Research Policy 45 (2016) 1558–1569

Research Policy

journal homepage: www.elsevier.com/locate/respol

Institutional power play in innovation systems: The case of Herceptin®

Piret Kukk[a,*], Ellen H.M. Moors[b], Marko P. Hekkert[b]

[a] Fraunhofer Institute for Systems and Innovation Research ISI, Breslauer Str. 48, Karlsruhe 76 139, Germany
[b] Copernicus Institute of Sustainable Development, Innovation Studies, Utrecht University, Heidelberglaan 2, 3584 CS Utrecht, The Netherlands

ARTICLE INFO

Article history:
Received 9 December 2015
Received in revised form 25 January 2016
Accepted 25 January 2016
Available online 16 February 2016

Keywords:
Institutional change
Personalized medicine
System building
Technological innovation systems

ABSTRACT

New technologies must be accompanied by institutional change. Innovative actors therefore need to do institutional work or take a role as an institutional entrepreneur in order to shape the institutions in the best interests of their technology. However, the literature on system building and on institutional entrepreneurship have little overlap. The goal of this paper is to bridge these two bodies of literature to gain additional insights into how institutional change evolves in a technological innovation system. We show how the pharmaceutical firm Roche acted as a powerful institutional entrepreneur by influencing the health-care system in England to create a market for the personalized cancer drug Herceptin®. We demonstrate that institutional change can be preceded by a range of innovation system-building activities that are not directly intended to bring about institutional change but are required in order for institutional change to take place. Through this case study, we show how the system-building and institutional change literature can complement each other.

1. Introduction

The technological innovation system (TIS) framework has emerged over the past few years as an analytical tool to study the dynamics of new and emerging technology fields (Carlsson et al., 2002; Edquist, 2005; Hekkert et al., 2007; Markard and Truffer, 2008a). Rooted in evolutionary economics, it highlights the importance of dynamic interplay between institutional structures and the various groups of actors (Carlsson and Stankiewicz, 1991; Carlsson et al., 2002) that, together with technology and networks, are considered key structural elements of innovation systems (Hellsmark, 2010). Because the TIS framework was initially intended to be used in conjunction with firm strategy literature in order to explain the *systemic* aspects of innovation and to derive recommendations for policy makers in their respective technological areas (Bergek et al., 2008; Hekkert et al., 2007; Jacobsson and Bergek, 2004), the majority of TIS studies take a *meso-level* perspective.

Some authors in innovation studies have recently expressed concern about the lack of effort directed toward exploring how micro-level activities by different innovating actors influence the innovation system (Hellsmark, 2010; Markard and Truffer, 2008a; Musiolik et al., 2012). Because of this, the *deliberate* activities of specific actors, or so-called system builders, are overlooked. They are associated with a strong vision aimed at creating and shaping the system in their own interests (Hellsmark and Jacobsson, 2009).

It is important to analyze these deliberate actor strategies for system building in TIS studies in greater depth (Farla et al., 2012; Truffer et al., 2012). Several studies have illustrated the importance of entrepreneurs as prime movers (Carlsson and Stankiewicz, 1991; Hellsmark, 2010; Markard and Truffer, 2008a; Negro et al., 2007) in shaping innovation systems, but we still lack insight in *how* actors shape different innovation systems.

Some TIS scholars have taken a more actor-oriented approach and analyzed the importance of deliberate activities of actors or networks that commit themselves to system building as they undertake different activities to support an emerging technology (Cetindamar and Laage-Hellmann, 2002; Hellsmark, 2010; Hellsmark and Jacobsson, 2009; Markard and Truffer, 2008a; Musiolik and Markard, 2011). All these studies can be categorized as system-building literature and build on the seminal work of Hughes (1987).

Even though these studies are important, they have not provided deeper insights into the mechanisms behind system building aimed at institutional change.

Therefore in this article we highlight the process of system building aimed at achieving *institutional change*. In general, institutional frameworks are not aligned with the needs of radical

* Corresponding author. Tel.: +49 17684059527.
E-mail addresses: piret.kukk@isi.fraunhofer.de, piretkukk@hotmail.com (P. Kukk), e.h.m.moors@uu.nl (E.H.M. Moors), m.p.hekkert@uu.nl (M.P. Hekkert).

http://dx.doi.org/10.1016/j.respol.2016.01.016

innovation, and therefore institutional change is necessary. We thus expect that activities related to institutional change in cultural-cognitive, normative, or regulative institutions (Scott, 2001), or in any combination of all three, are an important part of system-building activities. Many papers in organization studies theorize specifically on institutional change strategies. Compared to system-building literature, organization studies is much more developed. For example, it distinguishes among different types of actors behind institutional change, such as institutional entrepreneurship, in which a powerful heroic entrepreneur with a lot of resources single-handedly changes institutional arrangements (DiMaggio, 1988; Leca et al., 2008; Maguire et al., 2004), and the institutional work, in which institutional change takes place through many different types of activities by a wide variety of actors that aim to achieve institutional change (Lawrence et al., 2011; Maguire et al., 2004). Interestingly, the literature on institutional change does not focus explicitly on innovation and technological change, nor does it explicitly take into account relations between other forms of system-building activities and institutional entrepreneurship or institutional work.

In this study, we aim to bridge the literature on system building with the literature on institutional entrepreneurship and institutional work. By bringing mechanisms on institutional change into the discussion, we contribute to a better understanding of actor strategies in system building. Moreover, by showing how institutional change strategies are related to broader system-building strategies in the context of innovation, we also contribute to knowledge on institutional change.

The purpose of this paper is to provide insights in different system-building patterns by a powerful actor in a TIS that aim to achieve institutional change.

Our main research questions are therefore:

(1) Which system-building activities did the key actors undertake to facilitate market approval and diffusion of their technologies?
(2) How did the key actors deal with institutions that influenced their technology, and which strategies did they implement together with other stakeholders to shape the institutional structures in the interest of their goal?

In order to study the importance of institutional change in the context of broader system-building strategies, we focus on personalized cancer medicine, a technological area of biomedical innovation in which technological and institutional change is strongly interrelated.

Medicine is a highly regulated field, in which bringing a new product to market involves a lengthy institutional process to guarantee its safety and quality. Personalized medicine represents a new paradigm in health care and cancer treatment that enables the provision of more effective treatments with fewer adverse effects for particular patients, based on their specific genetic characteristics. Implementation of this innovative medical treatment requires various significant changes in the health-care sector. This is because, unlike traditional cancer therapies (e.g., chemotherapy, radiation, or surgery), personalized cancer drugs work only on specific patients who can be identified using biomarker-based testing. No other type of drug has required this kind of testing, therefore, changes in treatment and testing protocols and routines are needed. How these kinds of cognitive institutional changes regarding diagnosis are implemented is therefore crucial for the adoption of personalized medicine. The concept of personalized medicine also challenges regulators concerning the alignment of regulatory institutions involved in approval and reimbursement policies to assess the costs and benefits of this new and expensive combination of drugs and diagnosis within health care, considering that resources are not unlimited. Such a transmission process in medical innovation from scientific discovery to new products and services (i.e., the adoption of personalized medicine) depends on cognitive changes in institutions and a learning curve in hospital-based medical practices (Morlacchi and Nelson, 2011; Nelson et al., 2011) and patient preferences and competence (Windrum and García-Goñi, 2008).

The fundamental role of hospitals in innovation systems in the delivery of health care has been highlighted in earlier literature (Metcalfe et al., 2005). The clinical trials to test new cancer drugs take place in cancer centers that are usually part of large university research hospitals. These trials in drug development are run by principal investigators, medical oncology specialists employed by the hospitals. The majority of cancer treatment, such as monoclonal antibodies in personalized medicine, are delivered in hospitals intravenously, exclusively under the supervision of oncologists. Hospitals are the hubs of clinical practice. They not only are service providers but also contribute to biomedical innovation and, together with patients, are the key adopters of new medical technologies.

Therefore as we analyze institutional entrepreneurship by a large and resourceful pharmaceutical firm, we are also analyzing the role of hospitals and patient organizations as key stakeholders in institutional change related to the use in England of the personalized breast cancer drug Herceptin®.

Compared to other Western European countries, England has a complex and demanding institutional environment for gaining market access for drugs, such as an independent drug regulatory agency. The National Institute for Health and Clinical Excellence (NICE) has long, detailed, and evidence-based assessment procedures in place to guarantee the effectiveness and cost benefit of new drugs. This proved problematic in the adoption of personalized medicine in hospitals at the beginning of 2000 (Wilking et al., 2009). However, the country has undergone significant improvement over the years, which makes England an interesting case study. We want to understand how the key actors (i.e., the manufacturer, hospitals, and patient groups) operated in this difficult institutional environment in order to overcome the systemic hurdles they faced at the beginning of the market introduction of Herceptin® and which approaches they took to overcome the underdeveloped key processes in the system.

The paper is structured as follows. The following section starts with a brief description of the technological innovation system, system building, and institutional entrepreneurship literature and explains our analytical framework. Section 3 addresses the methodology. A description of Herceptin® and the problems involved in its adoption are elaborated in Section 4. Section 5 offers the results of an empirical analysis of our framework. Section 6 concludes.

