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The role of users in innovation in the pharmaceutical industry

Ruud E.H.M. Smits and Wouter P.C. Boon

Department of Innovation Studies, Copernicus Institute for Sustainable Development and Innovation, Faculty of Geo-sciences, Utrecht University, Heidelberglaan 2, 3584 CS Utrecht, The Netherlands

Traditionally, innovation in the pharmaceutical industry is organised according to the linear model. Over the past two decades this model lost its meaning as a result of rising costs, increased competition, new scientific developments and better-informed, more demanding users. The linear model is not well equipped to involve these new actors and to include their feedback. Starting from a systemic approach, the involvement of actors in pharmaceutical innovation processes, more in particular users, is put central. It is discussed and illustrated with three cases why a systemic model may be more effective to cope with present developments and why users should be involved. To wind up, conclusions are drawn regarding the implications of a systemic approach for policymakers, researchers and firms.

Introduction

Traditionally, innovation in the pharmaceutical industry is very much organised from the perspective of the linear model, that is, basic science findings are translated into clinical compounds that are subsequently marketed as drugs. The 'drug research and development pipeline' model of pharmaceutical companies is a clear demonstration of this. For many years, this model have been useful to manage R&D-driven pharmaceutical innovation processes. Firms, universities and specialised suppliers were the most important actors and they fitted rather well in this linear model. Over the past two decades, the linear model concept increasingly lost its meaning. Rising costs, increased competition, new scientific and technological developments, and better-informed, more demanding users who pressurize for higher added-value products, and more niche market products changed the context in which pharmaceutical innovations take place. The linear model is not well suited to involve these new actors in innovation processes. Dependence on this model might result in risks of provoking resistance and making insufficient use of the creative potential of these actors. This trend is not exclusive for the pharmaceutical sector. Many other sectors witness the same development and some of them – for example, in ICT, consumer electronics, food – already anticipated on it.

This paper focuses on the involvement of important, but often-overlooked actors in pharmaceutical innovation processes: users, such as patient advocacy groups, medical professional organisations and insurance companies. Major questions we will address are:

Why is it important to involve these actors and how can this be done in an effective and efficient way?

The outline of this paper is as follows. First, we will explain how we perceive innovation and why a more systemic, open model is better able to cope with problems in pharmaceutical innovation processes. In this context the implications for the R&D pipeline model, which neglects the systemic character of innovation processes, and is used by the majority of pharmaceutical firms, will be discussed. Hereafter we focus on one particular type of actors, the users. We will discuss the reasons why they should be involved and illustrate the diversity of user–producer interactions (UPIs). Using three cases we will demonstrate this variety, at the same time show that carefully designed UPIs are possible and how firms and other actors involved may benefit from them. In the last section, we will draw conclusions regarding the implications of a more systemic approach for policymakers, researchers and firms.

Corresponding author: Smits, Ruud E.H.M. (r.smits@geo.uu.nl)

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A different view on innovation processes: from linear to systemic

Innovation is a complex process. Despite this, for many years a rather simplistic model of innovation processes dominated the scene. This model became known as the linear model of innovation and was well characterised by the slogan of the 1934 World Expo in Chicago: 'Science finds, Industry applies, Man conforms'. Failures on the market and new insights from innovation theory deepened insights into innovation processes. Scholars such as Nelson and Winter [1], Rip [2], Bijker *et al*. [3], Etzkowitz and Leydesdorff [4] and Ziman [5] emphasised that science and technology coevolve with social and economic pressures, which is – almost by definition – not a deterministic process. Furthermore, other authors [6–8] point out the numerous and frequent interactions and feedback processes between users and producers in innovation processes. Today, innovation is no longer seen as an autonomous process dominated by scientists and industrialists, but as part of a 'game' in which a heterogeneous set of actors is involved [9,10]. In this paper we define innovation as 'from an economic and/or societal point of view successful combination of hardware, software and orgware' [15]. 'Orgware' refers to the context in which innovations settle. For instance, drug development will not lead to innovations if they are not reimbursed by insurers or accepted by users. Most pharmaceutical companies and industry trade groups regard reimbursement as part of a successful innovation process. The basic idea behind this definition is that we only then may speak of an innovation as it has demonstrated its success on the market.

