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USER PRODUCER INTERACTION IN CONTEXT. FROM INTEGRATION TO CONFIGURATION IN THERAPEUTIC ANTIBODY DEVELOPMENT

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Abstract:
Science, Technology and Innovation Studies show that intensified user producer interaction (UPI) increases chances for successful innovations, especially in the case of emerging technology. It is not always clear, however, what type of interaction is necessary in a particular context. This paper proposes a conceptualization of contexts in terms of the flexibility of the technology, and the heterogeneity of user populations resulting in different configurations. The paper identifies and classifies eight types of user producer interaction and analyzes how these different types of UPI have influenced the transition from an integrated system into a configurational technology in the development of therapeutic antibodies. Relevant UPI types, such as demand articulation, learning by using, broadening and frame adding are discussed, and a shift is noticed in configuration from an integrated system based on the basic characteristics of antibody technology and a homogeneous patient population towards a configurational technology, as antibodies becoming more humanized and heterogeneous patient groups could be treated by the same therapeutic antibodies. Finally, some directions for further research are suggested based on the utility of the UPI classification.

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Keywords: UPI typology, integrated system, configurational technology, antibodies

Introduction

Innovation studies show that intensified user producer interaction increases chances for successful innovations. Through interaction users and producers are better able to overcome uncertainty about customers' needs and preferences and about the characteristics of technology; the needs of users can be identified and their role in innovation processes strengthened (Clark, 1985). Producers are interested in societal acceptance of their products, in access to users' knowledge and in mobilizing the creative potential of users (Smits, 2002; Oudshoorn & Pinch, 2003). Users are increasingly recognized as important sources and co-developers of innovations. Various studies show that users often develop

new functions for technologies, solve unforeseen problems and propose or even develop innovative solutions (Von Hippel, 1976; Lundvall, 1988; Coombs *et al.*, 2001; Lüthje *et al.*, 2005; Rohracher, 2005). A growing body of literature in the field of Science, Technology and Innovation Studies (STIS) addresses the variety of ways in which users can be involved and the question how interaction between users and producers can contribute to the quality of innovation processes. We think there is now opportunity and need to wrap together the results of these studies and try to bring some order in the variety of what we call 'types of user producer interaction', that is: the characteristics of how the process of user producer interaction is organized and how it develops.

In this study we discuss some types of interaction based on a particular structuring of contexts and investigate how these types affect the nature and direction of technological innovation. Starting point in this study is that user producer interaction (UPI) is an umbrella concept covering various types of interaction, such as user representation (Akrich, 1995), demand articulation (Boon *et al.*, 2008), and learning by using (Rosenberg, 1982). Types of interaction are interactive learning processes between users and/or producers aiming at the reduction of uncertainty about the relation between product and demand characteristics. More specifically, these are interactions that lead to outcomes such as articulated demands, improved modes of interaction, lessons about prolonged use and domesticated technologies. It is via these specific objectives that UPI can contribute to more general, meso-level objectives of user producer interaction, such as enhanced competitive strength of enterprises, improved acceptance and societal embedding of new technologies, improved learning capacity of social networks, or enhanced democracy (Smits & den Hertog, 2007). In this study we will analyze how different types of UPI have influenced the transition from an 'integrated system' into a 'configurational technology'.

Integrated systems are configurations with an emerging generic identity, which governs how components are integrated. Examples of integrated systems are mass market products like fashionable clothes, computer games and mass produced consumer electronics. In each of these examples, a multitude of design directions is possible from a technological point of view, but one dominant design finally turns out to offer the best fit for most users.

Configurational technologies are adaptable configurations composed of loosely coupled and changeable components. Configurational technologies can be applied in a diversity of user contexts, because they can be tailored to the specific desires, needs and requirements of users. Examples are computer software, robots, bicycles.

In the next section we will further elaborate on the distinction between these two constellations. Then we introduce a number of concepts denoting different aspects of UPI that were found in the STIS literature. We illustrate our findings with the case of therapeutic antibody technology. In the development of antibody technology we will see a shift in configuration from integrated system (based on the basic characteristics of antibody technology and a homogeneous patient population) towards becoming a configurational technology, as antibodies becoming more humanized and heterogeneous patient groups could be treated by the same therapeutic antibodies.

Integrated systems and configurational technologies

Integrated systems and configurational technology have in common that they are examples of relatively flexible technology. Flexibility is defined in opposition to rigidity. The *rigidity* (versus *flexibility)* of a technology is defined by the strength of the design logic, that is: the degree to which functionality and performance are determined by the interrelatedness of elements that make up a technology. This degree determines the space for acting and learning and hence the relative importance of different types of user producer interaction. For example, very flexible technologies have weak design logics and are relatively easily adjusted to specific user requirements. Learning will be largely oriented at the mobilization of local expertise. Rigid technologies, in contrast, have a strong design logic specifying particular affordances and limitations. They demand a receptive environment, and learning will largely be oriented at the possibilities for market creation, the mobilization of societal support and institutional change.

Flexible technologies may be offered as integrated systems or as loosely coupled configurations (Fleck, 1993; Fleck, 1994; Franke & Von Hippel, 2003). Loosely coupled configurations consist of mutually interacting components, both technical and non-technical, which may be deployed in a variety of ways to offer variable affordances and meet diverse user requirements. The main difference with integrated systems is that their performance characteristics are shaped during diffusion and implementation processes instead of prior to it. Flexible technologies are generally offered as configurational technology when there is a high degree of heterogeneity of the user population (Fleck, 1993; Stewart & Williams, 2005).[1]

[1] Note that there are several sources of heterogeneity: user contexts are often unique as a consequence of contingent historical developments (e.g. existing technology, routines and institutions) (Fleck, 1994; Garrety & Badham, 2004); there may be different kinds of users of the same technology that have different needs and concerns (e.g. medical professional, nurses, patients, hospital administrators in case of medical technologies) (Oudshoorn & Pinch, 2003); and these users may have very different capabilities and knowledge bases (depending on e.g. education, skills, experience) (Akrich, 1995).

