Policy challenges of user involvement. Why a celiac disease pill is conceived but not embraced?

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Abstract

The failure to involve users in research and development (R&D) processes continues to be a major reason for unsuccessful R&D. This failure can be understood by focusing on regimes (comprising heuristics, rules and routines) that orient and coordinate the activities of actors with regard to innovations. We describe the case of a pill for celiac disease patients and show that the conception and development of the pill was shaped by a *technological regime* that provides R&D actors with rules to routinely acquire relevant information about users and the market. Reserved patient organisations did not play a role. To understand the reserved reception of the pill, we elaborate the concept of a use regime. The reservations are understood as an expression of an existing diet-based *use regime* that guides the way the target group of the pill is currently dealing with celiac disease. The lack of interaction between the R&D actors in the consortium and the patient organisation appears to be a manifestation of the lack of alignment between the technological and use regimes. Based the regime literature, finally, three scenarios for the future development of the pill are discussed.

Keywords: Use regime, user involvement, technological regime, innovation, celiac disease

1 Introduction

There are many good reasons to involve users in innovation processes (Nahuis et al., 2012; Smits and den Hertog, 2007). Enterprises would be better equipped to anticipate capabilities, demands and concerns that are present among potential users of the technology (Akrich, 1995; Williams et al., 2005). They would be able to improve their product portfolio and competitive strength by organising feedback from users to learn about effects of prolonged use of technology (Rosenberg, 1982). They could improve the learning capacity of the social networks

they are part of, by supporting the build up of an infrastructure for interaction with users (Lundvall, 1988). They could improve societal acceptance by facilitating processes of integration and embedding of new technology (Fleck, 1988; Rip et al., 1995; Silverstone and Hirsch, 1992). And they could better respond to democratic values considering that users often bear the consequences of social orders designed into technological artefacts (Sclove, 1995; Winner, 1986).

Paradoxically, the failure to involve users in research and development (R&D) processes continues to be a major reason for unsuccessful R&D. Since the 1970s, a multitude of studies have shown that difficulty in dealing with use and user-related issues in design account for the majority of failures (Hyysalo, 2009). While the merits of user involvement are clear, there seem to be a lot of barriers to effectively organise it. In his endeavour to explain this producer-user paradox, Hyysalo (2009) reviews three different frameworks on socio-technical learning: (i) the "learning by doing/using/interacting" framework, (ii) the "social learning in technological innovation" framework, and (iii) an eclectic micro level framework applied to a large set of Finnish studies of new health technology. Each of these frameworks more or less broadly focuses on learning and the conditions under which this can take place.

We contribute to this literature by adding and discussing a fourth framework. This framework focuses on *rules and routines* that orient and coordinate the activities of actors with regard to innovations. When rules are shared in communities of practice, they constitute a regime. We distinguish between *technological* and *use regimes* and show how this distinction helps interpreting a case study of a patient organisation that is involved in a R&D consortium, but nevertheless only plays a marginal part. The patient organisation has several reservations about the development path being taken within the consortium. Our claim is that the lack of interaction between the R&D actors in the consortium and the patient organisation is a manifestation of the lack of alignment between the technological and use regimes respectively.

This claim can be divided in two propositions that we subsequently discuss in this paper. The first is that the technological regime provides R&D actors with rules to routinely acquire relevant information about users and the market. If this information suffices, then there is no perceived need to involve representatives of patients in deliberations about the proper course of action. We describe how the technological regime coordinates the conception and development of a pill for celiac disease patients regardless of the reservations of the patient organisation.

In the second part, the reserved reception of the pill is understood against the background of an existing diet-based use regime that guides the way the target group of the pill is currently dealing with celiac disease. There appear to be tensions between the technological and use regime precisely where alignment would be required. Accordingly, the second proposition is that 'incumbent users' develop strategies to counteract the emergence of a technological regime that does not fit, or even threatens, the incumbent use regime.

In spite of the lack of cooperation from the patient organisation and the improbability of a shift in the use regime, R&D actors continue spending efforts in the development of a celiac pill. In the discussion we therefore shortly speculate on three different scenarios in which the pill nevertheless may find its way to the market.

2 Technological regimes

Scientists and engineers deal with uncertainties in R&D by employing rules and heuristics to identify and screen promising projects and to decide when to take which steps. Confronted with multiple possibilities and unclear demand characteristics, some guidance is essential. A good heuristic may be satisfactory, because it splits complex interrelated problems into parts and specifies certain divisions of labour as to who deals with what part. Heuristics also provide scientists with proximate targets, particular cues and clues, and various rules of thumb (Nelson and Winter, 1977).

