COMMENTARY

MEDICAL INNOVATION, UNMET MEDICAL NEED, AND THE DRUG PIPELINE

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ABSTRACT

This paper outlines and illustrates the working of a theoretical approach from the social sciences for analyzing medical innovation, unmet medical need, and the drug pipeline. Using the social history of three drugs made from recombinant DNA (insulin, human growth hormone, and tissue-plasminogen activator) the paper shows how drugs can be both technically and organizationally efficient while the needs they satisfy can be created or identified. The paper posits that drugs that require more organizational efficiency tend to satisfy identified, rather then created needs.

***Key words**: Recombinant DNA, technical efficiency, organizational efficiency, anthropology*

Over the last three years a team of anthropologists at the University of Calgary have been seeking to understand the drug pipeline.[1,2] The pipeline, or pipe, is a metaphor from the pharmaceutical industry for the creation and refinement of drugs. The team's research has revealed that industry players conceive of the pipe as the source of novel technologies for satisfying unmet medical needs. From the vantage of the financial sectors and the pharmaceutical industry, disease is a market opportunity and the pipeline is a machine for creating new products to maximize opportunity.

This paper will outline the theoretical framework the Calgary researchers have adopted to make sense of the pipeline metaphor. As a source of novel technologies, the pipeline plays an important role in medical innovation and serves as a fount of new therapies to treat and manage disease. Drawing comparisons between 3 types of drug made from recombinant DNA – insulin, human growth hormone (HGH) and tissue-plasminogen activator (t-PA) - the paper will illustrate the variety of ways drugs can be innovative and satisfy needs.

The drug pipeline

The metaphor of the "drug pipeline" orients the behaviours and thoughts of actors in the financial and market sectors of the North American economy.[3] More than an analogy between different concepts and experiences, the drug pipeline encapsulates time, physical settings, and social groups. The generic term "drug entity" is used to refer to an object passing through the pipeline because the prospective medicines have indeterminate identities owing to the heterogeneous nature of the groups and values that make up the drug pipeline. The labels for and properties of a prospective medicine change depending upon when and where it is in the drug pipeline, as will become evident in the discussion below.

It takes about 13 years for a "drug entity" to make it through the pipeline.[4] The 13 years divide into a sequence of temporal stages and phases. Temporal stages are associated with certain physical settings so that as a drug entity moves through time it also moves through space. Physical settings include wet labs, dry labs, and clinics; sites where the drug entity undergoes

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testing to determine its relative safety and efficacy. Other important physical settings include boardrooms, financial markets, and government offices; sites where the drug entity secures financing, competes for share price with rivals, and gains regulatory approval for entering the market.

Movement through the pipeline transforms the drug entity. In each setting at each stage the drug entity has a certain identity, a definitive status. It starts in the wet labs as a biological material with "interesting properties" and becomes a novel compound (a base from which to make other compounds) or a candidate compound (a compound ready for testing in animal models).

Once passing the rigors of further laboratory testing, the candidate compound enters the clinic where it is subject to controlled tests to determine its safety and efficacy in human beings. At the end of clinical testing, the drug entity enters the regulatory arena as a candidate medicine. Given regulatory approval, the drug entity becomes a certified drug.

The physical settings of the pipe are associated with what researchers in the social studies of science have referred to as social worlds. A social world is inhabited by actors who share regular mutual responses to the context of their lives, and who form some kind of organization or network.[4] Each social world is also a cultural area (characterized by a certain set of beliefs, values, etc.), whose boundaries are set by the limits of effective communication.[5] In our pipeline study we have used the term domains to refer to the different social worlds (and their respective physical settings) that make up the drug pipeline.

The drug entities in the pipeline do not transform themselves; actors in physical settings perform routines that serve to alter the drug entities both physically and conceptually. Actors from the domain of science work in wet and dry labs while actors from the domains of medicine and industry respectively perform in clinics and boardrooms. The recurrent patterns of behavior found in the different domains are formalized procedures akin to the rites of passage anthropologists have recorded in traditional cultures.[6,7]

A rite of passage is a means of formally recognizing and precipitating alterations in a person's status, of marking a person's passage from one stage of existence to another (e.g. from child to adulthood, from living to deceased member of society). The social biography of an individual is made up of the changes in status that characterize the ideal lifecycle in the traditional society. Similarly, drug entities that pass through the pipeline have a social biography[8] made up of the "rites of transformation" (formal and routine behaviors including lab experiments, clinical trials, regulatory hearings, and patent application) that occur in the different physical settings and temporal stages.