Our definition of *user heterogeneity* is derived from the Social Construction of Technology (SCOT) approach (Pinch & Bijker, 1987; Bijker, 1995; Kline & Pinch, 1996). In this approach a user group is distinguished from other social groups, such as engineers, advertisers and other users groups. Each of these so-called 'relevant social groups' shares a particular meaning of an artefact. With regard to the early development of the bicycle, for example, Pinch and Bijker (1987) distinguish the relevant user group of young men from the group of women and elderly, because each group associated a different meaning with the bicycle ('macho machine' versus 'unsafe machine'). We define user heterogeneity then as the existence or emergence of multiple relevant user groups. User groups are relevant when they are actively involved in disputes and interactions, for instance because they have a problem for which one variant of the technology might offer a better solution than another. Accordingly, heterogeneous users put various, and sometimes conflicting, requirements to a certain technology.

The heterogeneity of users manifests itself during learning processes and user producer interaction, especially in early phases of development. For example, the construction of scenario's, demonstrations and the articulation of demands and needs reveal the extent to which users attach similar meanings to emerging technologies and to which demands diverge or converge (Boon, 2008). However, user groups generally have coherence beyond the fact that their members share a certain meaning of an artefact: members share other properties as well, such as the meaning of related artefacts (predecessors, complementary products). To capture this coherence, Bijker (1995) has introduced the notion of a technological frame. Meaning attribution, and hence social group identification, takes place with reference to these more widely relevant and historically patterned technological frames. In other words, user heterogeneity manifests itself during processes of learning and interaction. But user heterogeneity may already exist prior to these processes in the form of different technological frames.

The *flexibility of technology* and the *heterogeneity of users* are two dimensions which define four particular technology-user constellations in which UPI types can be classified:

1. *Commodities*
    - Rigid technology: supplied without qualitative differentiation across a market segment, strong design logic
    - Homogeneous users: relatively uniform user contexts and well delineated market segments
2. *Ambiguous technologies*
    - Rigid technology: limited possibilities for adaptation, strong design logic
    - Heterogeneous users: specific requirements, conflicting interests in technology
3. *Integrated systems*
    - Flexible technology: configuration with emerging generic identity which governs how components are integrated
    - Homogeneous users: relatively uniform user contexts and well delineated market segments
4. *Configurational technologies*
    - Flexible technology: adaptable configuration composed of loosely coupled and changeable components
    - Heterogeneous users: unique user context, specific needs and requirements

At any given moment in time, a technology in its context can be typified in terms of one of these four constellations. In this paper, we focus on the latter two constellations. More specifically, we investigate the possibility of a shift from integrated systems to configurational technology. Since the difference between these constellations is a matter of degree, such shifts are always possible in principle. For example, in terms of user populations, from one dominant frame to a dominant frame and an added frame, to two dominant frames etc. In terms of configuration, from one to infinite configurations. Configurational technologies may evolve into more integrated systems when configurational activity becomes path-dependent, user requirements converge and system standards emerge. This may be the result of convergence on the dimension of user heterogeneity. Often, the number of social groups, their frames and the flexibility of the technology decreases over time, when social groups achieve consensus about the dominant meaning of an artefact ('closure'). But this shift towards systematization and generic identity of a technology certainly does not need to happen. With examples from robotics, production systems and IT applications, Fleck (1993) argues that in many situations local contingencies continue to resist standardization and systematization.

Technologies may also evolve from systemic into configurational technology over time. New user groups emerge and add another frame to the same technology. This may have strong implications for technological design, for example when enthusiast user communities acquire technical skills and learn how to deconstruct generic systems to reconfigure them into technologies that serve their own purposes. In this way, users transformed the bicycle into a

mountain bikes for sportive adventure in the 1970s. Other examples are the transformation of the T-Ford into a stationary power source in rural America (Kline & Pinch, 1996) and the reorientation of genetic technology application from hospital services towards pharmaceutical drug development (Martin, 2001). In these examples, the emergence of new users resulted in differently configured technologies. In other examples, new user groups may also be formed around resistance to a given technology (e.g. nuclear power plants or wind energy parks) or around new applications of essentially unchanged technology (e.g. giving aspirin for treatment of cardiovascular diseases).

In the next section we discuss various types of user producer interaction that we have identified in the STIS literature in order to derive hypotheses about how UPI might contribute to the transition of integrated systems into configurational technology.

Types of UPI

There is a growing literature that addresses user producer interaction (UPI) in technological innovation. This literature accommodates many insights about the different types of UPI, their objectives and their underlying assumptions about the circumstances in which these types are especially important. The literature is, however, divided in a number of different theoretical strands. Inspired by Stewart and Williams (2005), Oudshoorn and Pinch (2003; 2008) and Nahuis *et al.* (2008), we subsequently discuss evolutionary economics, technology assessment, social construction of technology, semiotic approaches and cultural studies. The types of interaction derived from these literatures are described in boxes 1 to 8. In these boxes we systematically evaluate the relevance of the UPI type alongside the contextual dimensions that were distinguished in the previous section.

Evolutionary economics

Evolutionary economists have importantly contributed to the theory of user-producer interaction. They have conceptualized technology development in terms of variation and selection (Nelson & Winter, 1977). Competing variants of the same technology can live next to one another for some time, until a dominant design emerges (Utterback, 1994). Like in biological evolution, technology development is understood as an alternating process of trial and error in which the fittest survive. But unlike in biology the variation process is not completely blind. Innovators anticipate the selection environment (Van den Belt & Rip, 1987) and try to determine user needs and requirements in advance (Teubal, 1979). The concept of ‘demand articulation’ has been brought up in this context (Rip, 1995; Boon *et al.*, 2008; Moors *et al.*, 2008). Demand articulation is a learning process, because users do not have

precise demands, needs and requirements in advance. This learning process is based on interactions between users and producers. Demand articulation is our first type of UPI (see box 1).

Box 1. Demand articulation

Demand articulation is "an iterative, inherently creative process in which stakeholders try to unravel preferences for and address what they perceive as important characteristics of an emerging innovation" (Boon *et al.*, 2008). Demand articulation is a process through which technological opportunities and technological frames are getting linked. If this happens by multiple groups with reference to multiple frames, then the heterogeneity of users might increase and pressure is exerted to develop technology in a configurational mode. If social groups share the same interpretation and succeed to achieve consensus, then an integrated system is more likely to emerge (see also below, frame sharing).