Heuristics are central to both the concept of technological regime and technological paradigm. Technological regime refers to a "sense of potential, of constraints, and of not yet exploited opportunities [which] focuses the attention of engineers on certain directions in which progress is possible, and provides strong guidance as to the tactics likely to be fruitful for probing in that direction" (Nelson and Winter, 1977, p.57). Focus and guidance are provided by heuristics, which apply to engineers exploiting the potential of a particular technology. The concept of technological paradigm describes similar guidance: "A technological paradigm (or research programme) embodies strong prescriptions on the directions of technical change to pursue and those to neglect." (Dosi, 1982, p. 152). These prescriptions are implied in positive and negative heuristics that serve as a base for 'normal' progress in R&D.

Although there are some differences between the concepts of technological regime and technological paradigm (Franssen, 2002), they both aid to explaining regularities in the development of technology with reference to shared rules, routines and heuristics. For the

purpose of this study we discuss four of these heuristics – focusing device, technical model, user representation, and technological roadmap – which are complementary in the sense that they address different kinds of questions (what, how, for-whom, and when). Each of them offers guidelines for R&D decision making.

- A *focusing device* is a heuristic employed in emerging regimes, when researchers are still mainly searching for opportunities (Dosi, 1982; Rosenberg, 1976).They do not search randomly, but limit their search to areas where they expect profits while building on existing competences. As Dosi puts it: "Within a large set of possibilities of directions of development, notionally allowed by 'science', a first level of selection (at least in the overwhelming majority of research activity in the enterprise sector) operates on the basis of rather general questions like: 'Is any practical application conceivable?'; 'is there some possibility of the hypothesized application being marketable?', etc." (Dosi, 1982, p. 152). A focusing device thus pertains to the coupling of a scientific principle to a technological and a market vision.

- Ideas about possible applications are initially quite abstract, but need to become more concrete to raise the interest of potential collaborators, funders and users. Then, a *technical model* becomes an important guiding heuristic (Disco et al., 1992; Van der Meulen, 1998). "Technical models are representations of technical artifacts that define functional dependencies between parts of the artifact and between critical parameters, dependencies between various performances of the artifact and dependencies between the parts, the parameters and performances" (Van der Meulen, 1998, p. 19). Technological models are much more detailed than focusing devices. Furthermore, they break design problems into parts, thus enabling divisions of labor between actors with different technological or marketing capabilities.

- *User representations* are an important input for technical models. Engineers and designers construct representations of users to inform functional requirements for product development. These representations are ideas about who users are, what they want and what they are capable of (Akrich, 1995; Hyysalo, 2006). User representations are constructed by employing representation techniques, such as surveys, user testing, user feedback, personal experience, experts, and comparison to other products (Akrich, 1995). In established regimes user representations are relatively stable and directly inform

technical decisions; in emerging regimes actors tend to rely on familiar representation techniques (too often on their own imagination).

- A fourth heuristic is a *technological roadmap*, which refers to the coordination and organization of the *process* to realize a technical model. A technological roadmap is a framework to develop, organize, and present information about the critical system requirements and performance targets that must be satisfied by certain time frames, in order to identify technologies that need to be developed to meet those targets, and to provide the information needed to make trade-offs among different technology alternatives (Garcia and Bray, 1997; Phaal et al., 2004; Robinson and Propp, 2008). So, unlike the other heuristics, time frames are important elements of a technological roadmap. A technological roadmap is essentially a management heuristic.

Technological regimes refer to the influence of these kinds of heuristics on the activities and interactions of actors involved in technological innovation. Heuristics frame answers to questions like: What are the key problems in a certain target group? How might the technology offer a solution? In what kind of future would that work? What does the realization of this future entail? These questions could, but need not, be asked to users. In case of a stable regime, for example, R&D actors base decisions on routines and experiences with similar products, and they might not want to consult users explicitly. If they can rely on alternative sources of user information, they might choose to ignore reservations uttered by particular real users, like in the early development of a celiac disease pill.

3 Case part 1: The Celiac Disease Consortium

To elucidate why a celiac disease pill initially was conceived but not embraced by celiac disease patients, we followed a single case study approach focusing on the Dutch Celiac Disease Consortium. Data were gathering by interviewing representatives within the consortium (interviews DSM, LUMC, NCV). The starting point of this case study was marked by the start of the Aspergillus Niger project at DSM in 2000, coinciding with the growing interest for application of this enzyme. Furthermore, data were gathered from publications and websites.

Celiac disease (CD), or gluten intolerance, is a chronic autoimmune digestive disorder characterized by the inability to digest a protein called gliadin, a component of gluten, which is present in many foods (wheat, rye, barley). It is an inflammatory disorder of the small intestine

affecting genetically predisposed individuals when they ingest gluten (Maki et al., 2003; Rizzello, 2007). Symptoms include frequent diarrhea, bloating, and weight loss, growth retardation, osteoporosis, miscarriage, low birth weight. It affects as much as 1.0% of the population, about 3 million patients in the western world (CDC, 2011). Patients are condemned to safe foods, because there is no causal therapy available. A lifelong strict gluten free diet remains the only treatment for CD.