As it transforms from state to state within the pipeline, the drug feeds back on the social relationships that produced it. In this sense, a drug has social agency because it can influence, alter, and reinforce patterns of personal behavior, and social relations and interaction.[9] A drug's social agency, the degree to which it reinforces, influences, or alters personal behaviours, social relations and interactions is related to the type of need the drug satisfies, and the type of therapeutic reform it spawns. The three rDNA drugs (synthetic insulin, t-PA, and HGH) illustrate the social agency of drugs, and shed light upon the connection between innovation and need. In order to assess the three drugs, the paper will first provide more detail on need and innovation as they pertain to drugs and the pipeline.

Medical need

In relation to medicine, the term need can refer among other things to gaps in knowledge, technical deficiency, resources for services, treatment and therapy, and measures for resisting disease. This paper is more interested in "unmet medical need" a concept that is current in the culture of the pharmaceutical industry.[10] In one sense, unmet medical needs can be identified in patterns of morbidity and mortality within a population. Typically the focus is a clinically identified sub-population (e.g., a group of people suffering from a recognized medical condition) for which there is a shortage or lack of effective therapies and treatments.

Contrary to identifying or discovering unmet medical needs in patterns of morbidity and mortality, there are cases where actors define, as unmet medical needs conditions or states of being that they have not traditionally conceived of in

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medical terms or as problems demanding medical solutions. Rather then being a reflection of the prevalence and incidence of morbidity and mortality in a population, created unmet medical needs reflect states of being that dominant values and belief frames cast as being undesirable and which one should seek to circumvent and resist. Created unmet medical needs are thus closely tied to the process of medicalisation – extending the authority and capacity of medicine to solve non-medical problems, or expanding definitions for what are medical problems.[11]

Unmet medical need bridges the target population of marketing efforts with the patient population of clinical care. It serves as a boundary object between the domains of medicine and industry. The term boundary object is current in social studies of science where researchers have used it to refer to concepts, ideas, or objects that bridge the interests, actions, and understandings of actors from different domains.[12,13,14] In general contexts, in situations involving actors from different domains the boundary object has a loose, general definition. When actors use it in local contexts, when they communicate with other members of their particular domain, the boundary object has a tight, specific meaning.

The flexibility of the concept "unmet medical need" captures both the market understanding of disease that characterizes the domain of industry and the clinical understanding of disease that characterizes the medical domain. The general meaning of the concept aids in allying the interests and understandings of medicine and industry. The goals of easing patient suffering and combating disease are overlain with the goals of investing capital and acquiring profit. At the same time, the narrow definition of the boundary object in local contexts assists in preserving differences between domains. In local contexts, actors can ignore the alternative meanings that are present in global contexts. Thus actors in the domain of medicine need not consider disease as a market opportunity when they talk or think about their lived experience of patient encounters or when they write prescriptions for their patients.

Innovation

Like other forms of technology, an analyst can assess a drug in terms of its technical efficiency and its organizational efficiency. The distinction between technical and organizational efficiency has to do with a difference between invention and innovation. Invention is the creation of a new technology while innovation refers to the emergence of the relationships and interactions necessary for applying or using the technology. Following this line of thought, the success of an invented technology is measured by the degree to which it fulfills a certain function – its relative technical efficiency when compared with other inventions that fulfill the same function. The organizational efficiency of technology refers to how well it can be incorporated into current patterns of relationship and interaction, or how its implementation leads to the adoption or establishment of new, more productive patterns of interaction or relationship.

The contrast between the organizational and technical efficiency of drugs is well illustrated by Ilana Lowy's ethnographic study of the interleukin-2 (IL-2) national level clinical trials run by the National Cancer Foundation in France during the early 1980s. Drawing from the work of the sociologist Andrew Abbott[15], Lowy[17] contends that in complex organizations, "Technical efficiency – the efficiency of isolated acts (in medicine, the development of efficient ways to prevent, detect, and cure disease) – is often subordinated to organizational efficiency – the ability to articulate tasks efficiently in a complex environment (in medicine, to ensure efficient collaboration among professionals)." (pp. 53)

In her study, Lowy illustrates that IL-2 failed to fulfill its therapeutic function, to cure cancer patients, and therefore the experimental trials and protocols lacked technical efficiency. Notwithstanding their technical flaws, the experimental trials were an organizational success. Making and using IL-2 demanded close interaction and collaboration between bench (immunology and the domain of science) and bedside (oncology and the domain of medicine). At the same time, the research marked an early instance of large-scale, well funded, centrally planned, multi-centre trials, efforts that connected actors and settings from the domains of industry, government, science, and medicine. The IL-2 trials were a logical extension of organizational innovation in clinical trials of chemotherapy beginning in the 1950s. This organizational innovation consists of establishing networks that

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connect experts and sites, settings and actors in the drug pipeline, and thereby demarcate new arenas for medical activity.