A major starting point from innovation studies concerns the observation that organisations are not innovating in isolation but in the context of a system [11–13]. As a consequence their performance is dependent on the quality of that system, particularly on the quality of the subsystems (R&D, users, intermediary and supportive infrastructure), and on the mutual tuning of these subsystems [14,15]. Another consequence of the systems approach is that more heterogeneous actors, often at different levels and operating in various arenas, are involved in (the management of) innovation processes [16]. This far more interactive model resembles the open innovation concept [17] in which the sources of innovation are widely distributed and learning through collaboration (R&D outsourcing, takeovers, alliances, etc.) is crucial. In a way this concept of 'open innovation' is not new. Innovation always took place in a multi-actor context. However, the R&D-driven pharmaceutical system till recently only included a limited set of rather homogeneous (knowledge, interests) actors, that is, firms, universities and specialised suppliers. As already stated, over the past decades many new actors want to be, and are getting involved in this system. Also in the pharmaceutical and health industry the open innovation model is discussed, for example, in the context of the WHO, and public–private partnerships for rare diseases [18,19]. Innovation systems and open innovation literature clearly shows the importance of including a diverse set of actors while studying technological innovations, ranging from the 'usual suspects' such as the government, universities and companies, to unaccustomed ones like intermediary organisations and users. In the following section, we dive further into innovation processes in the pharmaceutical sector, we discuss why the linear model is coming under pressure, and we indicate a higher involvement of non-traditional actors in pharmaceutical innovation processes.

Innovation in pharmaceutical industries: the linear model under pressure

During the 1980s and 1990s, many authors [20] began to claim that the linear layout of the drug research and development pipeline could be enhanced by feedback and feedforward steps, and even cyclic interactions within the companies and with basic and clinical research partners. In some stages of the model information is produced, or more passively, has come to light, that has a bearing on research and development of new medicines in other stages. These interactions occur between different stages in which different stakeholders, such as small high-tech companies and university hospitals are involved. Examples include interactions between:

- *University and companies within the pre-project stage* [21]: industrial research reveals working mechanisms of diseases or drug targets. University researchers use these findings to delve into the underlying working mechanisms. These results can, in turn, be used by the industry.
- *The preclinical and clinical development stage*: research results of clinical trials can be used as starting points for new preclinical, and even basic research. Also by investigating the viability of targets early on through the use of animal or organ models, *in silico* ADME models and computational drug–target interaction modelling [20].
- *Within the clinical trial phases themselves* [22]: in what is called 'adaptive trials' dosages, patient pool sizes, etc. change under the influence of incoming data. Also in traditional clinical trials interactions occur revealing unexpected fields of indication and even subsequent information on underlying working mechanisms of drugs or diseases. A well-known example is the case of sildenafil (Viagra), a drug that was first created for angina, but appeared to have the side effect of strong and persistent erections. Subsequently, once again traditional clinical trials proved this and after market introduction this drug appeared to be a success. It is now also marketed for pulmonary hypertension patients as Revatio [23].
- *The commercialisation and development stage*: in Phase IV, post-marketing research is done. This means that a drug is approved and used on the market while pharmaceutical companies together with the medical profession conduct 'in-life testing' and monitor the impacts in terms of efficacy and especially safety [24]. If drawbacks occur on these indicators, for example, if adverse side effects arise, then the company or regulatory body will take appropriate action. This is all the more poignant in classes of people that were not included in clinical trials (children, women, the elderly), in fast-track approvals, and in the case of orphan drugs (where only small groups of people could have been tested). This monitoring can yield unexpected fields of indication as well. An example is thalidomide: at first it was intended as a sedative for pregnant women, but it turned out to cause skeletal birth defects. Later a physician successfully applied it as a last resort to treat an inflammatory condition called erythema nodosum laprosum (ENL). Recently, pharmaceutical companies look at new uses of existing drugs in a more systematic way under the term of 'drug repositioning' [25].