One of the main contributions of evolutionary economics to economics in general and to innovation studies is that it has opened the black-box of technology development that neo-classical economists have kept closed (Rosenberg, 1982). It does no longer treat innovation as an exogenous factor to explain economic growth, but scrutinizes the conditions for innovation themselves. One very important condition (by which variation and selection are coupled) is learning by using, especially if one takes into account that by far most innovations are incremental innovations. Learning by using can contribute to the optimization of performance, servicing and maintenance characteristics of capital goods (Rosenberg, 1982). Learning by using is the second type of UPI that we distinguish.

Box 2. Learning by using

Learning by using "begins only after certain new products are used. […It] constitutes a feedback loop into the design aspect of new product development" (Rosenberg, 1982, p. 122/124). With examples from the aircraft industry Rosenberg shows that many performance characteristics of components (e.g. their lifetime) cannot be properly understood until after prolonged experience. R&D efforts insufficiently yield such understanding. Learning by using is very much like demand articulation, but should be situated in a later phase of technology development. People learn by using when they expose the technology to diverse circumstances that cannot be fully anticipated in the context of design.

Learning by using typically leads to improvements of technology after producers are provided with important feedback. Yet, in some areas of technological development, users may also be actively involved in innovation and design beyond providing producers with important feedback. They come up with creative ideas for product development or even make improvement themselves. To capture this role of users as sources of innovation, the notion of 'innofusion' (Fleck, 1988; Fleck, 1994) is introduced. It refers to the adjustments to the technology made on the base of learning by using.[2] Innofusion is the third type of UPI.

Box 3. Innofusion

Innofusion is a contraction of diffusion and innovation (Fleck, 1988). It denotes the adaptations and improvements that users suggest or make when they implement technology into their local situation. Making use of the flexibilities in design, users customize technology to their specific needs and create an optimal combination of affordances and constraints. Innofusion is not so much an interaction type itself, but denotes the situation where learning by using and innovation during the implementation of new technology are prevalent. The presence of innofusion indicates that the technology is configurational, offering the possibility for customized solutions (Fleck, 1988; Fleck, 1994; Stewart & Williams, 2005).

Technology Assessment

Technology Assessment started in the context of technology policy some forty years ago as an early warning instrument to assess the possible impacts of new technologies (Smits & Leyten, 1991; Smits *et al.*, 1995; Schot & Rip, 1997). One of its most pronounced members, Constructive Technology Assessment (CTA), emerged at the crossroad of traditional TA and evolutionary economics. CTA strives after strategies to manage technological innovation while including both positive and negative impacts. It regards the couplings between technology variation and the selection environment as opportunities for constructive intervention. These interventions are justified by the insight that impacts are not fully determined by mere technological norms, but can be anticipated, evaluated and deliberately given shape, provided that this happens in an early phase when different directions for development are still open. CTA is a proactive, user oriented and interactive approach to

[2] This view on the agency of users should not be conceived as a democratic solution to technocratic tendencies in the context of design, as Von Hippel (Von Hippel, 2005) seems to suggest. Democratization encompasses much more than merely user innovation (Nahuis, 2007). Moreover, suppliers often succeed to appropriate the knowledge generated by users in due course and readdress the same issues more effectively in the context of design.

technology development (Schot, 1992; Rip *et al.*,1995; Smits *et al.*,1995). Apart from demand articulation, it strives after broadening of the perspectives of actors (Rip & Schot, 2002; Van Merkerk, 2007). Broadening is the fourth type of UPI that we discern in the literature.[3]

Box 4. Broadening

By broadening their perspectives, the actors involved become aware of how technologies might affect others, and are stimulated to address societal questions and to accept a shared responsibility for sometimes barely predictable outcomes (Schot, 1996). Broadening is defined as "widening the perspectives of actors in terms of identifying a broader set of actors and aspects" (Van Merkerk, 2007, p. 42). This, for example, happens when a CTA practitioner develops scenarios of possible developments and brings together in a workshop a set of actors implicated in one or more of these scenarios to discuss what their roles in the innovation process are or can be (Van Merkerk, 2007). Broadening is a process in which the opportunities and threats of new technologies are assessed by actors in different frames. Without converging (like frame sharing, see below), broadening leads to increased heterogeneity of users, and hence puts pressure on designers to develop technology more in a configurational mode.

Social Construction of Technology

The evolution of technology development has also been studied from a sociological point of view, thereby stressing the social nature of selection between technological options. How is it possible that options, which are not the most optimal from a technological point of view, are nevertheless selected? The Social Construction of Technology (SCOT) approach explains the emergence of dominant designs as the closure of societal debate in which artefacts that are initially characterized by high 'interpretative flexibility' gradually acquire a more fixed meaning ('closure') when consensus is achieved about problem definitions and appropriate solutions (Pinch & Bijker, 1987; Kline & Pinch, 1996). Social groups (institutions, organizations, as well as organized or unorganized groups of individuals) negotiate the meaning of technology in stakeholder meetings, markets (including advertisements), public debates, experiments and demonstrations, as well as in actual use (Pinch & Bijker, 1987; Kline & Pinch, 1996;). A crucial element in the closure of technological controversy is the

[3] Van Merkerk (2007) develops six effect indicators that stand proxy for broadening and enriching: enhancing knowledge, changing attitudes and opinions, initialized actions, anticipation, reflection, and learning. He combined these indicators to determine whether broadening and enriching changed the thinking, acting, and interacting of actors, but also admits that, although broadening and enriching are different things, it was difficult to assess the two effects separately in the evaluation.

increased sharing of a technological frame around certain artefacts. Frame sharing means that interactions move actors in the same directions and, as a consequence, relevant social groups establish a consensual frame and a dominant meaning of the artefact (Bijker, 1995). Frame sharing is the fifth type of UPI that we discuss.

Box 5. Frame sharing

A technological frame both emerges from and structures the interactions among the actors of a relevant social group. It consists of goals, key problems, problem-solving strategies, tacit knowledge, testing procedures, users' practice, perceived substitution function, and exemplary artefacts. When actors are sharing these elements, then a technological frame emerges 'around' an artefact. In principle, new technologies are assessed with reference to multiple existing frames. Social groups, who are involved in the reproduction of frames, may want to translate aspects of their frames in such a way that the new technology could offer solutions for the problems and needs defined by the old frame. In this process, old frames gradually become obsolete. If heterogeneous social groups start articulating the new frame in a converging way, we speak of frame sharing. Frame sharing is an important driving force of the emergence of integrated systems, because the frame provides a particular identity and logic to the technology.

