoverer of each of the 144 new and effective uses of the 29 drugs in our sample was determined by exploring articles, patents, and by surveys of apparent discoverers.

"Seminal" published articles (the first published report of a new use) were identified using a computerized database (OVID, Ovid Technologies) and contact information for first authors obtained.

Patents are also a form of publication used to report discoveries, and pharmaceutical manufacturers, especially, can be expected to often use this mode of discovery reporting. We therefore searched for all patents where the name of the disease and the name of the drug were present in the same patent. To do so, we searched the data base for any notation of the drug in question and the disease or disorder of interest. The decision to conduct a broad based search rather than searching only in the explicit claim was in recognition of the heterogeneous nature of patent language and specificity. For example, some patents identified included only very specific disorders within the claim whereas others included generalized terms such as inflammatory disorders. Foreign patents were not searched. Under the Patent Cooperation Treaty applicants filing a US patent have a temporary right to file specified foreign patents. This right to file expires one year after US filing. Given the size of the US market for pharmaceuticals as compared to the total worldwide market, we assumed that the US patent would be filed in advance of any other patent application.

After checking on both patent and journal publication data bases, we coded the discoverer of each new drug application based upon priority of discovery as follows:

(1) If there was no patent filed by a "central" developer prior to publication by a "field" author then it was field discovery.

(2) If there was a patent *and* a journal publication and the article was published after the patent filing date but before patent publication then it was parallel discovery by the authors of these two forms of publication. (If both authors were clinicians then it was coded as a field discovery. To be conservative in our findings, we coded all cases involving publications with "mixed" authorship in the central research category in our tallies.)

(3) If the article was published after publication of the patent, the patent filer was assumed to have priority of discovery.

To confirm and deepen our findings regarding field discovery of new applications for existing drugs, first authors of seminal publications were contacted using electronic mail and offered a standardized questionnaire. If the discovery was made in the field, data was collected on the circumstances of its discovery along with key characteristics of the clinician(s) making the discovery. A total of 102 email addresses were obtained and the authors were contacted. The initial response rate was deemed inadequate. Non-responders were recontacted. A total of 33 authors responded in total. Overall the response rate was 32%. This is consistent with the response rates previously seen in physician surveys and other industries.

Findings:

Sources of off-label application discovery

Recall that we define central discovery of new off-label drug applications to be those made in the course of an organized research discovery process involving a pharmaceutical manufacturer or other laboratory. We define field discovery of new off-label drug applications to be those identified by clinicians in the care of patients. Of the 144 new uses identified for the 1998 new drug approvals, 84/144 (50%) were initially categorized as field discovery based upon simple inspection of the authorship and contents of the seminal article. This simple method proved quite accurate: follow-up questionnaires addressed to first or identifiable authors confirmed this initial assessment in 100% of the cases. A total of 33 responses were obtained. 29 of the authors responding to our survey of clinicians were assumed to have been participants in a

field discovery. All confirmed this original assessment. Although 32 authors of research that was assumed to be of central origin were contacted, only four responded. Three of these respondents confirmed the original assessment. One author reported that the off-label application discovery attributed to him was in fact due to field discovery rather than central discovery. With this correction made, we determine that 59% of the new off-label drug applications in our sample were the result of field discovery and 41% were the result of central discovery.

Table 3 lists the drugs approved, the number of new uses noted in Micromedex and the source of discovery. There is considerable heterogeneity in the source of discovery of new uses with thalidomide having the highest number of uses identified in the field (89%) and sildenafil having the highest number of new uses identified in company initiated research (72%).

Characteristics of "field" indication discoverers and their methods

The term "Lead user" has been applied to a small group of product users who have been found to be responsible for a significant portion of innovation by users. Lead users have been identified in a wide array of activities. Lead users display two characteristics:

a) Lead Users face needs that will be general in the marketplace but face them months or years before the bulk of that market encounters them and,

b) Lead users are positioned to benefit significantly by obtaining a solution to their leading-edge needs.

We find, in agreement with studies of the sources of innovation in other fields, that our field discoverers were lead users. That is, they had a high need for the new indication to better serve the needs of their personal caseload. 72% of the respondents noted a high level of importance of the discovery to the care of their patients. The needs of these clinicians also foreshadowed general demand, as measured by the number of follow-on studies that developed their discovery further.

Characteristics of indications

The indications developed by field discoverers were judged to be clinically important by our survey respondents. The discoveries were rated as the first drug that can be used to treat the

indicated condition and/or as a significantly better way to treat this condition in 100% of cases. Further research is needed to establish the relative economic importance of field vs. manufacturer-discovered new drug indications. From simple inspection, it is clear that the indications developed by field discoverers were not in economic "blockbuster" categories at the time they were discovered. However, the categories, as one would expect in the case of innovations by lead users, have expanded since the time of discovery (as was the case, for example, with the field discovery of cosmetic uses for Botulinum toxin A).

As is shown in Table 4, 60% of field discoverers reported that they had made their discovery by applying their understanding of the pharmacology of the drug to the clinical problem. Serendipity, information from others and other factors appeared to have played lesser roles. The high proportion of discoveries made via a deep understanding of the method of action of a drug and of specific disease processes again fits with our expectations for innovation by lead users.