These illustrations show that interactions can be beneficial for the success rates and effectiveness of pharmaceutical innovation processes. Nevertheless, interactions have hardly been structurally embedded in most organisations. Therefore, some authors [20] advocate the solidification of these interactions between different phases of the drug R&D pipeline by pursuing a strategy that aims at faster feedback loops, for example, by forming small, decentralised task groups that are able to accelerate internal decision-making.

The major conclusion of the foregoing is that in various phases of the innovation process a large role is, or could be played by actors external to the pharmaceutical company and their close companions such as universities and specialised suppliers. Hara [26] advanced this point as well: after claiming that the linear model cannot be upheld even in the case of the pharmaceutical industry with its pipeline, he emphasised that heterogeneous, interactive networking is important in the drug-shaping process. A diverse set of actors can influence the level of success of an innovation (process) and the pharmaceutical industry should therefore build communicative channels with these external parties through which learning and proper evaluating is possible.

Obvious examples of such influencing are situated in the later stages of the pipeline, such as the involvement of medical specialists in clinical trials, discussions that are held with national reimbursement agencies, etc. Anxieties over ethical, legal and social impacts of medical and pharmaceutical R&D often also cause external parties to react, sometimes in a rather unfavourable way. Examples include animal rights and pro-life activists, but also governments in developing countries that do not subscribe to international patent law [27]. A simple denial of these institutions does not work and can even turn out to be counterproductive. It is often better to involve these stakeholders in the innovation processes and incorporate their viewpoints. However, given the already mentioned heterogeneous character of this set of actors, involving them in an effective and efficient way in the management of innovation processes is not easy. The next sections focus on one important actor that till now has often been neglected: the user. First the reasons to involve users are discussed further. Then, three cases present types of UPIs, the results they may produce and their implications for actors involved.

Five reasons to involve users

In recent years scholars from many disciplines have emphasised the role of users in innovation processes. At the same time, these scholars ascribe different – however not mutually exclusive – roles to users in technological change and/or innovation processes.

Users can play a role as more or less active consumers, as modifiers, domesticators, designers and, in fact, also as opponents of technological innovation. Von Hippel [28] showed that in many sectors, such as the medical equipment industry, users are by far the most important 'sources of innovation'. The more economic approaches mainly are associated with concepts such as user–producer relationships, the role of lead users in innovation processes and the idea of demanding users, as formulated, for instance, by Porter [29]. Furthermore, the position of different types of users during the development and diffusion of a particular application or product can vary considerably. In addition to these more economics-inspired perspectives, recent decades have seen the rise of various other views on the role of users in technological innovation. Recently, Oudshoorn and Pinch published an overview [30] of the main non-economic approaches to users. All these different concepts have in common that they recognise that users can play an important role in innovation processes, and, more than that, users can actually be a source of innovation.

From the literature at least five reasons to involve users in innovation processes are discerned [31]:

First, the market does not adequately meet all societal problems: there is a market failure. For example, companies are not keen to develop drugs for rare disorders or neglected diseases (conditions prevalent in developing countries) because the related markets do not provide enough economic incentives. Therefore, users can try to put appropriate measures for stimulating R&D for these diseases on the agenda of governmental agencies and companies. In relation to this, a WHO project called 'Priority medicines for Europe and the world' [32] aimed to construct, in consultation with scientists, the industry and patient groups, a list of diseases that should be the cornerstones of public investment in drug R&D.

Second, also in market-oriented sectors it is beneficial for companies to keep track of the wishes of users because knowledge on these will improve the adoption rate of their products. Medical professional organisations and authoritative medical specialists can play the role of so-called 'lead users' whom other physicians look at while deciding whether to adopt a therapy or diagnostic tool [26,33]. To go one step further, producers can enhance their products by mobilising the creative potential of users by making use of their 'experiential knowledge'. An example is patients who have ideas on drug toxicology [34].