2. Theoretical background

This paper departs from the innovation system (IS) concept as it offers a suitable framework for analyzing the dynamics and growth of a system involving novel technologies or products (Carlsson et al., 2002; Edquist, 2005; Hekkert et al., 2007).

The central idea behind the IS approaches is that the determinants of any technological change are found also in a broader social structure around entrepreneurs (Carlsson and Stankiewicz, 1991; Freeman, 1987; Lundvall, 1992), which means that firms do not innovate in isolation (Edquist, 1997) but, rather, are part of a larger context that can be defined as an IS (Lundvall, 1992).

A technological innovation system (TIS) is part of the wider IS concept and focuses on a specific technology. It is defined as "a set of networks of actors and institutions that jointly interact in a specific technological field and contribute to the generation, diffusion and

utilization of variants of a new technology and/or new product" (Markard and Truffer, 2008b, p. 611).

In addition to structural components, a process perspective of TIS has been developed to enhance the analytical framework (Bergek et al., 2008; Hellsmark, 2010). It highlights the interactions of actors and institutional structures in a specific field of technology (Carlsson et al., 2002; Markard and Truffer, 2008a), and a number of key processes that have been identified need to operate successfully in a well-functioning system (Bergek et al., 2008; Hekkert et al., 2007; Jacobsson and Bergek, 2004). The focus on processes is a relatively new addition to the TIS approach (Suurs et al., 2009; Van Alphen et al., 2010) used to analyze system dynamics and to compare system performance (Hekkert et al., 2007; Truffer et al., 2012).

However, as Markard and Truffer (2008a) highlighted, TIS studies base their analysis on the system level. This is because the IS framework was intended to be used in conjunction with business strategy literature to explain the *systemic* aspects of innovation for policy making (Bergek et al., 2008; Jacobsson and Bergek, 2004; Naubahar, 2006). The concern is that, if such a focus is used, the community might overlook the role of actors and actor groups at a micro level in the creation and functionality of a TIS (Farla et al., 2012; Hellsmark, 2010; Markard and Truffer, 2008a). Neither pays attention to the deliberate activities of specific actors in the current TIS framework, who are associated with a strong vision and interest in shaping the system or its institutional structure according to their interests (Hellsmark, 2010; Hellsmark and Jacobsson, 2009). Therefore TIS is not always just a heuristic construct created for analytical purposes (Bergek et al., 2008; Carlsson et al., 2002; Edquist, 2004) but, rather, a real system with structural elements and actors dedicated to system development (Hughes, 1979; Hughes, 1987; Musiolik, 2012).

This kind of system building by dedicated actors is about the strategic creation or modification of institutional and organizational structures (Musiolik et al., 2012), in order to "address system weaknesses, to reduce further uncertainties and to strengthen the TIS" (Hellsmark, 2010, p. 48). These kinds of system-building strategies depend heavily on the availability of resources and the existing socio-technical systems (Farla et al., 2012) in pursuing more favorable conditions to develop and spread the adoption of new technologies and products (Garud and Karnøe, 2001; Hughes, 1979; Van de Ven, 1993).

Some studies have looked at the role of specific actors in TIS functionality: Cetindamar and Laage-Hellmann (2002) conducted a comparative analysis of a company's impact on the performance of clusters. Hellsmark and Jacobsson (2009) analyzed the extent to which an individual has the capacity to influence the formation of a TIS. They addressed the individual as a system builder with "transformative capacity" on the TIS. Following this, Musiolik et al. (2012) analyzed the role of networks as system builders in fuel cell-based TIS in Germany. The concept of system building is considering all possible key processes involved in system building and therefore offers valuable insights from an actor-oriented perspective on creating innovation systems by analyzing the role and transformative capacity of specific actors as system builders. However, the TIS community would benefit from further insights into the precise evolution of the process of change, the typical system-building patterns, the order of specific key processes, and how they reinforce one another to change the system.

As highlighted in previous work, actors may also deliberately change or adapt existing institutions or create new ones (Markard and Truffer, 2008a), and these kinds of institutional change activities have a positive correlation with the degree of institutionalization of the field (Beckert, 1999). According to North (1994, p. 361), "institutions are the rules of the game, organizations and their entrepreneurs are the players." This relates to the long-standing debate on structure versus agency in the social sciences community (Leca et al., 2008). Scientific discussion over how structures and agencies actually interact is ongoing. Earlier work found that structures (institutions) should be privileged over agency, and therefore institutional change was seen as a result of an exogenous stimulus (Leca et al., 2008). The contrary view that institutions are the result of different activities by the actors (Dolfsma and Verburg, 2005) is much better equipped to deal with institutional change, because it emphasizes the role of actors. The literature on institutional entrepreneurship is one institutional theory that benefits from detecting endogenous reasons for institutional change (Leca et al., 2008).

The literature on institutional entrepreneurship is useful for conceptualizing the role of system builders in institutional change in an innovation system (Leca et al., 2008). It analyzes specific activities "of actors who have an interest in particular institutional arrangements and who leverage resources to create new institutions or to transform existing one" (Maguire et al., 2004, p. 657). According to Weik (2011), institutional entrepreneurs can be categorized into three groups based on the type of activities in which they are interested in undertaking: (1) creators of new institutions; (2) destroyers of existing institutions; and (3) those interested in changing established institutions. Institutional entrepreneurship as initially introduced by DiMaggio (1988) is about heroic entrepreneurs who are able to change institutions. He introduced the term *institutional entrepreneur* to characterize actors or actor groups with adequate resources to contribute to the creation of new institutions or change the existing ones in which they expect to be "an opportunity to realize interest that they value highly" (DiMaggio, 1988, p. 14).

Other frameworks closely related to institutional entrepreneurship encompass what entrepreneurs or actors do in general to create or change institutional settings, such as institutional work (Lawrence et al., 2011), which focuses on micro-level activities that are aimed at achieving institutional change. According to Lawrence, institutional work "describes the practices of individual and collective actors aimed at creating, maintaining and disrupting institutions" (Lawrence and Suddaby, 2006, p. 215). Compared to institutional entrepreneurship, institutional work concentrates more on diverse forms of agency and activities that contribute to institutional change (Lawrence et al., 2011; Maguire et al., 2004). Its main interest is "work" as such—all the different activities (creating, maintaining, and disrupting institutions) that actors or actor groups can engage in regarding institutional structure (Lawrence et al., 2011). Institutional work studies how and why the activities in support of institutional change occur, and with what effect, by focusing on distributed agency: how coordinated and uncoordinated efforts by a large number of different actors lead to institutional change (Lawrence and Suddaby, 2006). The focus of institutional work is on practice and process and not only the outcome, as in institutional entrepreneurship, which diverts attention from one dominant institutional entrepreneur (Lawrence et al., 2011).

Because the literature on institutional change is theoretically more developed than that of system building, it also has a more systemic overview of how change evolves. As proposed by Tolbert and Zucker (1996), institutionalization can be seen as a three-step process of consecutive phases: (1) habitualization, (2) objectification, and (3) sedimentation. The first step, also called a pre-institutional stage, is characterized by unstable structures, a low level of coordination, and a lack of legitimacy for the innovation, a low level of knowledge, and the absence of routine use of the technology. The second step involves increased social consensus, for example, legitimacy among decision makers and accelerated adoption (of the technology). The last step means full institutionalization, characterized by wide acceptance by all

the actors involved (possible adopters) to assure the long-term continuation of the relevant structures (Tolbert and Zucker, 1996).

Scott (2001) has proposed that the process of institutionalization be organized as three separate "pillars" needed for a stable institutional structure: cultural-cognitive, regulative, and normative systems. According to Scott (2001): (1) cultural-cognitive systems are represented by shared identities, common beliefs, and logics; (2) regulative systems are the laws and regulations by executive and legislative bodies that are needed for formal legitimacy; and (3) social expectations, values, and norms by professional associations (e.g., lobby or patient groups) that constitute normative systems.

3. Methodology

We chose to study the importance of system building in general and on institutional change in particular regarding the diffusion of Herceptin® in TIS in England for the following reasons.

First, Herceptin® is one of the first biomedical personalized breast cancer drugs developed that has the potential to significantly improve treatment outcomes. The implementation of Herceptin® is challenging the regulators with respect to the alignment of regulatory institutions involved in approval and reimbursement policies because, as a new combination of diagnosis and drugs, it requires the development of innovative pricing and reimbursement policies. The implementation of this first personalized medicine for cancer also calls for cognitive institutional change to transform the overall medical-care protocol for breast cancer patients. As an example of an important biomedical innovation, it represents an emerging technological field that can cut across established professional and organizational boundaries and disrupts established medical routines and treatment protocols in hospitals (Christensen, 2000; Swan et al., 2007) by changing various established institutions. Because a majority of radical medical innovations require new institutional structures, we expected in advance that institutional change would play an important role in the creation of a market for the Herceptin® TIS, considering that personalized medicine is an entirely new paradigm in cancer treatment that the existing health-care system and the various actors involved have not yet adopted.

Second, until now TIS scholars have dedicated most of their efforts to the energy sector (Truffer et al., 2012). Other sectors with different characteristics, such as pharmaceuticals, which is one of the world's most highly regulated, have not gained as much attention. Therefore, an exploratory single case study was worth conducting in this sector.