A related type of UPI is frame adding. Adding a new frame to an existing one involves the reinterpretation of an artefact for which there is already an established market. Kline and Pinch (1996) discuss how the automobile in rural America was adapted and reshaped as a source of power within the frame of farm business. This reinterpretation of the T-ford as a traction engine not only neutralized a quite common interpretation in rural areas of the automobile as a dangerous 'devil wagon' compared to the safer horse and buggy, it also gave rise to the development of several accessories, like kits that took power from the crankshaft or rear axle. These kits turned the automobile into a useful machine "consisting of tractor-like drive wheels, a heavy axle, reduction gears to lower the speed to about three miles an hour [in order to] pull plows, harrows, mowers, binders, and other implements in the field" (p. 787). With this example Kline and Pinch show how users, who are oriented by another frame, adapt established products to their own situation. Frame adding is the sixth type of UPI.

Box 6. Frame adding

Frame adding means that new social groups reinterpret and adapt already stabilized technologies to their specific needs (Kline & Pinch, 1996). Frame adding is the opposite process of frame sharing. If a new frame emerges, this does not necessarily mean that old ones vanish. Multiple frames could co-exist with regard to the same technology. As the example above shows, frames could even be added in a later phase. The co-existence of multiple frames is an important driving force for the development of configurational technology.

Semiotic approaches

Semiotic approaches also emphasize the 'interpretative flexibility' of technological artefacts when they consider technologies as if they are texts, but these approaches rather elaborate on the consequences of this flexibility for the configurational work of technology developers. Designers and engineers somehow have to deal with diverging technology interpretations by users. In a case study of usability trials, Woolgar (1991) has shown how innovators observe users' confusions, mistakes and other possible interpretations in order to take measures to constrain the degrees of freedom and teach people how to use the technology. Innovation is henceforth conceived of as a process of 'configuring the user', a process of delimiting the range of possible interpretations.

Box 7. Configuring the user

Configuring the user means "defining the identity of putative users, and setting constraints upon their likely future actions" (Woolgar, 1991, p. 59). While this definition suggests that producers force users into a certain role, Mackay (2000) insists that organizational and extra-organizational aspects also influence the interaction between producers and users and that the direction is much more bi-directional than Woolgar suggests. Nevertheless, the concept still denotes the necessary encouraging and teaching of users who are interested in exploring the opportunities of new technology. Configuring the user is important once first users are recruited and technologies enter the wider world. It is a process in which users increasingly acquire common identities and capabilities, while the technology is simultaneously acquiring a specific identity and design logic. Configuring the user is thus a process in which frames are getting articulated; it contributes to frame sharing and, if successful, motivates the development of integrated systems.

A variant of the text metaphor is the film script metaphor. This metaphor strongly emphasizes how designers inscribe certain representations of and preferred actions for users into the technical content of artefacts, which suggest or prescribe how these artefacts could or should be used (Akrich, 1992, 1995). For example, non-standard plugs and screws do not allow reparation of a broken device by lay people, but instead foster users to return it to the manufacturer. But how do designers construct adequate representations of users? How do they determine the needs and capacities of users? Akrich mentions six representation techniques ranging from designers' own imagination to market research and feedback. The process of user representation is of interest for our purposes, because it is a way for producers to deal with the uncertainty on the demand side when products are radically new and there is no established market yet. User representation is the eight type of UPI.

Box 8. User representation

User representation is the outcome of "techniques employed by system designers to construct and then appropriate […] representations (in a cognitive and political sense) of what the supposed users are and what they want" (Akrich, 1995, p. 168). User representation is a precondition for many other types of UPI. Because there are often too many users interacting with producers individually, producers seek ways to capture the identity, capabilities and level of heterogeneity of users via representation techniques. Depending on how producers represent user heterogeneity, they will offer new products more likely as integrated systems or configurational technologies.

To show the potential value of these eight types of user producer interaction, i.e. demand articulation, learning by using, innofusion, broadening, frame sharing, frame adding, configuring the user and user representation, and to analyse whether and how these interactions contributed to a transition in configuration from an integrated system towards a configurational technology, we illustrate our findings with a case study on user-producer interaction in the development and application of the therapeutic antibody Remicade®, a chimeric monoclonal antibody of Centocor for widespread immune-mediated inflammatory diseases, such as rheumatoid arthritis and Crohn disease.

The evolution of antibody technology

Before we zoom in on user involvement in the development and application of the therapeutic antibody Remicade, we have to set the scene of monoclonal antibodies (MAbs) development. Appendix 1 sketches the evolution of monoclonal antibodies development

over the past 30 years in general. The Y-like antibody configuration dictates the dominant logic or architecture, governing *how* MAbs could be designed (Figure 1).

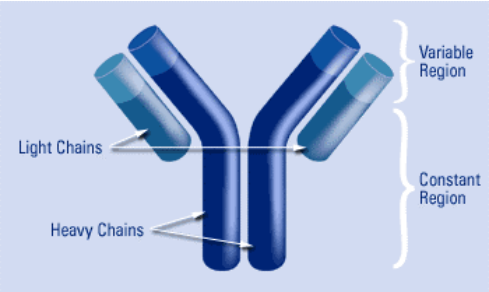

Fig 1: Antibody structure (Medarex, 2009)

Due to their configurational flexibility (via the variable and constant regions), different types of antibodies could be designed from a technological point of view. Chimeric, humanized and fully human have replaced polyclonal and murine monoclonal antibodies (Figure 2). Slowly, the technology of antibody production has gone mouseless. The technological focus changed. It has moved into the realm of molecular biology, in which bacteriophages, gene libraries in plasmids and bacterial hosts are engineered to produce either whole antibodies or derivatives of antibodies with desired properties. 'Humanizing' the antibodies or replacing the mouse constant domains with human sequences (chimerization), limits hypersensitivity reactions to foreign protein, increases the half-life of antibodies in human plasma and improves their function within the human immune system (Rang 2006). Additionally new technologies, including conjugated antibodies and antibody fragments (Fabs) are expected to rise in importance in the future (Pavlou *et al.* 2005), thus key technological trajectories in monoclonal antibodies are diversifying and becoming more flexible.