The adoption of new drugs can be a matter of organizational innovation, technical innovation, or a mixture of the two. Thus, IL-2 had excellent potential for chemotherapy because of its organizational efficiency rather then its technical efficiency. In contrast, the organizational efficiency of antibiotics such as penicillin and streptomycin was far less important in their adoption then the fact that they were supremely efficient in a technical sense. In the following sections, this paper will show that rDNA drugs mark instances where adoption takes place on the basis of a varied mixture of technical and organizational efficiency.

rDNA drugs

In the early 1970s, a cadre of molecular biologists succeeded in creating recombinant DNA.[17,18,19,20,21] The new technology offered a potential means of developing new drugs and a method for mass-producing drugs. Advocates for the experimentation and technology typically referred to rDNA as a means of creating drugs like insulin and human growth hormone for needy patients. Insulin and human growth hormone were two of the first proteins to be synthesized using rDNA. They entered the marketplace in the early 1980s, followed by t-PA in 1987.

Recombinant insulin and human growth hormone offered alternatives to animal and cadaver derived drugs that were already on the market and respectively entrenched within clinical practice for treating diabetes and pituitary dwarfism. The biotechnology company responsible for first developing rDNA versions of insulin and HGH, Genentech, was partnered with two large pharmaceutical companies, Eli Lilly and Novo Nordisk.[22,23] Partnership gave Genentech cash flow, and the opportunity to refine technologies with the aim of synthesizing other human proteins to treat other diseases. Pharmaceutical companies benefited from access to the technology and new form of the drugs, and from removal of Genentech as a potential competitor in the insulin and HGH markets. Unlike its role in the manufacture of insulin and HGH, Genentech was intent on using rDNA technology to discover and develop its own new drugs, and the clot dissolving t-PA was the realization of this goal.

Synthetic insulin and recombinant HGH respectively targeted insulin-dependent diabetics and children suffering from pituitary dwarfism, while t-PA was designed as an intervention for individuals suffering acute ischemic events (e.g., MI, stroke, PAD, blood clots in lungs). Synthetic insulin satisfied an unmet medical need reflected in a select group of insulin-dependent diabetics who poorly tolerated animal insulin. The drug also offered an alternative to animal insulin in that unlike the animal derived drug it did not pose the threat of transmitting disease (e.g., bovine spongiform encephalitis) to humans, and ultimately it could be manufactured at a lower cost in time and money then could animal insulin. The initial target population for the drug was small (users who did not well tolerate the animal insulin) but the technical efficiency of rDNA technology soon led to the capture of a much larger target population (all insulin-dependent diabetics).

Like synthetic insulin, recombinant HGH met a medical need reflected in a recognized patient population (pituitary dwarfs). The market potential represented by this medical need was much smaller then the market potential of insulin. In the case of recombinant HGH, once companies gained approval and began production, supply exceeded clinical demand, and companies and medical researchers began searching for other conditions for which the drug was suited to treat. In 1996, subsequent to approval for treating dwarfism, the FDA approved the drug for treating adults who are deficient in insulin-like growth factor-1 (IGF-1). In 2003 the FDA approved use of HGH to treat children of idiopathic short stature.[24] The latter case exemplifies how unmet medical need verges on being created rather then discovered, and on how new technologies and products can lead to medicalisation. In addition to being used to treat shortness as a medical condition, HGH finds use as a treatment for the "symptoms of aging"[25], has a marked potential for use in treating obesity[26], and finds a ready market among individuals intent on "enhancing" their bodies (e.g., body builders, athletes).[27]

Recombinant t-PA satisfied an unmet medical need reflected in a population of patients

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suffering acute ischemic stroke; and it also had the capacity to treat other acute vascular events such as myocardial infarction (MI). Unlike synthetic insulin and HGH, t-PA did not have to challenge previously established therapies, though it did have to compete with other new therapies such as streptokinase (a drug that was initially felt to be superior in treating MI but had yet to show efficacy for treating stroke).[28] Synthetic HGH and insulin could be administered in the same fashion as their cadaver and animal derived predecessors. In order for t-PA to be technically efficient it had to be delivered as a thrombolytic within a certain window of time (within 6 hours after symptom onset in the case of heart attack and three hours in the case of ischemic stroke).