Third, public and patient involvement can also enhance the (cost)effectiveness of companies' R&D processes. Often patient groups stimulate research through charity funds or by stimulating the government to invest money. Disease advocacy groups largely attributed to convince people to back the California $3 billion stem cell research initiative that was approved in 2004 [35]. For some patient groups, such as the UK Alzheimer's Society and the French Muscular Dystrophy Association, these financial contributions are linked to steering the direction of the R&D agenda [36]. Moreover, some patient groups try to influence the set-up and assist in the organisation of clinical trials; notably the HIV/AIDS [37] and breast cancer trials [38] in the US. Also other organisations such as the Cochrane Collaboration (http://www.cochrane.org) could be mentioned in this respect. It can even be the case that patient groups take a 'producer turn'. Sharon and Patrick Terry, parents of two children with PXE, stimulated research, own the resulting patents and exploit them through a company [39]. Increasing the (cost)effectiveness of innovation processes is all the more needed in the case of rare and neglected diseases, because R&D costs should be transferred to a small or low-income group of patients. There are indications that user involvement for these kinds of diseases is stronger [40].

Fourth, the introduction of new technologies might have considerable repercussions on society. To make sure that this does not result in societal resistance, different stakeholders, such as animal rights groups and pro-life organisations, can and should have their demands heard. Moreover, it is important for technology acceptance, such as biotechnology, to have 'champions' among public groups who stress its benefits [41]. In the medical sector patient advocacy and medical professional groups often claim this role.

The *last* reason concerns the democratic value of innovation processes. Not only is much of the basic research publicly financed but also innovation strongly influences people's lives. Therefore they have a moral right to influence decision-making on these innovation processes.

Policy measures and business strategies to involve users

UPI is a heterogeneous concept serving many different goals. Variety is caused by different goals (e.g. collecting new ideas, developing a shared vision, improving the introduction onto the market), differences in innovation trajectories (e.g. related to the phase of development) and differences regarding the demand side (e.g. niche or mass market). These differences ask for a careful, tailor-made design of UPIs in which each actor has its own role to play. This heterogeneity makes it difficult to design successful UPIs. This section seeks to illustrate the variety of user involvement in pharmaceutical innovation processes, while also give pointers to how to design UPI. We do not have the pretension to be exhaustive and therefore focus on three important actors: public policymakers, firms and users themselves. Their roles will be discussed and further illustrated with three cases. From these cases it also will become clear that, although one actor dominates the innovation process, users are always involved.

For *policymakers*, these systemic developments have important implications. Although the more traditional innovation policies, apart from their mission orientation, were basically legitimised by the concept of market failure, modern innovation policies also have to deal with system imperfections [10,42]. This implies a considerable broadening of the policy domain, better opportunities for tuning and joint action, and a shift from top-down to more horizontal (systemic) policies. In doing so, policymakers should realise that they have at least two different roles to play in innovation: the government is responsible for a high-quality innovation system, and the government is a major problem-owner (public health, safety). As such it is an important actor in pharmaceutical innovation processes. Hereto government should develop 'systemic instruments' that are able to tackle relevant subsystems of innovation systems in a coherent, orchestrated way [10].

Examples are instruments that stimulate the public technology procurement, for example, in the case of vaccines for SARS or neglected diseases [43], the management of interfaces (e.g. between firms and users); and facilitating the debate and the necessary input for such a debate through technology assessment studies. The latter proved to be essential in the context of ethically contested technologies, such as genetically modified food, gene therapy and stem cell therapy [44–46]. Although technology assessments are not new, research has been done in recent years to improve the methodological toolbox [47–50]. In this context, governments also should play an initiating role in the organisation of debates leading to visions of the future of sectors in the economy. These visions can, as examples from Japan [51], the UK [52], Finland [53] and Taiwan show, play an important role in programming of research, initiating necessary changes in the innovation systems, and make clear how the different actors can contribute to realise the developed vision. By doing this, the government helps to create an environment in which firms find better conditions to start and manage innovation trajectories. The 'Priority medicines' project is an example of governments acquiring this role.