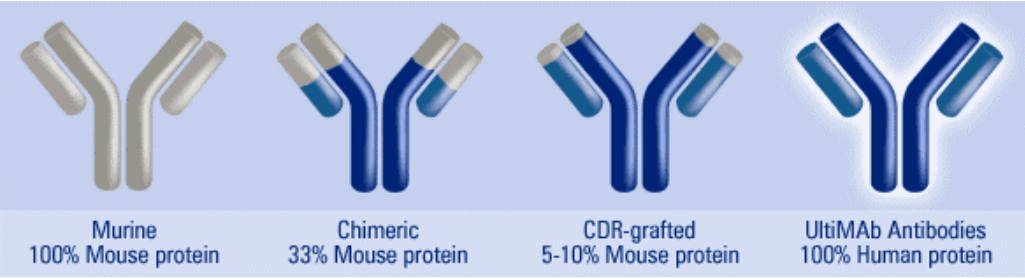

Fig 2: Evolution of the antibody technology (Medarex, 2009)

Scientists were increasingly focusing on decreasing antibodies' immunogenicity, increasing its efficacy and half-life in patients' plasma, in that way searching for the best fit for most patients (users) being treated with monoclonal antibodies. The immunogenicity problems

inspired the development of humanized antibodies to get rid of the unwanted HAMA[4] response. The focus shifted from the development of polyclonal to chimeric and more humanized monoclonal antibodies. At the same time, patients were influencing these developments by demanding for less hypersensitivity reactions, for broader indications and earlier access to MAbs treatments for life-threatening diseases.

To illustrate this dynamics in more detail, the next part focuses on user producer interactions in the development and application of a particular monoclonal antibody, Centocor's Remicade®[5] (or infliximab), a chimeric monoclonal antibody that binds to the human tumor necrosis factor alpha (TNF)[6], developed for the treatment of Crohn's disease, rheumatoid arthritis, and over time also indicated for other immune mediated inflammatory diseases.

User producer interaction in the development and application of Remicade[7]

In 1979, Centocor was founded as a biotech company with the premise that monoclonal antibodies could be used to treat a variety of illnesses in a specific manner. At that time, monoclonal antibodies were a relatively new technology. Due to their high degree of specificity to what they targeted, they were often referred to as magic bullets. Unlike small chemical molecules, monoclonal antibodies had fewer side effects and were raising high future expectations. Centocor's business plan was to enter licensing agreements with outside researchers to isolate an antibody, obtain the rights to it, and then prove its clinical relevance for diagnostic use. With their capability to target specific antigens, monoclonal antibodies showed great promise for being used therapeutically and diagnostically.

In the 1990s, antibodies had not been authenticated as an acute therapy. There were many nonbelievers in industry who recognized the academic endeavor, but thought that a monoclonal antibody drug would never have commercial applications. ReoPro, Centocor's monoclonal antibody blocking the pathway to platelet aggregation, broke that barrier, by demonstrating that antibodies do work, getting FDA approval in 1994, and opened the door to develop Remicade. For its development, Centocor collaborated with Mr. Vilcek, PhD at

[4] HAMA = Human Anti Mouse Antibodies, allergic reaction that can neutralize the effect of the MAbs by neutralizing the binding activity and by rapidly cleaning the antibody from circulation in the body.

[5] Anno 2008, Remicade is Centocor's most successful blockbuster monoclonal antibody with a yearly turn-over of more than $4 billion. Centocor, now being a wholly owned subsidiary of Johnson & Johnson, is the world leader in monoclonal antibody production and technology, focusing on biological therapies to patients suffering from debilitating immune disorders (www.centocor.com, 2009).

[6] TNF plays a role in the body's defense against infections. It is a naturally occurring protein involved in normal human inflammatory and immune activities. But when produced in excess, the cytokine TNF is harmful, especially during chronic inflammatory processes and auto-immune disorders. Preventing the action of TNF prevents the inflammatory responses it causes.

[7] This case study is mainly based on Shook's book (2007) *Miracle Medicines* about seven lifesaving drugs and the people who created them, Drews (1999), Pavlou *et al.* (2005) and Rang (2006).

New York University. Vilcek's work led to the development of an monoclonal antibody that binds to TNF-alpha receptors and blocks the cytokine's action, which was the start of Remicade. The Centocor scientists started concentrating their efforts on indications such as rheumatoid arthritis. The original Remicade from Vilcek group was a mouse antibody and Centocor scientists engineered it to make it more human. When that was accomplished, they worked on getting Remicade ready for clinical trials. They contacted specialists at the Institute of Rheumatology in London to do the first clinical trials. Remicade was given by infusion, and within 3 days they already saw dramatic clinical benefits for patients, demonstrating that Remicade worked on rheumatoid arthritis. More clinical trials were set up. Sander van Deventer, a noted gastro-enterologist and internist at the Academic Medical Center in Amsterdam had anticipated in sepsis trials that Centocor had conducted in the early 1990s. Van Deventer had a particular interest in inflammatory bowel disease and was fascinated with the prospects of how monoclonal antibodies could work against TNF (by the sepsis studies). Van Deventer was familiar with Centocor's researchers who identified high levels of TNF in animal models in rheumatoid arthritis and Crohn's disease. Van Deventer himself had observed that TNF was elevated in the tissue of the gastrointestinal tract in patients with Crohn's disease. He knew about the results of the Centocor trials in London, treating patients with rheumatoid arthritis, and he had a theory that although arthritis was a disease of the joints, Crohn's disease that happens to be in the intestines, is also involved with TNF[8]. When Van Deventer had a 14-year-patient, with very severe Crohn's disease, being put on various medications without any results, Deventer contacted Centocor to immediately request a supply of Remicade. Although the drug has not yet been approved, Centocor was able to grant this request for compassionate use[9]. Upon receiving infusions, Van Deventer's patient was no longer debilitated. He wrote an article in the influential Lancet journal about his successful treatment of Crohn's disease with Remicade. Then, Centocor also started, together with the Crohn specialist Van Deventer, clinical trials with Crohn's patients.