In Jan 2004, the Dutch Celiac Disease Consortium has been started, supported by the Netherlands Genomics Initiative, and being a collaboration of university, industry and patient communities. General mission of the consortium was to address the key problems surrounding celiac disease by developing the scientific basis for safer foods and for effective diagnosis, prevention and therapy of CD. Partners involved in the development of and discussion about the celiac disease pill were the Leiden University Medical Center, DSM Food Specialties, and patient organization the Nederlandse Coeliakie Vereniging NCV (CDC, 2011).

3.1 Focusing device

An enzyme that is able to break down gluten started to function as a focusing device. For CD patients gluten proteins are toxic, partly due to the fact that their gastro-intestinal tract is not very effective in breaking down gluten. Gluten is rich in amino acid proline, which complicates protein degradation by the enzymes in the gastro-intestinal tract. As a result, toxic gluten fragments are left behind. The CDC has succeeded in showing that an enzyme, developed and patented by DSM, from the fungal species Apergillus Niger is capable of breaking down these proline-rich proteins efficiently. The enzyme was initially investigated for its potential to improve bitter food products. It turned out that bitterness was related to proline, being also a large constituent of wheat, and so the link with gluten allergy was formed (DSM iv, 2007). Furthermore, this enzyme has also proven to be effective under the conditions present in the stomach. As such, the enzyme can strip gluten of its toxic properties before it causes damage to the small intestine (DSM, LUMC interviews 2007; CMC 2011). The CDC provided proof of principle that degradation of gluten with this so-called AN-PEP (Aspergillus Niger Prolil Endoprotease) enzyme can potentially be used as an oral supplement (pill) to allow gluten consumption by CD patients (DSM iv, 2007). This is tested in a small clinical trial. (DSM, LUMC ivs, 2007). Accordingly, AN-PEP started to serve as a focusing device for exploiting the promise of a celiac disease food additive for incidental use to tolerate gluten in the diet.

3.2 Technical model

In order to test its feasibility, efficacy and safety, the enzyme's functioning in the gastro-intestinal (GI) tract is being modeled. The model is a simplified representation of the functional dependencies between the enzyme and parameters in its working environment. In the rather simplified pre-clinical models, Stepniak et al. (2006) modeled the actual working mechanism of the enzyme in the gastrointestinal (GI) tract *in vitro* (test tube or petri dish experiments in a controlled environment). For example, they treated a gluten suspension with AN-PEP in presence of pepsin at pH 4.5 to mimic the physiological conditions present in the human stomach.

After establishing efficacy and safety, the model was made more complex to better mimic real circumstances. Mitea et al. (2008) designed a dynamic system, the so-called TIM system for ANPEP, having compartments for the stomach, duodenum, jejunum and ileum, thereby closely mimicking digestion in the human gastrointestinal (GI) tract. All parameters in this GI model could be adjusted to simulate average physiological conditions in the gastrointestinal tract of young healthy adults after the intake of a specific meal type. The TIM system acted as a model simulating the lumen of the human gastrointestinal tract, including peristaltics and juices secretion.

However, no other specific enzymes were present in the TIM model. To determine whether other enzymes in the human GI have an additive or interactive effect on proteolysis, more complex *in-vivo* models were required (Mitea et al., 2008). Because no animal/mouse model for celiac disease was available to mimic human celiac disease pathways, the *in-vivo* efficacy of AN-PEP enzyme for gluten degradation had to be addressed in clinical studies involving celiac disease patients in order to study the pathogenesis of CD, the efficacy of compounds, treatment regimens, and the safety of the product. The first *in-vivo* study showed effects in some patients. Currently, a study in Maastricht is running on healthy volunteers, measuring the reduction of toxic gluten epitopes in presence of AN-PEP (Edens, 2011).

In sum, some inventive *in-vitro* technical models have been developed to mimic ANPEP efficacy and to show that it works. Further questions were addressed in *in-vivo* studies using ever more complex models of a whole, living organism and its basic biological functions, including the specific temperature, pH values at which the enzyme shows its activity and interactions between enzymes. Technical models thus functioned as heuristics to understand

dependencies between the enzyme and its working environment, while increasing the complexity of the models enabled step-by-step raising new research questions.