Third, the adoption of this drug in England presents an interesting case for analysis because, compared to other Western European countries, England has a supportive environment for biomedical innovation: it has excellent research facilities, internationally recognized pharmaceutical companies, and a sufficient supply of technology, scientists, and know-how (Swan et al., 2007). However, the country also has a nationally distinctive, complex, and demanding institutional environment with respect to market access for personalized cancer drugs. This is mainly due to complex health technology assessment procedures for new drugs, whose outcome determines whether the cost of a drug will be covered by the National Health Service (NHS) (Abelson and Collins, 2009). At the beginning of 2000, the reimbursement and availability of these procedures initially proved highly problematic (Wilking et al., 2009).

However, at the beginning of the past decade, significant institutional changes and improvements occurred in England that made personalized medicine more widely available to patients. Therefore institutional change was significant in creating a market for such drugs, and it made England an interesting case study of how these changes took place over time and what the role of various stakeholders was. The duration of this case is seven years, from 1999, when Herceptin® came on to the market, until 2006, when the drug was approved for the treatment of early-stage breast cancer.

The study employs a multi-level approach. First, we identified and mapped all the relevant actors, networks, and institutions of the Herceptin® TIS in England. Empirical data were collected, making use of different sources, such as scientific literature, "gray" literature (professional journals, industry reports, policy papers, and books), and various websites. Thereafter, using the same sources, a qualitative event analysis was conducted to trace important developments in the case. In this event analysis, system-level events related to the development and implementation of Herceptin® in England over six years were identified and divided into different system-building classes based on the system function by Hekkert et al. (2007) (see Table 1). The classification was verified by another researcher to increase the validity of the primary results. All the differences in the classification were analyzed and reclassified, if necessary. The results of the event analysis were used to develop a narrative describing the evolution of the Herceptin® innovation system in England.

We complemented and developed our narrative further by conducting 15 semistructured interviews with experts from different stakeholder groups, such as industry, academia, medical practices, nonprofit organizations, drug regulators, and policy makers (see Table 2). The experts interviewed were identified from Internet searches, scientific articles, policy papers, and snowball sampling using the criteria of being involved in or having profound knowledge of the adoption or implementation of Herceptin® in England. The interviews took place from November 2012 to March 2013. We personalized the interview guide for each expert based on his or her field of expertise. To explore the different actor strategies and understand their actual behavior and underlying motivations, we asked the stakeholders a series of questions about the history of the creation of the market for Herceptin® and the regulatory environment of the market. We asked them to identify the main

Table 1
Examples of event classification according to system-building activity (based on TIS functions in Hekkert et al., 2007).

EVENTS around Herceptin®	Entrepreneurial activities	Knowledge creation	Knowledge diffusion	Guidance of search	Market formation	Resource mobilization	Creation of legitimacy
Regulatory approval by EMA					x		
Positive assessment by NICE					x		
Collaboration between Roche and Dako to develop companion diagnostic	x						
Reimbursement decision by NHS						x	
Beginning of the HERA clinical trial		x					
New scientific evidence published about phase III clinical trials			x				
Launch of governmental Cancer Strategy				x			
Meeting organized about Herceptin			x				
Supportive political statement							x

Note: EMA = European Medicine Agency; NICE = National Institute of Clinical Excellence; NHS = National Health Service; HERA = Herceptin Adjuvant Trial.

Table 2
Overview of interviewees.

ID	Role	Date of interview (by phone)
a	Industry executive	1-15-2013
b	Cancer charity representative	11-7-2012
c	Public health professional	11-22-2012
d	Industry executive	12-7-2012
e	Industry executive	11-9-2012
f	Oncologist	12-3-2012
g	Health-care specialist	11-7-2012
h	Industry executive	1-28-2013
i	Industry executive	11-20-2012
j	Oncologist	11-29-2012
k	Oncology pharmacist	1-7-2013
l	Health economist	1-31-2013
m	Oncologist	2-12-2013
n	Health economist	2-19-2013
o	Pathologist	3-7-2013

stakeholders involved in the adoption of the technology, the problems they encountered, and how they were dealing with them. All the interview results have been completely anonymized to protect the identities of the interviewed experts. The contradictions between the narrative and interview results were checked with follow-up interviews to gain additional insights. So, the interviews became more refined during the interview process. To increase the validity of the outcome, we also compared all our interview findings against the results of the event database. If any contradictions arose, we conducted additional searches to include all the possible information sources studied.

4. The development of the Herceptin® technological innovation system in England

The case study concerns the implementation of the breast cancer drug Herceptin® in England from 1999 to 2006 (see Fig. 1). Herceptin® is a recombinant human monoclonal antibody that specifically binds to the human epidermal growth factor receptor 2 (HER2/neu), which is overexpressed in 25–30% of breast cancer patients' tumor cells (Slamon et al., 2001), thus hindering the growth of tumor cells. It is an example of a "personalized drug" because, unlike traditional therapies (e.g., radiation, chemotherapy), it does not affect all the cells but, rather, works on a specific molecular target, which is present in only a subgroup of patients. It is a very expensive drug: treatment with Herceptin® costs from £20,000 to £30,000 per patient per year (Kroese et al., 2007), which is equivalent to the average annual income in England.

Pharmaceuticals have one of the most highly institutionalized markets, with high barriers to entry, in which products cannot enter the market without approval by the relevant regulatory authority (Netzer, 2006). Herceptin®, like all the other personalized medicines in the European Union, first had to be approved by the European Medicine Agency (EMA) (Netzer, 2006). Only after the European Commission (EC) licensed it based on EMA approval did it become available for use. However, it was not included in the NHS coverage plan in England until after a positive opinion had been rendered by the NICE. During the period from the EMA approval to the NICE assessment, the decision as to whether the NHS would cover Herceptin® treatment for a given patient was made by local Primary Care Trusts (PCT) (i.e., administrative bodies in England, part of the National Health Service and responsible for commissioning primary and secondary health services) (Mayor, 2005a).

The first part of the Herceptin® narrative covers the system-building activities by the actors between the beginning of 2000, when the drug was launched on the market for the treatment of late-stage breast cancer, and 2002. The second part describes the actors' activities from 2003 until 2006, when Herceptin® was launched for the treatment of early-stage breast cancer and its aftermath.

4.1. Simultaneous launch of the NICE and Herceptin® TIS in England

The NICE is an independent advisory body in England that conducts assessments on the cost effectiveness of drugs as well as their safety and clinical effectiveness (Paul and Trueman, 2001). It directly affects whether the cost of a drug is covered by the NHS. The establishment of the NICE just when Roche was preparing

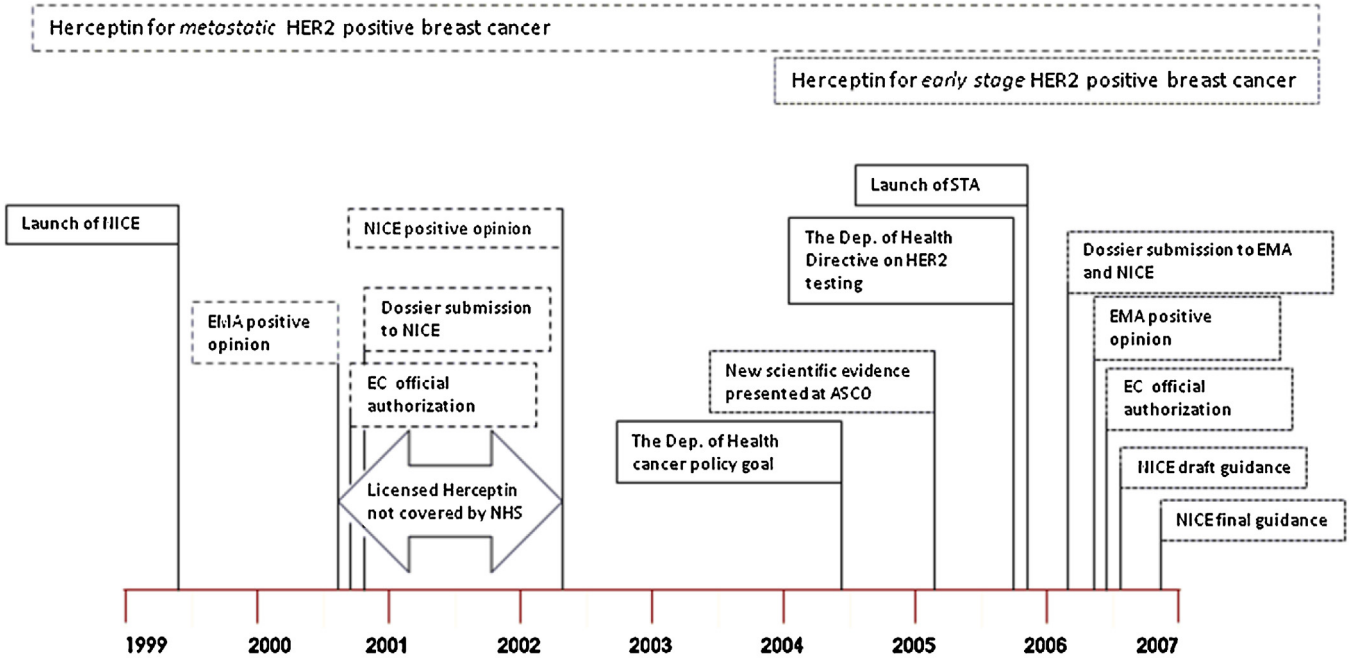

Fig. 1. Key events regarding Herceptin® adoption in England.*Note:* ASCO = American Society of Clinical Oncology; EC = European Commission; EMA = European Medicine Agency; HER2 = human epidermal growth factor receptor 2; NHS = National Health Service; NICE = National Institute of Clinical Excellence; STA = Single Technology Appraisal.

to submit Herceptin® for authorization approval (Fig. 1) put the company in a complicated position regarding its system-building strategy for the drug (Industry executive a and d). Clear approval and reimbursement policies drive the creation of a market for new drugs, but this was not the case for Herceptin® because at the time that the company was conducting clinical trials in hospitals, the NICE did not yet exist. The newly established NICE wanted Roche to supply all the evidence documented upfront, which was much more data than any other national authority had ever requested (Industry executive a). Because the NICE's specific requirements on cost effectiveness were not known in advance, the particular health economics type of data about this expensive drug during the late-stage clinical trials had not been collected, because this was not commonly done in the mid-1990s (Industry executive a). Under these conditions, the NICE had to determine a reasonable price for improving and prolonging lives—something that had not been done before either. Keeping these circumstances in mind, it was evident that the NICE's review of Herceptin® was going to be a long and complicated institutional process.