Centocor's priority for Remicade was to pursue a first indication for the immune-disorder rheumatoid arthritis, as it would be a real success to be the first biotech company to come out with a drug for such a crippling disease. However, when the above mentioned promising results with Van Deventer's Crohn disease patient were known, it opened the debate over whether Crohn's disease was a better first indication to pursue. After all, the

[8] Crohn's disease is an inflammatory disease of the gastrointestinal tract that often affects the intestine and colon. It is a type of chronic inflammatory disease. Its symptoms can include abdominal pain, diarrhea, fever, loss of appetite, weight loss. Intestinal complications may include bowel obstruction, bowel perforation, and fistulae. Crohn's disease can also cause intestinal hemorrhage as well as cancer of the bowel and the small and large intestine (Shook, 2007;220).

[9] Normally a pharmaceutical firm is not permitted to provide an unapproved drug to treat a patient (which is not in a clinical trial), except in a case that falls into the category of compassionate use.

gastroenterologist and internist Van Deventer had a theory that Crohn's disease is also involved with TNF and that Remicade probably could be a good therapy. He articulated his demand for Remicade in treating a very sick Crohn disease patient with Remicade, and when that treatment turned out to be successful, he broadened the indication area of Remicade. This is also a clear example of learning about more indication areas by compassionate use of Remicade in Crohn's patients. For Centocor, another frame of treatment had been added to their MAb technology, the frame of treating Crohn disease patients, not earlier associated with the chimeric antibody Remicade.

The company had a drug that showed exceptional promise for not one but two indications, and both were significant, deliberating diseases. Centocor recognized there was a need for both indications and they decided to first develop the drug for Crohn's disease, because phase III trials for rheumatoid arthritis were more expensive and took longer to get to market. So, probably, profit potential was the main driver for this choice, but it is interesting to further explore how the representation of Crohn patients were at that moment aligned with the firm strategy and its moral legitimation.

Centocor decided to get Remicade, as the first anti-TNF product, to the market and then they would be able to expand the development of Remicade more quickly because it would become a revenue generating drug. They decided to focus on Crohn's disease. From earlier failure with another Centocor product Centoxin, they learned that it is more difficult to get a drug approved if the clinical trials are too broadly designed. With Crohn's disease there was a clearly defined patient population with an enormous need. Centocor started with a narrow patient population where its benefits would be very clear. Rather than going for an indication to treat all Crohn's disease patients, Centocor limited its indication to treat patients with moderate-to-severe Crohn's disease who not responded to traditional treatments and might find short-term relief with their antibody product. Because Centocor framed the indication of Remicade for moderate Crohn's disease, and for a smaller number of patients who failed conventional therapy, the size of the market segment was smaller and fell under the orphan drug categorization for the disease. As an orphan drug, Remicade would be entitled to certain tax benefits and be put on the fast track for FDA reviewing. Obtaining this orphan drug status for Remicade was for Centocor a way to deal with the uncertainty on the demand side (user representation), as monoclonal antibody treatment was radically new and there was not established market yet.Traditional treatment at that time had included corticosteroids and other immune-suppressing drugs and antibiotics and a new Crohn's disease treatment had not been introduced in three decades. Hence, there was virtually no other competitive drug in the market. In 1998, Centocor filed an orphan application for an unmet medical need, and they received a six-month review from the FDA, considerably shorter than normal. Then, Centocor had to go before an advisory committee. At the

advisory committee hearings, open to the public, there were some Crohn's disease patients in the audience, describing their personal stories about how the disease had affected their lives. They were saying, 'This is a terrible disease, and now we have a drug that can really make a difference. Please don't take it away from us. It works and we desperately need it' (Shooker, 2007:224). Those patients had an immense impact on the hearing, putting a face on the disease by articulating their demand for treatment. The committee advised that the company should go forward with Remicade. As an orphan drug, it was put on the fast track for a prompt approval by the FDA. In 1998, Remicade received this approval. In 1999, the FDA approved a second indication for the use of Remicade for the treatment of rheumatoid arthritis in patients. Over time, the experience with monoclonal antibodies increased on both the drug developer and regulator sides, and more regulatory initiatives were supporting faster development of these drugs (Weinberg *et al.* 2005).

Remicade is administered by intravenous infusion over a two-hour period and administered by a physician or nurse. Prior to drug's approval for Crohn's disease by the FDA, Centocor had to exhibit to physicians, mainly gastroenterologists, that their patients would benefit by receiving the drug by infusion. Previous medicines for Crohn's disease were taken mostly by pill Would the infusion be done in a hospital? Would it be done in a doctor's office (outpatient infusion) In the beginning, there was resistance. Then there was a healthcare coverage problem: Centocor had to work with physicians and insurance companies on how outpatient treatment would be reimbursed. If it was taken in a doctor's office, this would reduce the cost substantially.It could also be administered by trained nurses and medical technicians. Today there are may infusion sites, but prior to launching, there were none for R.A. or Crohn's disease. Thus, Centocor was configuring the healthcare specialists (physians, nurses etc) by advertising their antibody product to them, teaching them how to administer Remicade and how to set up the logistics. More treatment responsibility was given to the physicians, who could titrate the Remicade doses[10], This is also an example of configuring the user to carry out the script of Remicade, adjusted to the needs of the patient.

At early drug discovery stage, there was not enough knowledge about immune mediated inflammatory diseases for Centocor scientists to know that their work would unlock the secrets of the immune system, and that they would develop a medicine that would specifically attack the underlying causes of many unrelated clinical syndromes that share common pathways. Learning about the commonalities of various clinical syndromes (learning by using) gave rise to searching for other indication areas for Remicade and specifications for improved design about dosages, administration forms etc. A learning loop

[10] As Remicade is a weight-adjusted dose, so it can be titrated up and down as the dosage interval can be shortened or lengthened, according to what works best for a particular patient.

took place, known by the concept of innofusion. While it sometimes happens that a medicine developed to treat a specific disease can also effectively treat another disease, Remicade is unique inasmuch as it can treat multiple diseases, diseases that heretofore were believed unrelated. Broadening took place when Remicade was used in various clinical practices by heterogeneous patient groups.