To meet these time constraints the various actors involved in delivering care to patients need to work in teams. In the case of stroke, this has taken the form of organizational innovation in linkages between EMS personnel, emergency room staff, radiologists, and neurologists, and the formation of dedicated stroke care units.[29] Oddly enough, medical experts recognize that this organizational innovation has a positive impact on health outcomes[30] and yet they openly debate whether t-PA is technically efficient – whether the drug fulfills its intended function (to dissolve blood clots in cerebral arteries without perilously increasing the risk of intracranial hemorrhage).[31]

The technical efficiency of synthetic insulin has also generated considerable debate.[32] A segment of the population of insulin-dependent diabetics does not tolerate the shift from animal based insulin to synthetic insulin, giving rise to increased hypoglycemic unawareness.[33] In addition, differences between the biochemical structures of the animal and synthetic-based drugs require that patients shifting to the synthetic version alter the times and quantities of drug they inject. The technical efficiency of the drug is not absolute, while the therapeutic reform it demands is relatively slight.

The technical efficiency of HGH is undeniable, though there is some concern that the drug poses health risks. The degree of organizational innovation HGH spawns in medicine is negligible in terms of practice. Notwithstanding, the drug has motivated alterations in diagnostic criteria, in what medical practitioners deem to be medical problems. The plethora of spam and websites devoted to the sale of HGH suggest major organizational innovation outside the domain of medicine.[34] Thus a large market exists for the drug but companies and medical researchers have yet to define the respective population of customers in clinical terms (as populations or sub-populations suffering from disease).

TABLE 1 rDNA drugs and their relative efficiency.

	Organisational efficiency	**Technical efficiency**
HGH	+	+++
Insulin	++	++
t-PA	+++	+

TABLE 2 rDNA drugs and created or identified unmet medical need.

	Created need	**Identified need**
HGH	+++	+
Insulin	++	++
t-PA	+	+++

Table 1 compares the three rDNA drugs in terms of their relative organizational and technical efficiency while Table 2 shows where the three drugs lie on the continuum of created and identified unmet medical need. The drug (HGH) that has the least amount of organizational efficiency and the greatest amount of technical efficiency is used to satisfy the greatest degree of created needs – needs that are not traditionally conceived of as problems to be solved via medical means. In contrast, the drug (t-PA) with the greatest amount of organizational efficiency and the least amount of technical efficiency is used to satisfy the greatest degree of identified need – need that is traditionally conceived of as a medical problem. Synthetic insulin falls roughly in the middle of both the continuum of organizational

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and technical efficiency, and the continuum of identified and created unmet medical need, between the extreme cases of HGH and t-PA.

CONCLUSIONS

The three rDNA drugs illustrate variation in the ontological relationship between technology and need. In the case of HGH, the technology is used to satisfy a need for which it was not initially intended, and in this sense, the invention precedes or is ontologically prior to the need. The innovation of HGH lies in the conceptualization of non-medical problems ("normal states of being") as medical problems – a first step in the creation of unmet medical needs. In the case of insulin, the need precedes the technology yet in quantitative terms the need is relatively slight (the small percentage of patients who do not well tolerate animal insulin). The innovation of insulin stems from the production method, and the patentability of both the product and the methods for making the product. Finally, the case of t-PA shows how unmet medical need precedes technology and motivates both invention (the creation of a new technology to solve a problem) and innovation (the adoption of new patterns of social interaction and relations).

Mass production of drugs using rDNA has clinical consequence. Prior to rDNA, industry was pressed to meet clinical demand. Armed with rDNA production methods, industry is able to outstrip demand. In this sense, the adoption of rDNA drugs is a supply-side phenomena. The medicalisation of shortness, aging, and obesity, and the emphasis on body enhancement associated with HGH illustrates technology preceding need, and how forces outside the domain of medicine shape clinical practice (both actions and knowledge).

The rDNA drugs are a product of relationships and interactions between actors form the various domains of the drug pipeline. Science, in the guise of molecular biology, created rDNA and offered industry a new means of mass-producing drugs. Initial linkages between industry, academia, and government naturally extended to envelope medicine, the ultimate determiner of use. Ties between the different domains are fostered by the use of boundary objects such as "unmet medical need". The efficiency of the drugs can be measured in both technical and organizational terms, and it appears that the greater the organizational efficiency associated with a drug the more clearly or strongly identified (rather then created) the unmet medical need the drug satisfies.

Acknowledgements

Research Funded by GE^{3}LS and GENOME PRAIRIE

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