In order to create market access for its drug, Roche took a number of strategic steps (i.e., system-building activities) in support of this process (see Table 3). Even though Roche was not able to *directly* influence the NICE's assessment (i.e., regulatory institutions), by taking these steps it was trying to ensure faster adoption in hospitals once the drug received a positive assessment from the NICE (Hedgecoe, 2004). In order to contribute to the diffusion of knowledge about the drug and to create clinical experience with the drug (i.e., cognitive institutions), Roche gave hospitals (i.e., other key actors within the TIS) the opportunity to purchase the drug directly from the manufacturer (Hedgecoe, 2004) and dedicated further resources toward implementing an Expanded Access Program (EAP) to give 168 patients Herceptin® free of charge (Miles and Wroath, 2001) (Table 3).

These two highly strategic and effective system-building activities definitely contributed to the habitualization of the technology. However, they did not necessarily create sufficient awareness and legitimacy that hospitals would be motivated to change their existing treatment routines for breast cancer patients after the drug was covered by the NHS. Because of British reservedness and because innovative drugs had not achieved legitimacy, hospitals in England tended to adopt new practices more slowly in general (Cancer charity representative b). Therefore, because, at the beginning of 2000, many doctors had no idea what personalized medicine was about or what "expression of HER2" means, nor did they understand the molecular pathways involved in cancer (Cancer charity representative b), Roche started a public awareness campaign and initiated meetings with oncology specialists from different hospitals across the country (i.e., system building aimed at changing cognitive and normative institutions) (Public health professional c). Engaging in knowledge diffusion to ensure that oncologists and pathologists in hospitals received and understood all the information was a massive project (Industry executive d). The company also set up meetings with patient organizations (Kent, 2000) (Table 3) and published the data about trial outcomes widely (Industry executive e), as part of its efforts to spread knowledge about Herceptin® broadly and reach out to the medical community.

The launching of Herceptin® coincided with the period when access to information on the Internet improved substantially. Roche made use of this emerging medium and set up a Herceptin® website (Table 3). Therefore the source of information became more professional and trustworthy, which substantially improved the dissemination and quality of information (Industry executive d). As one of the oncologists interviewed (Oncologist m) put it: "people come absolutely equipped... they have done their background reading, so we can have a serious conversation about risk and benefits about the approach rather than spending a lot of time on some of the more simple of aspects of it."

Even though Roche acted as a powerful system builder (and institutional entrepreneur), it also collaborated with other actors by hiring a public relations company to market Herceptin® in the UK as a whole (Lepper, 2001) (Table 3).

4.1.1. Implementation of HER2 testing

Because HER2 protein overexpression occurs in only 25–30% of breast cancer patients (Slamon et al., 2001), detection of HER2 status (i.e., overexpression) in a tumor and identification of the patients who might benefit from the drug are prerequisites for prescription of the drug (NICE, 2002). Breast tumors were already analyzed for HER2 even before Herceptin® was developed, because the overexpression of this protein correlates to resistance to certain types of chemotherapy and to a higher probability of recurrence (Burstein, 2005). Therefore HER2 was considered a legitimate prognostic factor in the global oncology community (Ménard et al., 2001), but that was often not the case in England (Hedgecoe, 2004).

Before Herceptin® was approved for use, Roche analyzed the future market and found that at hospitals in the UK only 6% of the patients with metastatic breast cancer were tested for HER2, whereas in other large European countries, the rate was six- to sevenfold higher (Enzing et al., 2006). One explanation for the resistance to testing was financial concerns (Enzing et al., 2006). Some sources have pointed to the lack of skilled staff in hospitals (House of Commons, 2005) and to a general clinical attitude (House of Commons, 2005), in which clinicians in hospitals are cautious to prescribe drugs with lower scientific legitimacy that are associated with possible unknown side effects. Therefore cognitive institutions faced problems because of the lack of legitimacy and the generally conservative attitude among the medical community, which inhibited the willingness of oncologists to prescribe the drug (Cancer charity representative b; Oncologist f). In England at the beginning of 2000, one might say that hospitals did not have enough knowledge diffusion between the oncology and pathology communities. Thus the testing of the different biomarkers was not performed in a comprehensive and cost-effective way and lacked coordination. The entrance of Herceptin® in 2000 kicked off the debate over personalized medicine and testing of the biomarkers (Public health professional c).

Because, in personalized medicine, use of the drug and the diagnostic testing are highly co-dependent, it was clear to Roche that a change in testing habits (i.e., in cognitive institutions) was needed and HER2 tests had to become part of routine testing for cancer patients in hospitals. Hospitals became active partners with the company in biomarker diagnosis. Two years before Herceptin® was launched, Roche allocated resources to help three hospitals set up HER2 testing. With support from Roche, Nottingham City Hospital, Glasgow Royal Infirmary, and Royal Marsden Hospital in London provided free HER2 testing for all breast cancer patients in the country (Ellis et al., 2000; Marsh, 2001) (Table 3), and the test results at these hospital laboratories were freely available to all laboratories in the country (Ellis et al., 2000). According to one of the experts interviewed (Pathologist o): "if Roche had not paid for the diagnostics, the uptake would have been a lot slower."

After almost two years after the EMA gave Herceptin® the green light, the NICE eventually published its guidance on the drug, and Herceptin® was included in NHS coverage (NICE, 2002) (Fig. 1). This period during which Herceptin® was introduced on the English market can be characterized by Roche's strategically planned system-building activities. Many of them were resource-intensive activities with the goal of changing cognitive institutions by familiarizing hospitals and patients with the innovative drug, changing the existing treatment and testing routines in hospitals, and, last but not least, obtaining market approval for Herceptin®

Table 3
System-building activities regarding Herceptin® (1999–2002).

System building for Herceptin® and HER2 testing by the manufacturer	Knowledge diffusion	Market formation	Resource allocation	Creation of legitimacy
Enabling the hospitals to buy the drug directly from the producer		x		
Implementation of Expanded Access Program				x
Meetings with medical specialists and patient organizations	x			
Setting up the Herceptin® website	x			
Partnering with professional public relations company	x			
Sponsoring centers for HER2 testing (Nottingham City Hospital, Glasgow Royal Infirmary and London Royal Marsden Hospital)			x	

(Table 3). These aims were achieved mostly by activities that could be categorized as three system functions: *allocating resources*, *investing heavily in knowledge diffusion*, and trying to gain *legitimacy* for its innovative drug. However, it is important to note that, even though overcoming the regulatory barriers to gain market access for Herceptin® was problematic, during this first period none of the system-building activities *directly* targeted regulatory institutional change; rather, they were directed at normative and cognitive institutions.

4.2. Herceptin® for early-stage breast cancer: Changing institutions

The second period started with a different systemic setting from the first. Knowledge diffusion about Herceptin® had already been accomplished, and medical specialists in the hospitals and patient groups involved in this IS were familiar with this new technology, therefore using the drug had already become routine. The key actors seemed certain that the drug would gain access to the market. Now the main goal was to change the institutional structure through different system-building activities in order to accelerate adoption of the drug (Table 4).

At the American Society of Clinical Oncologist (ASCO) meeting in 2005, research evidence was presented showing that the use of Herceptin® in patients with *early-stage* HER2 breast cancer not only reduces the risk of recurrence but also increases progression-free survival (Piccart-Gebhart et al., 2005; Tuma, 2005). This was the first – and powerful – evidence that Herceptin® could help patients not only at a late stage but also at an early stage of the disease. Around that time, the Department of Health published a policy goal to bring cancer treatment at English hospitals up to a level that was comparable to that at the best hospitals in other European countries by 2010 (Department of Health, 2004) (Table 4).

The patient groups acted rapidly on this promising news, because at that time women at English hospitals with a diagnosis of *early-stage* breast cancer were not commonly tested for HER2 (Pharmaceutical Field, 2008). The group "Fighting for Herceptin" submitted a petition to the Prime Minister Tony Blair to increase the legitimacy of Herceptin® by demanding access to it for the treatment of early-stage breast cancer (Mayor, 2005b) (Table 4). At the time, however, the drug was not yet licensed in Europe for that use, and PCTs were left to decide whether the drug should be prescribed and paid for by local PCTs in individual cases.