The development of other administration forms (intravenous instead of subcutaneous) of antibodies could be regarded as a process in which the patients are configured and actively learn how to use the antibody technology in relation to their specific circumstances. Intravenous treatment means going to the hospital for half a day every two weeks versus self injection of the antibody in their own home. It formed a way to integrate the antibody technology intro their daily life via improved and more accessible ways of administration (domestication).

From 1998 onwards, Remicade was granted FDA approval for other indications, initially for the treatment of other forms of Crohn's disease and rheuma. By the end of 2006, other approved indications of Remicade included psoriasis, ankylosing spondylitis, and ulcerative colitis, bringing the total to 14 indications that are being prescribed in 121 countries. Remicade could now be regarded as a franchise drug in a configurational constellation. Over time, a more humanized flexible monoclonal antibody medicine emerged that treats many diseases of a heterogeneous group of patients.

To conclude, the development and application of the therapeutic antibody Remicade is an interesting case, in which a transition was visible over time from an integrated system, based on basic development of a mouse antibody for a homogeneous rheumatoid arthritis patient population, towards a configurational technology, in which a more humanized antibody emerged (chimerization) from various possibilities, which could treat heterogeneous diseases. This evolution towards becoming a configurational technology, with a lot of variety, opened up various treatment possibilities for patients with an immunogenic disease. The same antibodies turned out to be active in more disease areas, broadening up the indication areas. Figure 3 depicts this transition.

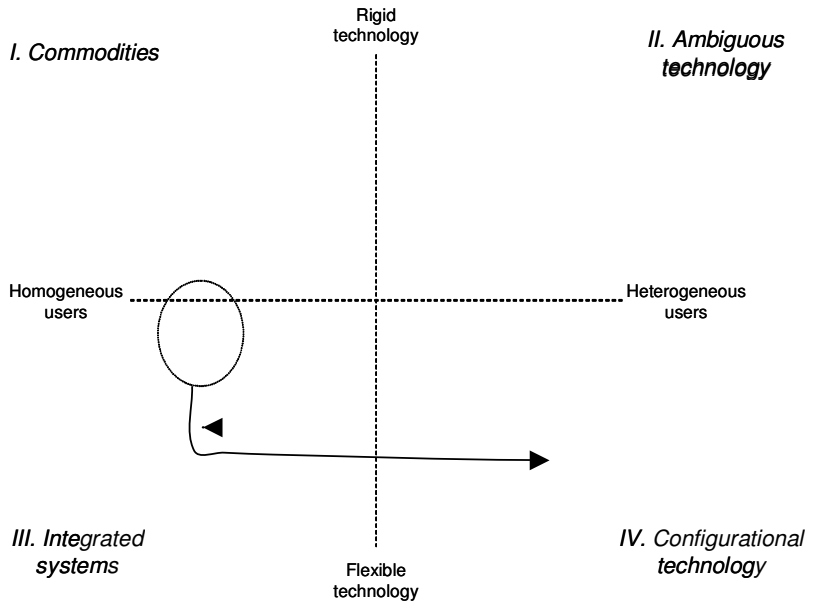

Figure 3: Development of therapeutic antibody Remicade

Summarizing, in the early phase of antibody technology development, all constructed monoclonal antibodies were murine of nature (rigid technology), mostly constructed by academic scientists, sometimes in cooperation with biotech firms (such as cooperation between Vilcek and Centocor).In its evolution from the 1980s onwards, the antibody technology rapidly became more flexible (arrow down in left-under quadrant in Fig. 3), indicating that various designs in the antibody structure were technically possible. These designs of the binding regions (i.e. murine, chimeric, humanized, human) *configured the users* (e.g. specialists, physicians, nurses, patients) into a certain role regarding the use and contra-indication of the developed antibody. Specific healthcare specialist and patient *demands* regarding improved antibody designs with less immunogenicity and hypersensitivity reactions, *broadening* the indication to other TNF related immune disorders, became more *articulated.* The appearance of other users groups, using the antibody for their immune disorder, could be regarded as a form of *frame adding,* the Crohn's disease specialists and their patients being new social groups reinterpreting and adapting the already stabilized antibody technology to their specific needs/diseases. Regarding the succession of antibody variants, *learning by using* by hospital specialists, physicians, nurses and patients became increasingly important.

When the development of more humanized antibodies went on and the first mAb antibody blockbusters, such as Remicade, appeared on the market, healthcare specialists, physicans, pharmacists and patients are further using these successful antibodies for other

indication areas via mechanisms of off-label use, etc. For example, Remicade, first developed for Crohn disease and rheuma arthritis, turned also to be effective for psoriasis. By broadening the indication areas of antibodies, the heterogeinity of users increases.

Post-marketing research of monoclonal antibodies on the market, and drug repositioning are important learning loops, also known by the concept of innofusion. New functionalities of the developed antibodies and other, more fine-tuned administration forms are particular aspects of the *broadening* process between a heterogeneous group of users and the flexible antibody technology.

Conclusions and discussion

Innovation processes take place in systems of innovation, in which producers and users depend on each other's knowledge and capacities. Such context dependency is especially strong when new technological opportunities are just emerging and there is still uncertainty about technology, demand, and legal, ethical and social implications. User producer interaction is indispensable in these circumstances. Users have to learn how to assess the use-value of new technology, to articulate needs and concerns, to intervene in important design decisions, to get technologies to work, to adapt technologies to their specific circumstances, and to establish modes of interaction. Producers have to learn what users want, how new technologies fulfill such needs, how to deal with concerns and resistance, how to cooperate with users, how technologies perform in a particular user context, whether interfaces are clear, what adaptations should be made, and how to receive feedback at all. Different types of user producer interaction serve this variety of objectives.

In this paper we have identified eight types of user producer interaction (UPI) in the STIS literature. The relevance of these types of interaction depends on their contexts, which we have conceptualized on two dimensions, i.e. the flexibility of technology and the heterogeneity of users. The main result of this conceptualization is a distinction between four user-technology constellations – commodities, ambiguous technologies, integrated systems and configurational technologies. To illustrate the value of this conceptualization, this paper focused on the flexible monoclonal antibody technology, and its transition from an integrated system constellation towards becoming a configurational technology.