Case: WHO 'Priority medicines' project

The Dutch health ministry initiated a project during the Dutch presidency of the European Union in 2004 called the 'Priority medicines for the citizens of Europe and the world'. The World Health Organisation was asked to compile a list of areas, which should be given priority when propagating medicines R&D from the context of the society as a whole. Several methods, amongst others a stakeholder consultation, resulted in a list consisting of disease areas such as cancer, diabetes and malaria, and target groups such as children, the elderly and patients with rare diseases. The project influenced the formation of the Innovative Medicines Initiative (€2 billion as part of EU 7th Framework Programme), the WHO as illustrated by the OECD Noordwijk Medicines Agenda conference (2007), and discussions in other countries and charitable funds, such as the Dutch health ministry financing the 'Top Institute Pharma'. Nevertheless, questions could be raised about the real steering influence governments and users might have on the agendas of researchers and companies. The more prevalent diseases that are part of the priority list will be taken up regardless of government intervention because of their economic potential, whereas neglected and rare diseases call for more persuasive measures.

Based on explorative interviews held with involved experts.

Second, *firms* also have an important role to play. In a way the whole problem focuses on building better interfaces between the production of new knowledge and technology and the use thereof. In tackling this problem firms increasingly move down the value chain, loosening their exclusive grip on research, and trying to build bridges between research, production and the market. They can do this by embracing new business models, such as the shift of relying on internal R&D efforts to maintaining loose contacts with small high-tech companies outside the firm (the so-called 'open innovation model'). The dependence on small high-tech companies has been going on for some time now [54], but only recently is this accompanied by decreasing internal R&D investments, as developments at Pfizer, AstraZeneca, Bristol-Meyers and Johnson & Johnson show.[1] Another way for pharmaceutical companies to learn from other parties is by intensifying contacts with patients, medical professionals, etc. to get feedback on their products. However, this should be cautiously organised as direct involvement of companies with, for example, patient advocacy groups has come under close scrutiny [55]. The case of Philips Applied Technologies clearly demonstrates the need and the benefits of shifting down the value chain and building (better) interfaces with users. Philips has recently made the decision to focus more on medical technology, more in particularly on diagnostic tools based on molecular biology. The company has no direct links with pharmaceutical products. Nevertheless, the increasing linkages between diagnostics and therapeutics (e.g. in the pharmacogenomics context) and the way Philips is organising its innovation processes makes it an interesting case.

[1] Although we should add here that in most of these cases other motives could also be found, for example, the loss of patent protection on certain blockbuster drugs resulting in less (prognosticated) revenues.

Case: Philips Applied Technologies and Philips Medical Systems

Philips is one of the many examples of firms that try to improve its links with users in an early phase of the innovation process. Till recently Philips put an emphasis on research and it could be characterised as a real 'engineering firm'. Over the past decade however, Philips has clearly moved down the value chain. In this period the research budget of Philips decreased by 50% and more innovation-related downstream activities were reinforced. An important example is Philips Applied Technologies. This department (1200 people, located in Shanghai, Eindhoven, Leuven and Redhill) develops and maintains a number of strategic technologies (as for instance wireless) of which Philips thinks that they have a high innovative potential without knowing precisely how this would look like on the market. By developing strategic alliances with big market parties Philips tries to find out interesting applications of its technologies in the markets of these parties. When both parties see an opportunity, this potential innovation is developed and when it looks promising it is shifted to the relevant Philips division. By this, Philips developed an extra link between its technology development and the market, and succeeds in including the wishes and needs of consumers in a rather early phase of its innovation processes. The same applies to Philips Medical Systems, which is currently working on medical technology for disease prevention making use of molecular medicine and diagnostics.

Based on Van den Elst et al. [56].

Last, *users* also need to make an effort in bridging gaps between themselves and other parties. In many countries, patient groups started as organisations concentrating on mutual help and information provision. Only since the 1980s (in the US) and the 1990s (in European) have these groups shifted their attention to patient advocacy. In this capacity, they tried to influence corporate as well as governmental decisions by emphasising their interests. Also on ethical, legal and social aspects they tried to include the patients' voice and so-called experiential knowledge into the debates. Successful strategies for patient groups include forming alliances and coalitions with other actors, most notably medical professional groups, and approaching the media; or emphasising their 'independent' and 'neutral' stance in matters and in this way being a viable partner to discuss management or policy issues [57].