Discussion:

The finding that 59% of new drug uses arise from field discovery is, we think, of significant interest. Further research can refine this finding considerably. For example, why do only a few of the drugs among the 29 in our sample – notably thalidomide - experience most of the discovery of new off-label applications? On the basis of anecdotal evidence we speculate that this may be related to the pharmacology of the drug in question. Field discovery by clinicians may have a greater comparative advantage over centralized discovery by manufacturers when the precise mechanism of drug activity is less well understood and/or when the breadth of pharmacological action is greater. In these cases clinical "learning by doing" in the field is likely to identify many unexpected effects – both positive and negative.

Also, the present sample of newly-discovered off-label applications is quite limited in both size and scope. We examined 144 new applications for drugs newly approved in only one year – 1998. On the other hand, our findings are quite similar to those found in a range of other industries by other investigators. If further research does support our central finding that a significant subset of new indications for approved drugs are found by clinicians in the field, we think that there are significant economic and policy and regulatory implications.

From the economic perspective, it is well understood that the approval process for a New Drug Application is a time consuming and costly undertaking. Recent estimates suggest total development costs from bench to market exceed $800 Million and can take between 10 and 15 years to accomplish (21, 22). Field discovery of new applications for existing drugs, on the other hand, seems likely to be relatively rapid and inexpensive. First reports such as the seminal articles we identified in our study typically involve only a few clinical observations or a few patients in a clinical trial. Would it therefore not make both clinical and economic sense to study and improve and support the process by which clinicians discover and report new applications for existing drugs? Clearly, the present informal process has major inefficiencies in the collection and dissemination of findings: Seven additional similar discoveries were noted by the respondents to our survey indicated that they had found additional valuable applications for existing drugs that they had not reported in the literature.

An understanding that users are an important source of new innovations has enabled other industries to reduce product cycle times and improve product performance. (5) If much innovation and related improvement in patient care is derived from field discovery, the same advantages may be obtained by proper "reengineering" of the field discovery of new applications for existing drugs. One approach may be to provide for additional journal space for case reports and small series with prior and/or post publication peer review. This model is similar to an information collection and dissemination process modeled on "open source software" projects.

We should make it clear that we are not advocating unfettered experimentation on the part of clinicians. Mis-application of drug therapy has as large a potential to harm as it does to help. There is an obvious and appropriate concern with the wide spread dissemination of incorrect information in drug therapy. However, other disciplines have developed robust mechanisms that enable them to rapidly self-monitor and self-correct. For example, experiments in which incorrect information has been purposely inserted into open information compilations like the encyclopedia Wikipedia have shown very rapid discovery and removal of the faulty information by other users.

As an illustration of what might be done, at least one academic center has attempted to apply peer review to the process of field discovery as it applies to inpatient drug use. The Massachusetts General Hospital has for many years provided for institutional oversight and approval for innovative therapeutic and diagnostic interventions via the institutional review

board. The rationale for IRB involvement speaks to the presumed level of expertise and experience of the committee in evaluating the risks and benefits to the patient. It should be pointed out that there is no federal or state statutory requirement for IRB approval.

There are obvious limitations to this study and the conclusions drawn. The sample consisted of a single year of new drug approvals. The impact of field discovery may be different for different years or drugs approved. The response rates from clinicians were relatively low and there may have been a bias in the responses skewing the data toward field discovery. (23) Despite these inadequacies, the data suggest that field discovery is an important contributor to the identification of new uses for existing prescription drugs.

In conclusion, field discovery of new applications for existing drugs appears to be a significant component of the discovery process for FDA approved drug new use. Additional research should be conducted to determine the attributes of clinicians involved in field discovery and in the health policy and regulatory implications of this observation.

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Table 1: Source of innovations by nature of improvement effected

Type of improvement provided by innovation	Innovation developed by: %User	User	Mfr	Total
(1) New functional capability	82%	14	3	17
(2) Sensitivity, resolution or accuracy improvement	48%	11	12	23
(3) Convenience or reliability improvement	13%	3	21	24
			Total	64

Table reproduced from von Hippel (2005)
Data source: Riggs and von Hippel (1994)

Table 2: Proportion of respondents reporting developing and building or modifying products for own use in eight product areas

Product Type	% user-innovators
Industrial products	
Printed Circuit CAD Software (a)	24%
Pipe Hanger Hardware (b)	36%
Library Information Systems (c)	26%
Apache OS server software security features (d)	19%
Medical Surgery Equipment (e)	22%
Consumer products	
Outdoor Consumer Products (f)	10%
"Extreme" sporting equipment (g)	38%
Mountain biking equipment (h)	19%

Sources of Data: (7-15).

Table 3. FDA New Molecular Entity Approvals, 1998

Drug	New Clinical Indications (Post NDA)	Apparent Field Discovery
Tolcapone	1	1
Naratriptan	2	1
Montelukast	9	8
Lepirudin	8	3
Loteprednol	1	0
Tolterodine	0	0
Residronate	3	0
Sildenafil	21	6
Brinzolamide	0	0
Sacrosidase	1	1
Paricalcitol	0	0
Capecitabine	5	1
Tirofiban	3	1
Eptifibatide	2	0
Candesartan	7	1
Rifapentine	1	0
Rizatriptan	2	0
Thalidomide	36	32
Citalopram	18	14
Formiversen	0	0
Leflunomide	4	3
Efavirenz	1	0
Valrubicin	0	0
Sevelamer	0	0
Telmesartan	3	0
Recombinant Human Thyrotropin	1	0
Abacavir	0	0
Modafanil	8	7
Celecoxib	6	6

Table 4. Author Responses to Inquiry Concerning Factors leading to Off-Label Drug Use

Serendipity	Understanding of Pharmacology and Pathophysiology	Information derived from others	Other
11%	60%	9%	20%