Soon after Herceptin® was placed on the political agenda, the Department of Health issued a directive that required all the women with early-stage breast cancer to be tested for HER2 (Dowsett et al., 2007). This had a positive effect on the creation of the market for the drug (Table 4).

It was clear that after Herceptin® entered the market as a treatment for early-stage breast cancer, the demand for HER2 testing in hospitals would increase (Dowsett et al., 2007). As one of the interviewees (Health economist n) described it: "If the company would not pay for the test, it would have to be covered by the NHS," The NHS, however, did not have the resources to pay for yearly tests for HER2 for more than 40,000 patients (Pharmaceutical Field, 2008). Roche took advantage of the NHS's Cancer Networks (Hedgecoe, 2004) to change testing habits and implement wide-scale HER2 testing for early-stage breast cancer. The company hired a healthcare consultant that started a collaboration with all the hospitals in each Cancer Network, supporting them by training staff, extending general funding, donating HER2 diagnostic kits, or all three (Pharmaceutical Field, 2008). As one of the experts interviewed (Pathologist o) said: "Roche was assisting the testing, to make sure it was correct; it did not help them at all if people were put on Herceptin® incorrectly and it certainly did not help anyone if it was all wrong." The goal was to overcome the difficulties presented by the expected increase in demand for HER2 testing (Kanter, 2005). Therefore, Roche invested around £1.5 million in the NHS to implement HER2 testing at hospitals (Kanter, 2005). This kind of resource allocation contributed heavily to changing cognitive institutions regarding HER2 testing in England.

Several cancer charities and patient advocacy groups became allies of Roche in gaining public attention for Herceptin® (Table 4). CancerBackup, a forceful supporter of Herceptin®, has declared publicly that in 2005 it received £29,000 in funding from Roche (Templeton, 2006). That same year, Breast Cancer Care received

Table 4
System building activities regarding Herceptin® (2002–2006).

System building for Herceptin® and HER2 testing	Market formation	Resource allocation	Creation of legitimacy	Institutional change	Guidance of Search
Petition by a group "Fighting for Herceptin"			x		
Policy goal by the The Department of Health to improve cancer treatment in England					x
Directive by The Department of Health to have all early-stage breast cancer patients tested for HER2	x				
Collaboration between Roche and Cancer Networks to support HER2 testing	x				
Collaboration between Roche and cancer charities		x			
Survey about low access to Herceptin® published by CancerBackup			x		
"Dossier of delay" published by CancerBackup			x		
Fly-In events at Westminster organized by Breakthrough Breast Cancer	x				
Report by Karolinska Institute highlighted low access to Herceptin®	x				
Collaboration with opinion leaders to raise awareness about Herceptin®			x		
Demand to change the NICE assessment procedure by high level politicians				x	

£80,000 from Roche (Kelly, 2006). No information is available as to whether it influenced the independence of these organizations.

Unlike drug companies, the charities can lobby publicly for a faster system of approval, which implies regulatory institutional change (Boseley, 2006). Therefore, the breast cancer patient advocacy groups were most vocal in their support for Roche to reach out to a wider public and politicians to gain faster access to Herceptin® (Boseley, 2006), which put additional pressure on the government to grant the drug market access. According to one of the interviewees (Oncologist m): "I have no doubt that they [the charities] have been very significant.... the breast cancer lobby was very very loud.... they made a tremendous effort in terms of public information."

CancerBackup published a survey, conducted by Roche, that highlighted the low access to Herceptin® (Boseley, 2006). It also compiled a "dossier of delay," a list of 12 drugs, including Herceptin®, that needed to be made available for patients via fast-track approval instead of the standard procedure, which could be lengthy (Editorial, 2005) (Table 4). Because breast cancer was an issue of the moment, it also became an interesting topic for politicians so that they could express their support and make it a priority on the public health political agenda in England (Clarke, 2007). Breakthrough Breast Cancer organized a series of events at Westminster that were co-sponsored by Roche (Breakthrough Breast Cancer, 2012) to gain further legitimacy and to address members of Parliament about Herceptin® (Table 4).

In addition to working with patient advocacy groups, Roche also sponsored academic socioeconomic studies. In 2005 Karolinska Institute in Sweden published a report funded by a grant from Roche that pointed out the low access to personalized cancer drugs throughout the UK (Wilking and Jönsson, 2005) (Table 4). Roche also indirectly targeted individuals who enjoyed high regard in society to gain their support and raise awareness of Herceptin® (Boseley, 2006).

In September 2005, the NICE issued a press release that was likely a reaction to the enormous political and public pressure created by Roche's allies—that is, patients and advocacy groups. The agency describes ongoing discussions over a regulatory institutional change to allow faster appraisal of important new drugs (NICE, 2005a). A month later, after substantial pressure from patients and charities, the health secretary issued a press release saying: "I want the licence for Herceptin® to be granted as quickly as possible, without compromising people's safety, and to be available within weeks of the (European) licence being given" (Department of Health, 2005). The pressure had reached the point that she also demanded a change in the formal institutions: "and I have asked the NICE to start on a fast-track appraisal of the use of Herceptin in parallel with the licensing process so that they can issue their guidelines to the NHS on Herceptin within weeks of the licence being given" (Hewitt, 2005).

Prime Minister Tony Blair stood behind his colleagues in these exceptional circumstances by making a statement few weeks later about Herceptin®, suggesting that all PCTs should "go ahead and allow people to use it" (BBC, 2005) (Table 4).

Under enormous pressure from politicians and the media, on November 3, 2005, the change in regulatory institutions took place as the NICE announced the launching of a fast-track assessment process called "Single Technology Appraisal" (STA) for assessing Herceptin® and other potentially life-saving drugs to "enable single new drugs, and existing drugs with new indications to be rapidly assessed" (NICE, 2005b). This rapid assessment procedure created an opportunity for the NICE to issue its guidance up to six months earlier than before (NICE, 2005b).

In February 2006, Roche submitted its Herceptin® application to the EMA (Roche, 2006a). On April 28, 2006, the EMA announced its approval of the drug (EMA, 2006), only 10 weeks after the application had been submitted (Dyer, 2006), and, at the end of May, the European Commission officially authorized the use of Herceptin® in the treatment of early-stage breast cancer (Roche, 2006b) (Fig. 1).

Next, Roche submitted relevant Herceptin® data to the NICE (Roche, 2006c). The STA of Herceptin® did not start after the licensing decision but took place in parallel with the EMA process. On June 9, the NICE published a positive draft guidance for Herceptin® (NICE, 2006)—having done so in record time, just two weeks after the EU wide license had been granted.

This was an exceptional result, as no other cancer drug had previously profited from this new simplified and fast-track approval system, and Herceptin® became the first cancer drug ever assessed using the STA procedure at the NICE. This long-awaited decision gave oncologists the legitimacy to start prescribing the drug, confident of coverage by the NHS.

5. Theoretical implications

The purpose of this article is to provide insights in different system-building patterns that support institutional change by a powerful actor in a TIS.

This work allows us to understand how actors overcame difficulties involved in introducing a new technology in a highly institutionalized health-care environment. Our empirical evidence indicates that the activities of a key system builder can have a major impact on a TIS with respect to institutional structures and overall system dynamics. In order to better understand this impact on system building regarding Herceptin®, let us take a closer analytical look at our findings. We start with answering our first research question:

Research Question 1: Which system-building activities did the key actors undertake to facilitate market approval and diffusion of their technologies?

At the beginning, during the habitualization step, knowledge diffusion was underdeveloped and general knowledge about Herceptin® and its usefulness was low among patient groups and the medical community at hospitals. Because the drug lacked regulatory approval, it also had no legitimate users: medical specialists could not prescribe it for breast cancer patients. As we illustrated in Fig. 2, Roche focused its system-building activities on establishing cognitive and normative institutions in order to gain preliminary acceptance for its technology and to increase the level of knowledge among the key adopters (i.e., patients and hospitals), which would thereafter help to facilitate the increase in demand for the drug. The company also invested in knowledge diffusion at hospitals by setting up one-on-one meetings with oncologists, organizing events to raise awareness of Herceptin®, publishing the results of the clinical trials in professional journals, and even hiring a professional public relations agency to facilitate many of these processes. As a consequence, knowledge diffusion among the medical community at hospitals increased rapidly. This changed the role of hospitals from being merely service providers to being collaboration partners with Roche: thanks to active dialog between breast cancer patients and oncologists about the improved treatment options that Herceptin could offer, hospitals carried out an enormous amount of knowledge diffusion among patients and contributed to legitimization of the drug.