Patient organisations have the potential of influencing every stage of the drug innovation process and have proven to do so over the past years.[2] What should be emphasised is the fact that the involvement of users does not necessarily influence the ultimate outcome of the innovation process, for example, in terms of choices that are made between options, although examples can be found in rare muscular diseases. Another example is the explicit agreement patient representatives struck with regulatory authorities that they have no objections to the introduction of Tysabri (natalizumab), a monoclonal antibody used for treating multiple sclerosis patients, despite increased risks of a relatively rare adverse drug reaction (progressive multifocal leukencephalopathy). But there are other kinds of venues for influencing:

- Increasing effectiveness and speed of the innovation process by funding [58], and steering the agenda of [36] and even conducting [39] biomedical research. But also by involvement in clinical trials by mobilising and educating medical professionals and patients [59], funding and co-defining protocols [37,38].
- Proposing creative solutions or articulating (unforeseen) demands: patient groups advocate ideas, wishes and needs that were not apparent to other actors [60]. Moreover, patient groups also make sure that the patient perspective is not underexposed during ethical debates.
- Creating and improving the boundary conditions of innovation processes: patient groups can be partners in advocating regulatory change [61] or the need for basic and clinical research funding [35]. The implementation phase is part of the innovation process and therefore patient organisations are influential by advocating compassionate use or reimbursement.

The next case box focuses on the latter way of influencing the innovation process, for example, the attempt of patient groups to solve problems of expensive drug reimbursement.

Case: reimbursement of Herceptin

A recent case revolves around the reimbursement of the expensive breast cancer drug trastuzumab (Herceptin). In the Netherlands the reimbursement of expensive drugs that are used in hospitals has been an issue for ten years since the introduction of taxanes. The debate took a new turn when the first results of a large clinical trial on the efficacy of Herceptin in early-onset breast cancer were presented in 2005. The Dutch society of oncologists decided to include the drug in their guidelines of good practice. However, Herceptin had not been approved for early-onset treatment by then, so the drug was not reimbursed for this indication. This presented a problem to hospitals: their medical specialists needed to adhere to the good medical practice guidelines, whereas insurance companies were not compelled to finance these treatments. Moreover, for expensive intramural drugs in general up to 75% of the costs were backed by insurance companies, leaving hospitals with a concentration of expensive drug users with a problem. The looming problem of patients not getting optimal treatment induced the Dutch Breast Cancer Association to organise support for ensuring Herceptin treatment and reimbursement, and a more sustainable solution regarding reimbursing expensive intramural drugs. They did this by enlisting a heterogeneous group of organisations ranging from hospital representatives to the media to pressure the health ministry to come up with an acceptable solution. They used arguments like solidarity (the right to be treated), good medical practice, 'postcode lottery' treatment (regional differences in treatment, which they showed in a report) and the expectation of a future increase in expensive biotechnology products. In the UK a similar discussion was going on, also featuring looming regional differences in Herceptin treatment and reimbursement of early-onset use. Patient groups like fighting for Herceptin and individual patients in the media attracted a lot of attention. Critics claim that the National Institute for Health and Clinical Excellence (NICE) was pressured into admitting Herceptin to be reimbursed far too quickly [62]. These debates around reimbursement fit in with a general movement in which patient advocacy groups try to shift the balance between public and private payment [63].

Based on Boon and Kirejczyk (forthcoming).

[2] Despite this, we are also aware of more opportunistic ways for patient groups to influence innovation processes and policies. In this context the relationships between patient groups and the pharmaceutical industry are mentioned. See for an interesting discussions about this: Mintzes and Kent [64].

Conclusion

Changes in science and technology as well as in the context in which pharmaceutical firms have to manage their innovation processes will lead pharmaceutical companies to replace their linear perspective by a systemic, multi-actor perspective. Involving users in innovation processes is an important consequence hereof. The creative potential of users will add to the (societal and economic) quality of innovation processes and increase acceptance of innovations. Insights from innovation studies suggest that the pharmaceutical industry – to improve the societal and commercial rate of return on investments in R&D – should make an effort to involve users more and in an earlier phase in the innovation process, supply them with the information they need, and take their input seriously. Governments should help to create an environment in which involvement of users is stimulated and facilitated by developing shared, long-term visions on the development of economic sectors and by creating a strategic intelligence infrastructure that provides the information actors need to contribute to the realisation of such a shared vision.

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