How did the types of user producer interaction contribute to the transition of therapeutic antibody Remicade from an integrated system towards a configurational technology?

Various, subsequent possibilities of monoclonal antibodies evolved over time, and with the standardization of the humanized antibody technology, more active involvement of users became possible also became possible, by their need for increased antibody efficacy, less immunogenic responses, broader indication areas, other administration forms, and

regulatory and safety issues after market introduction. Also at the regulator sides, increased experience with monoclonal antibody technology supported faster development and approval of drugs (compassionate use, orphan drug regulation).Types of UPI such as demand articulation, learning by using, and frame adding were important in the transition from integrated system to configurational technology, when variants of antibody technology succeeded. Configuring the user, broadening and innofusion appear to be relevant for the application and diffusion of the configurational more humanized antibody technology among heterogeneous patient populations, which could be treated by the same therapeutic antibody.

A single case study is performed for the purpose of illustration. Future research should comprise more case studies in the different types of user-technology constellations. Since this research was limited to the types of UPI in different circumstances, much more can be learned from future research about the particular forms, mechanisms and conditions for effective user producer interaction. In this way, the classification offers an outlook on developing a 'toolbox' for organising and managing user producer interaction in context. the 'tools' will need to be interpreted in relation to the specificity and contingency of particular technologies and markets. Nevertheless, our research offers a starting point to unravel the various processes of user producer interaction and to the understanding of underlying mechanisms of innovation processes in different contexts.

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Appendix 1

Setting the scene of monoclonal antibodies development

Antibodies are part of a class of proteins with immune functions, called immunoglobulins. As one of the human body's most important defenses against disease, these naturally occurring proteins are produced by the immune system in response to antigens, being foreign substances to the human body.

The structure of an antibody is normally depicted as a capital letter 'Y' configuration (Fig. 1). It is a tetrameric molecule consisting of two identical heavy (H) chains and two identical (L) chains. These light and heavy chains are composed of two distinct domains: the variable region and the constant region (Fig X). The variable region serves as the antigen-binding site. Antibodies achieve their diversity through rearrangements of the genes in these antigen-binding fragments (Fab). The constant fragment (Fc) is the part that is identical for all antibodies of the same class. The Fc fragment is the part that links the antibody to other receptors and trigger immune response and antigen destruction (Ng, 2004). Antibodies also vary in the constant region, resulting in one of five immunoglobulin isotypes/classes (IgG, IgA, IgD, IgM or IgE). Through the variable and constant domains, antibodies can bind, neutralized and help eliminate pathogens and their toxins (Medarex, 2009).

Decades ago, antibodies were obtained by extraction from blood samples of immunized animals or human donors. These are *polyclonal antibodies*, because several different types of antibodies are obtained through this method, with IgG being the predominant component. Although polyclonal antibodies have been used for passive immunization and therapeutic treatments, they could induce hypersensitivities in use[11].

The next development was the production of monoclonal antibodies (MAbs) in the mid 1970s. This uses hybridoma technology, which involves the fusion of antibody-producing cells to immortal myeloma cells (Ng, 2004). MAbs are specific in binding to antigens. Because initially MAbs were produced using murine (mouse) spleen cells, human immune system could react against these murine MAbs. This allergic reaction is called human antimouse antibodies (HAMA) and it can neutralize the effect of the MAbs by neutralizing the binding activity and by rapidly clearning the antibody from circulation in the body, or even induce rashes, swelling, kidney problems; it may even be life threatening, causing significant toxicities with subsequent administrations of mouse antibodies

[11] The reason for this hypersensitivity is that polyclonal antibodies contain not only the specific antibody binding to the desired antigen, but also other antibodies, which our immune system will treat as foreign and act against.

Furthermore, the murine MAb may not be as effective as human antibodies because of their murine origin. The *murine antibodies*, were often rejected by patients whose immune system recognized them as foreign because they were not human proteins. Due to these limitations of murine antibodies, the next phase of development is to make these murine MAbs more like human antibodies, by using genetic engineering. A recent approach is to 'humanize' the antibodies to address the short serum half-life of murine MAbs, to reduce HAMA and to improve the efficacy of the MAbs. These strategies include replace certain fragments of the antibodies. Thus, subsequent generations of antibodies have been re-engineered to address these immunogenic complications, resulting in monoclonal antibodies that are less mouse and more human designed.

The first generation is the *chimeric antibodies*, consisting of both murine (~33%) and human protein sequences (~66%). Nonetheless, these chimeric antibodies could still trigger a human anti-chimera antibody response by the human immune system. Chimeric antibodies are designed to minimize the HAMA antigenic response triggered by the antigenic part of the mouse component, while retaining a high specificity. However, although the immunogenicity profile is reduced, chimeric antibodies can still trigger a HACA response (Human Anti Chimeric Antibodies), reducing the antibody's efficacy (Pavlou *et al.* 2005).

To further improve the efficacy and reduce antigenicity, only the specific antigen-binding region is derived from mouse, while the remainder of the antibody is constructed using human proteins. These are called '*humanized' antibodies*, which contain approximately 5 to 10% mouse protein sequences. These antibodies are associated with minimal or no immunogenic responses. The following step in the evolution of antibody technology is the development of *fully human monoclonal antibodies* (100% human protein sequences), obtained from human cells or by using transgenic mice in which mouse antibody gene expression is suppressed and replaced with human antibody gene expression, leading to favorable safety profiles and less rapid elimination from the human body, potentially reducing the frequency and amount of dosing required to affect disease targets (Medarex, 2009). In addition to developing more specific and less immunogenic antibodies research into enhancing the efficacy of action by conjugating them with a payload of chemotherapeutic drugs or radioactive isotopes, combining the specificity of the antibody to optimize target specificity with the therapeutic efficacy of the *conjugated product*. Antibody *fragments* are known as Fabs and consist of one antigen-binding arm of the antibody. Fragments lack the Fc portion, which serves to bind various effector molecules of the immune system. They can therefore be produced using microbial expression systems, significantly reducing the cost of production, and they are better at penetrating solid tumors, but activity of some mAbs have been reduced without the Fc region, reducing efficacy of Fab fragments (Pavlou et al 2005).