After the diffusion of knowledge improved and legitimacy was gained within the medical community at hospitals, the willingness to employ this new technology lagged because of the lack of access to it. The investment in knowledge diffusion had been successful: demand by medical specialists and patient communities was created (cognitive institution). However, further system-building processes had to take place to satisfy this demand (see Fig. 3). Before 2002, creation of the market lagged behind, because the drug had neither approval nor funding. Roche overcame this situation by starting with specific system-building activities that required vast

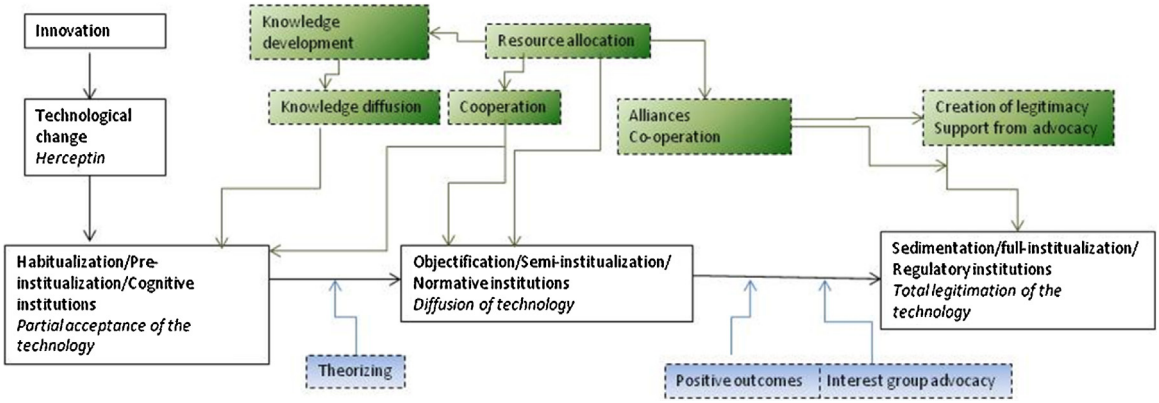

Fig. 2. Overview of the key processes involved in institutional change in the Herceptin® TIS (adapted from Scott, 2001; Tolbert and Zucker, 1996).Different system-building processes based on the current case (in green) are illustrated in the figure. The arrows indicate how these different system-building activities influence the institutional changes proposed by Scott (2001) and Tolbert and Zucker (1996). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

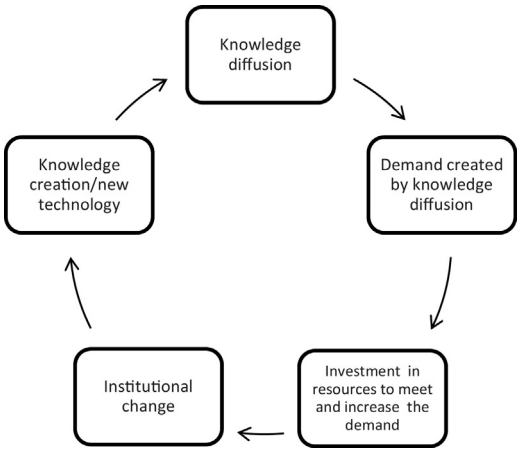

Fig. 3. The interdependence of key processes involved in the Herceptin® TIS based on the empirical findings in this study. At the beginning, knowledge diffusion was needed in order to increase knowledge in the community, which leads to an increase in demand. Thereafter, additional resources are needed to satisfy the increased demand, which eventually leads to institutional change. Changed institutions are in favor of new technology, which encourages further knowledge creation.

resources. Two incentives (the Extended Access Program and the potential for hospitals to purchase the drug directly from the manufacturer) made the drug available for a number of patients. Here, again, hospitals were Roche's key partners in creating a market for its drug. The hospitals served as further hubs of knowledge and market creation for Herceptin® by paying for the drug out of their own budgets and offering their infrastructure and medical specialists, thus enabling access to the drug for breast cancer patients. The role of hospitals is even more significant, as the diffusion of the Herceptin® depends heavily on the availability of appropriate diagnostic tests. Roche collaborated with three hospitals to set up HER2 testing centers to provide free tests to all laboratories in the country.

When the technology was first launched on the market, Roche engaged in a number of different system-building activities targeted at knowledge creation and diffusion among the main users of the technology (i.e., hospitals), which thereafter became important allies of the company in further market creation for the technology. These activities also involved the allocation of enormous resources by the key entrepreneur, which highlights the importance of resources not only in developing technologies but also in their later diffusion.

The answer to Research Question 2 helps us to understand how the institutional changes were manifested in the Herceptin® TIS.

Research Question 2: How did the key actors deal with institutions that influenced their technology, and which strategies did they implement together with other stakeholders to shape the institutional structures in the interest of their goal?

Because pharmaceuticals have one of the world's most highly institutionalized markets, we expected that institutions would have a big role in market formation in the Herceptin® TIS. We therefore included the concepts involving institutional change in our analysis so that we could identify – in addition to general system building – more institutional entrepreneur-type activities and how the actors dealt with institutions that were influenced their technology.

When we analyzed our empirical findings, it became apparent that the entire system-building process involved in the Herceptin® TIS is strongly related to institutional change, because the key actor invested massive resources in different processes to change established institutions (Fig. 2).

While preparing for Herceptin® to receive approval as a treatment for early-stage breast cancer, Roche had no legitimacy that it could use to directly support the adoption of the technology (e.g., gain rapid access to the market) despite its strong interest in institutional change. Therefore additional collaborations emerged (as shown in Fig. 2). The coalition of different actors with various interests and backgrounds did not emerge spontaneously to advocate for the rapid adoption of Herceptin®. Roche supported various actors in addition to hospitals, which shared a common interest with the company in bringing the drug to market more rapidly by changing regulatory institutions (i.e., the NICE's assessment procedure). Obviously, the ability to gain allies depends heavily on the social position and financial resources of the entrepreneur. Therefore cooperation is desired with different actors, depending on the precise type of institutional change it intends to pursue (Perkmann and Spicer, 2007). Previous literature indicates that the success of institutional entrepreneurs depends heavily on their various resources and the management of those resources in order to carry out institutional change (Fligstein, 1997). The powerful institutional entrepreneur started supporting HER2 testing facilities for the treatment of early-stage breast cancer, which would enable rapid adoption of the drug after it received approval and access to the market. Roche also sponsored academic studies that underlined problems with the existing cancer therapies and supported patient advocacy groups and other organizations, which in turn influenced the media. The company also helped patients inform the public about the restricted access to Herceptin® and pressured politicians

to get involved in the process. All these strategic activities, initiated by Roche but carried out by its allies, eventually led to institutional change: implementation of the fast-track drug approval process by the NICE (see Fig. 2).

Roche was a very powerful actor that tried to influence the national regulatory environment almost singlehandedly. However, it also became apparent that even a very powerful institutional entrepreneur must depend on other actors in an innovation system that play a different role in society and are better positioned to drive the change needed. We highlight the role of hospitals as key adaptors, whose willingness to adopt this novel biomedical technology played a key role in the initial creation of the market for Roche's drug. The knowledge diffusion among medical specialists at hospitals about the drug and the testing was the main requirement; on top of this, a change in treatment and diagnostic routines (cognitive institutions) served as a first step in further system building. Therefore this case study shows the key importance of changing the routines of key adopters in favor of the new technology. The study also illustrates that institutional entrepreneurs cannot always change the institutions directly and have to dedicate their resources strategically, rather than allocating them for other system-building activities that do not directly target institutions. We conclude that the company could not have done everything by itself and still had to put other actors in place, collaborate, and build connections and networks, in order to build up the pressure that culminated in institutional change. Even though it had many allies and they played their role, they were initially put in this position by an institutional entrepreneur that needed efforts by others and greatly influenced their activities.

From the perspective of institutional entrepreneurship, none of the resource-intensive system-building activities highlighted above can be categorized as institutional change. However, even though they did not explicitly target institutional change, they were crucial in the adoption of the technology and served as preparatory steps for achieving critical mass and gaining momentum that proved to be critical in realizing institutional change. Therefore, understanding institutional change in relation to innovation benefits from insights in other forms of system building that do not explicitly target institutional change.

6. Conclusions

This study contributes to our understanding of actor strategies involved in system building in a technological innovation system (TIS) and, more specifically, in *institutional change* that creates a more favorable environment for the adoption of an emerging biomedical technology.

It analyzed how system builders deal with institutions that are not beneficial to their technology and activities they undertake in order to shape the institutional structures that are important for the innovation system.

The empirical focus was on the pharmaceutical company Roche, which acted as a system builder and institutional entrepreneur in building a new TIS in England: the personalized medicine to treat breast cancer Herceptin®.

The paper shows that a single powerful company, which acts as a system builder and an institutional entrepreneur, can have a major impact on system dynamics in general and can be of key importance in creating and changing institutions. While facing the systemic hurdles that are not beneficial to its technology, the entrepreneur can apply different system-building approaches (e.g., resource allocation, knowledge diffusion, creation of legitimacy, market creation) alone or in collaboration with other involved stakeholders that all establish a groundwork, eventually leading to institutional change in order to strategically shape and improve the performance of the TIS in a highly regulated institutional environment. Indeed, the activities of Roche and its allies led to two major institutional changes: the implementation of regular HER2 testing as a cognitive institution and a change in regulatory institutions and the STA procedure, which significantly improved market access to personalized cancer drugs, such as Herceptin®.

This paper focused on a very resourceful entrepreneur and how it engaged in system-building activities in which demand for the technology was well articulated: breast cancer is a disease with one of the world's most powerful patient lobbies. Because Herceptin® was the first drug of its kind in clinical practice, a great deal of hope was associated with it among the hospital community and patient groups. In this respect, it is a unique case, as the timing and the push for market creation by a powerful manufacturer, combined with equally strong technology pull by main adopters, played out very well for overall system building in the TIS. This eventually led to institutional change. In this case, the preconditions for successful system building were exceptionally good and should, thus, not be seen as representative of the conditions that exist for other new medical technologies for different diseases backed by less powerful manufacturers or for diseases with a lower "social profile" than breast cancer.

This work also contributes to the literature on TIS. We demonstrate that, even though institutions are central in the structure of innovation systems, their role in the key processes could be emphasized more to clarify the dynamics of TIS. Therefore a functional analysis should pay more attention to processes related to "institutional change," especially in highly regulated markets. One possible avenue for future research is for the TIS community to focus more on "institutional change," so that it becomes more central to future development of the theory of TIS.

The stronger focus on institutional change in TIS functional analysis brings us also closer to institutional entrepreneurship literature, which is explicitly dedicated to studying the activities of actors who have an interest in specific institutional arrangements.

Second, by studying a highly regulated market, we illustrate that insights from different system-building activities (e.g., knowledge diffusion, resource allocation, the creation of legitimacy, the formation of networks) that help to create a critical mass are key to institutional change in a TIS. Therefore, in order to better understand institutional change, we also need to understand which system-building activities act as a groundwork for it. The activities that do not target institutional change could be researched further in future research. Also, we demonstrate that even a very powerful institutional entrepreneur cannot carry out institutional change by itself, and therefore other actors must be included to complete the tasks that the institutional entrepreneur cannot carry out on its own.

Our work also has social relevance for policy initiatives that support the development of emerging technologies. We have learned that user practices and routines in hospitals change gradually and are characterized by a great deal of inertia. In addition to being service providers in health innovation systems and participating in clinical trials in drug development, hospitals play a key role in creating legitimacy for new biomedical technologies that contribute to overall adoption in the health-care system. Massive resources are needed from private companies not just to develop the technology but also to ensure that medical specialists (both oncologists and pathologists) in hospitals are familiar with the new technologies and have the competence to use it. Under these conditions, in which new business models are required to develop drugs, which may call for new kinds of diagnostic testing and which differ from established technologies, policy makers may find it challenging to adapt institutions and to develop optimal policies that are appropriate to the needs of the modern health-care system. We therefore think that a flexible approach regarding regulation would be beneficial. This would support innovation without compromising the

efficiency and safety of the drugs. Until now, the TIS framework has not been fully able to explain institutional change and the role it plays in market formation in a highly regulated environment. Emphasizing institutional change in the TIS functional analysis could facilitate the development of a TIS framework that can meet the needs of policy makers in developing optimal policy strategies for emerging technologies to a greater degree.

As an explorative case study of a single firm, this work clearly has limitations regarding the generalizability of results. This work is about a specific TIS in one country, in which we use institutional change literature to draw more insights regarding system-building dynamics and mechanisms. Future research should explore cases in areas with less regulation to determine whether any of our observations are applicable in settings other than biomedical innovation and whether different strategies emerge for an institutional entrepreneur with fewer resources. Moreover, the role of hospitals has been downplayed until now in TIS studies. Future research should further investigate hospitals to gain a better understanding of their role in the adoption of personalized medicine and the associated diagnostic testing. Future studies could also shed light on how the adoption of personalized medicine has been handled in other countries and whether any system-building patterns emerge that could be used in further theory building by the academic community.

References

Abelson, J., Collins, P.A., 2009. Media hyping and the Herceptin Access Story: an analysis of Canadian and UK newspaper coverage. Healthcare Policy 4 (3), 113–128.

BBC News, 2005. Blair gives Cancer Drug Approval. BBC News 3rd November 2005.

Beckert, J., 1999. Agency, entrepreneurs, and institutional change: the role of strategic choice and institutionalized practices in organizations. Organiz. Stud. 20 (5), 777–799.

Bergek, A., Jacobsson, S., Carlsson, B., Lindmark, S., Rickne, A., 2008. Analyzing the functional dynamics of technological innovation systems: a scheme of analysis. Res. Policy 37 (3), 407–429.

Boseley, S., 2006. The selling of a wonder drug. The Guardian 29th March, 2006.

Breakthrough Breast Cancer, 2012. Financial Support to Breakthrough Breast Cancer from the Pharmaceutical Industry 2004–2012. Breakthrough Breast Cancer, London.

Burstein, H.J., 2005. The distinctive nature of HER2—positive breast cancers. N. Engl. J. Med. 353 (16), 1652–1654.

Carlsson, B., Jacobsson, S., Holmén, M., Rickne, A., 2002. Innovation systems: analytical and methodological issues. Res. Policy 31 (2), 233–245.

Carlsson, B., Stankiewicz, R., 1991. On the nature, function and composition of technological systems. Evol. Econ. 1 (2), 93–118.

Cetindamar, D., Laage-Hellmann, J., 2002. Micro-level analysis of firms in the biomedical/biotechnology system in Ohio and Sweden. In: Carlsson, B. (Ed.), Technological Systems in the Bio Industries. Kluwer Academic Publishers, Boston, London and Dordrecht, pp. 81–122.

Christensen, C.M., 2000. The Innovator's Dilemma. Harper Business, New York, NY.

Clarke, B., 2007. The Fight of My Life. Hodder & Stoughton, Great Britain.

Department of Health, 2004. Tackling Cancer in England: Saving More Lives. The Stationery Office Limited HC 166, London.

Department of Health, 2005. Hewitt fast-tracks cancer drug to save 1000 lives. Press Release 2nd October 2005.

DiMaggio, P., 1988. Interest and agency in institutional theory. In: Zucker, L. (Ed.), Institutional Patterns and Organizations. Ballinger Publishing Company, Cambridge, MA, pp. 3–21.

Dolfsma, W., Verburg, R., 2005. Bridging Structure and Agency: Processes of Institutional Change. Erasmus Research Institute of Management, Rotterdam.

Dowsett, M., Hanby, A.M., Laing, R., Walker, R., 2007. HER2 testing in the UK: consensus from a national consultation. J. Clin. Pathol. 60 (6), 685–689.

Dyer, C., 2006. Trastuzumab wins backing of European drug regulator. Br. Med. J. 332 (7549), 1050.

Editorial, 2005. Herceptin and early breast cancer: a moment of caution. Lancet 366 (9498), 1673.

Edquist, C., 1997. Systems of innovation approaches—their emergence and characteristics. In: Edquist, C. (Ed.), Systems of Innovation—Technologies, Institutions and Organizations. Pinter Publishers/Cassell Academic, London, p. 35.

Edquist, C., 2004. Reflections on the systems of innovation approach. Sci. Publ. Policy 31 (6), 485–489.

Edquist, C., 2005. Systems of innovation: perspectives and challenges. In: Fagerberg, J., Mowery, D.C., Nelson, R.R. (Eds.), The Oxford Handbook of Innovation. Oxford University Press, New York, NY, pp. 181–208.

Ellis, I.O., Dowsett, M., Bartlett, J., Walker, R., Cooke, T., Gullick, W., Gusterson, B., Mallon, E., Lee, P.B., 2000. Recommendations for HER2 testing in the UK. J. Clin. Pathol. 53 (12), 890–892.

EMA, 2006. European Medicines Agency: committee for medicinal products for human use 24–27 April 2006. Press Release 28th April 2006.

Enzing, C., van den Akker-van Marle, E., Detmar, S., et al., 2006. Case studies and cost-benefit analysis of HER2 and TPMT in four EU member states. *Part* 2 of an ESTO *study* on pharmacogenetics and pharmacogenomics: state of the art and social and economic impacts. In: Technical Report EUR 22214. European Commission, Luxembourg.

Farla, J., Markard, J., Raven, R., Coenen, L., 2012. Sustainability transitions in the making: a closer look at actors, strategies and resources. Technol. Forecast. Soc. Change 79 (6), 991–998.

Fligstein, N., 1997. Social skill and institutional theory. Am. Behav. Sci. 40 (4), 397–405.

Freeman, C., 1987. Technology Policy and Economic Performance: Lessons from Japan. Pinter Publishers, London.

Garud, R., Karnøe, P., 2001. Path creation as a process of mindful deviation. In: Garud, R., Karnøe, P. (Eds.), Path Dependence and Creation. Lawrence Erlbaum Associates, Mahwah, pp. 1–41.

Hedgecoe, A.M., 2004. The Politics of Personalised Medicine—Pharmacogenetics in the Clinic. Cambridge University Press, Cambridge.

Hekkert, M.P., Suurs, R.A.A., Negro, S.O., Kuhlmann, S., Smits, R.E.H.M., 2007. Functions of innovation systems: a new approach for analysing technological change. Technol. Forecast. Soc. Change 74 (4), 413–432.

Hellsmark, H., 2010. Unfolding of the Formative Phase of Gasified Biomass in the European Union: The Role of System Builders in Releasing the Potential of Second-Generation Transportation Fuels from Biomass. Department of Energy and Environment, Chalmers University of Technology, Göteborg (Ph.D. Thesis.).

Hellsmark, H., Jacobsson, S., 2009. Opportunities for and limits to academics system builders-the case of realizing the potential of gasified biomass in Austria. Energy Policy 37 (12), 5597–5611.

Hewitt, P., 2005. Speech Given at the Breakthrough Breast Cancer Fly-in 25th October 2005.

House of Commons, 2005. Tackling Cancer in England: Saving more Lives. Second Report of Session 2004–2005. The Stationery Office Limited HC 166, London.

Hughes, T.P., 1979. The electrification of America: the system builders. Technol. Culture 20 (1), 124–161.

Hughes, T.P., 1987. The evolution of large technological systems. In: Bijker, W., Hughes, T.P., Pinch, T. (Eds.), The Social Construction of Technological Systems. MIT Press, Cambridge, MA, pp. 51–82.

Jacobsson, S., Bergek, A., 2004. Transforming the energy sector: the evolution of technological systems in renewable energy technology. Ind. Corp. Change 13 (5), 815–849.

Kanter, J., 2005. Roche Step is Positive Signal on Herceptin. New York Times 9th December 2005.

Kelly, A., 2006. Feature: Big Bucks from Big Pharma. Third Sector 20th September 2006.

Kent, A., 2000. Not another magic bullet. Br. Med. J. 321 (7261), 644.

Kroese, M., Zimmern, R.L., Pinder, S.E., 2007. HER2 status in breast cancer—an example of pharmacogenetic testing. J. R. Soc. Med. 100 (7), 326–329.

Lawrence, T., Suddaby, R., 2006. Institutions and institutional work. In: Clegg, S.R., Hardy, C., Lawrence, T.B., et al. (Eds.), The Sage Handbook of Organization Studies. , second ed. Sage Publications, London, pp. 215–254.

Lawrence, T., Suddaby, R., Leca, B., 2011. Institutional work: refocusing institutional studies of organization. J. Manage. Inquiry 20 (1), 52–58.

Leca, B., Battilana, J., Boxenbaum, E., 2008. Agency and Institutions: A Review of Institutional Entrepreneurship. Harvard Business School Press, Boston, MA.

Lepper, J., 2001. Pharmaceutical giant Roche has appointed Ketchum PR to handle the global brief for its HIV products. In: PR Week 23rd February 2001.

Lundvall, B.-Å. (Ed.), 1992. National Systems of Innovation: Towards a Theory of Innovation and Interactive Learning. Pinter Publishers, London.

Maguire, S., Hardy, C., Lawrence, T.B., 2004. Institutional entrepreneurship in emerging fields: HIV/AIDS treatment advocacy in Canada. Acad. Manage. J. 47 (5), 657–679.

Markard, J., Truffer, B., 2008a. Actor-oriented analysis of innovation systems: exploring micro-meso level linkages in the case of stationary fuel cells. Technol. Anal. Strategic Manage. 20 (4), 443–464.

Markard, J., Truffer, B., 2008b. Technological innovation systems and the multi-level perspective: towards an integrated framework. Res. Policy 37 (4), 596–615.

Marsh, B., 2001. Women Lose Out in Breast Cancer Lottery Daily Mail 24th July 2001.

Mayor, S., 2005a. Primary care trust reverses decision not to fund trastuzumab. Br. Med. J. 331 (7526), 1162.

Mayor, S., 2005b. NICE to issue faster guidance on use of drugs by NHS. Br. Med. J. 331 (7525), 1101.

Ménard, S., Fortis, S., Castiglioni, F., Agresti, R., Balsari, A., 2001. HER2 as a prognostic factor in breast cancer. Oncology 61 (2), 67–72.

Metcalfe, J.S., James, A., Mina, A., 2005. Emergent innovation systems and the delivery of clinical services: the case of intra-ocular lenses. Res. Policy 34 (9), 1283–1304.

Miles, D., Wroath, A., 2001. UK Expanded Access Programme (EAP): Herceptin (trastuzumab) treatment for women with HER2 positive Metastatic Breast Cancer (MBC) 7th Nottingham International Breast Cancer Conference. Eur. J. Cancer 37 (5), 3.

Morlacchi, P., Nelson, R.P., 2011. How medical practice evolves: learning to treat failing hearts with an implantable device. Res. Policy 40 (4), 511–525.
Musiolik, J., 2012. Innovation System-Building: on the Role of Actors, Networks and Resources. The Case of Stationary Fuel Cells in Germany. Innovation Studies Group, Utrecht University, Utrecht (Ph.D. Thesis).
Musiolik, J., Markard, J., 2011. Creating and shaping innovation systems: formal networks in the innovation system for stationary fuel cells in Germany. Energy Policy 39 (4), 1909–1922.
Musiolik, J., Markard, J., Hekkert, M.P., 2012. Networks and network resources in technological innovation systems: towards a conceptual framework for system building. Technol. Forecast. Soc. Change 79 (6), 1032–1048.
Naubahar, S., 2006. Emergence and development of the National Innovation Systems concept. Res. Policy 35 (5), 745–766.
Negro, S.O., Hekkert, M.P., Smits, R.E.H.M., 2007. Explaining the failure of the Dutch innovation system for biomass digestion—a functional analysis. Energy Policy 35 (2), 925–938.
Nelson, R.R., Buterbaugh, K., Perl, M., Gelijns, A., 2011. How medical know-how progresses. Res. Policy 40 (10), 1339–1344.
Netzer, T., 2006. European Union centralised procedure for marketing authorisation of oncology drugs: an in-depth review of its efficiency. Eur. J. Cancer 42 (4), 446–455.
NICE, 2002. Guidance on the use of trastuzumab for the treatment of advanced breast cancer. In: NICE Technology Appraisal Guidance 34. NICE, London.
NICE, 2005a. NICE plans faster drugs guidance for the NHS. Press Release 23rd September 2005.
NICE, 2005b. NICE to issue faster drugs guidance for the NHS. Press Release 3rd November 2005.
NICE, 2006. NICE issues draft guidance on trastuzumab (Herceptin) for early breast cancer. Press Release 9th June 2006.
North, D.C., 1994. Economic performance through time. Am. Econ. Rev. 84 (3), 359–368.
Paul, J.E., Trueman, P., 2001. Fourth hurdle reviews NICE, and database applications. Pharmacoepidemiol. Drug Saf. 10 (5), 429–438.
Perkmann, M., Spicer, A., 2007. Healing the scars of history: projects, skills and field strategies in institutional entrepreneurship. Org. Stud. 27 (7), 1101–1122.
Pharmaceutical Field, 2008. Putting patients first. Pharmaceutical Field UK June 2008.
Piccart-Gebhart, M.J., Procter, M., Leyland-Jones, B., et al., 2005. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N. Engl. J. Med. 353 (16), 1659–1672.
Roche, 2006a. Roche files Herceptin for early-stage HER2-positive breast cancer with European Authorities. Press Release 17th February 2006.
Roche, 2006b. Herceptin approved in Europe for early use in HER2-positive breast cancer. Press Release 24th May 2006.
Roche, 2006c. Herceptin® (trastuzumab) NICE Submission: achieving clinical excellence in the adjuvant treatment of HER-2 positive breast cancer. Roche Submission to the NICE 7th February 2006.
Scott, W.R., 2001. Institutions and Organizations. Sage Publications, Thousand Oaks.
Slamon, D.J., Leyland-Jones, B., Shak, S., et al., 2001. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N. Engl. J. Med. 344 (11), 783–792.
Suurs, R.A.A., Hekkert, M.P., Smits, R.E.H.M., 2009. Understanding the build-up of a technological innovation system around hydrogen and fuel cell technologies. Int. J. Hydrogen Energy 34 (24), 9639–9654.
Swan, J., Goussevskaia, A., Newell, S., et al., 2007. Modes of organizing biomedical innovation in the UK and US and the role of integrative and relational capabilities. Res. Policy 36 (4), 529–547.
Templeton, S.K., 2006. Health charities get "covert" aid from drug firms. The Sunday Times, 3rd December 2006.
Tolbert, P.S., Zucker, L.G., 1996. The institutionalization of institutional theory. In: Clegg, S., Hardy, C., Nord, W.R. (Eds.), Handbook of Organization Studies. Sage Publications, London, pp. 175–191.
Truffer, B., Markard, J., Binz, C., Jacobsson, S., 2012. Energy innovation systems: structure of an emerging scholarly field and its future research directions. In: Strategic Research Alliance for Energy Innovation Systems and their Dynamics. Denmark in Global Competition. Lyngby, DK.
Tuma, R.S., 2005. Trastuzumab trials steal show at ASCO meeting. J. Nat. Cancer Inst. 97 (12), 870–871.
Van Alphen, K., Hekkert, M.P., Turkenburg, W.C., 2010. Accelerating the deployment of carbon capture and storage technologies by strengthening the innovation system. Int. J. Greenhouse Gas Control 4 (2), 396–409.
Van de Ven, A.H., 1993. The Development of an infrastructure for entrepreneurship. J. Bus. Venturing 8 (3), 211–230.
Weik, E., 2011. Institutional entrepreneurship and agency. J. Theory Soc. Behav. 41 (4), 466–481.
Wilking, N., Jönsson, B., 2005. A Pan-European Comparison Regarding Patient Access to Cancer Drugs. Karolinska Institutet, Stockholm.
Wilking, N., Jönsson, B., Högberg, D., 2009. Comparator Report on Patient Access to Cancer Drugs in Europe. Karolinska Institutet, Stockholm School of Economics, Stockholm.
Windrum, P., García-Goñi, M., 2008. A neo-Schumpeterian model of health services innovation. Res. Policy 37 (4), 649–672.