3.3 User representations

Who are the putative users of a celiac disease pill? The prevalence of CD worldwide is increasing. It is estimated to be 0.5 to 2.0% in most of the European countries and the USA (Rewers, 2005). More than 1/4 of the European population have the HLA-DQ2 molecule, which is found in about 90% of the CD patients (Harder, 2003). Most often, CD develops during childhood, but it can also manifest itself later on. The first peak of CD patients is at the age of 1 to 10 years, the second peak around 50 year (LUMC iv, 2007).

One researcher visualises CD patients who feel prisoned by the consequences of their condition. "CD patients follow a strict gluten free protocol at home, having for example a separate corner in which wheat products are forbidden. But when these patients now and then want to dine out or want to drink a bottle of beer, then such a pill would create a possibility." (DSM iv, 2007). This researcher also envisions a more general use of a CD pill. "Many people sometimes have troubles with their stomach or intestine, as gluten is a product difficult to digest. I can imagine that these people benefit by some support, a digestive, when they are not feeling well in their alimentary canal." (DSM iv, 2007). Another researcher observed that many CD patients wanted to participate in the clinical trials with the AN-PEP enzyme, which indicates that they are curious about a pill (LUMC iv, 2007). Recently, DSM did an internet study amongst 2600 CD patients in the UK. The patients indicate as the biggest benefit of an oral ANPEP dietary supplement the *freedom* to eat what they would like and to be able to *socialize* without thinking about their gluten free diet (Edens, 2011).

The main users of a celiac disease pill are thus represented as CD patients who normally following strict gluten free diet at home and sometimes want to follow a less strict food regime by using a CD pill.

3.4 Technological roadmap

Participants in the Celiac Disease Consortium followed a stepwise roadmap, specifying which decisions will be taken when. First, various applications for the AN-PEP enzyme have been explored and patented by DSM. Researchers distinguished a pharmaceutical and a nutritional route (DSM iv, 2997). They furthermore distinguished between administration via a pill or

administration via drinking water, via margarine with a trace of active enzyme included, or via tomato ketchup (DSM iv, 2007). Relatively independent from these routes, *in-vitro* studies in the context of the consortium were proving the efficacy of AN-PEP, and were followed by clinical trials. After the clinical trials, the R&D phase was considered to be succeeded by a marketing phase in which a decision about routes would be taken by the DSM marketing department.[1] When asked about the timing of involvement of patient organization NCV, DSM researchers mentioned that decision (DSM iv, 2007). So, the roadmap split the process in a R&D and a marketing phase, user involvement being something for the latter.

Summarizing: heuristics, such as focusing device, technical model, user representations and technological roadmaps help addressing and answering a set of key questions. Some of these questions could, but need not, be asked to users. In the studied case, there was no perceived need for interaction with the patient organization NCV in the early phase, which partially explains the lack of constructive interaction. Heuristics sufficiently guided R&D actors in their course of action.

But, it seems that NCV was not very interested to be involved either in that early phase.

According to former chairman of the Dutch CD patient organization NCV scientists were leading in the Celiac Disease Consortium, and the NCV had to rely on what the scientists came up with: "We can say: this is attractive and this is not" (Janssen, 2007). According to the consortium members the main role of NCV is "to help the CDC staying focused on the concerns of the patients". The next part turns to the use regime, for a better understanding of this lack of alignment between researchers and users.

4 Use regimes

In the last decade the technological regime concept has been broadened significantly by scholars who use it to understand technological transitions towards sustainability. Whereas the original concept served to explain why certain technological options are selected and developed instead of others, in transition (regime shift) research the regime itself becomes object of

[1] By the time of finishing this article, DSM is planning to launch a dietary supplement product, with AN-PEP being the active ingredient helping to digest gluten in stomach. It will be introduced as a capsule, the first food grade enzyme with proven activity towards degrading toxic gluten epitopes, at the US market late 2012/2013 (Edens, 2011).

analysis. For this purpose, Kemp, Schot & Hoogma (1998) argue that the initial regime concept is too narrow to account for all the interrelated technical, regulatory, cultural, psychological, demand, production, infrastructural, maintenance and environmental factors and barriers. A broader definition "combines rules and beliefs embedded in engineering practices and search heuristics with the rules of the selection environment" (Kemp et al., 1998, p. 182). Engineers' decisions are not only affected by design heuristics, but also by regulations and market-rules. Because the inertia of existing regimes can be attributed to the clustering of rules in different settings, it indeed makes sense to broaden the concept in the context of transition research.[2]

However, to explain a controversy between preferred directions for technological change, as in our case of a celiac disease pill, it remains fruitful to distinguish between rules that apply in different contexts and to different communities. In this respect, Geels (2004) has made an informative contribution to the regime literature. Because actors in different communities share different rules, Geels distinguishes between several kinds of regimes, e.g. technological regimes, policy regimes, science regimes, financial regimes and use regimes. According to this conceptualisation, socio-technical regimes (in transition) do not encompass the entirety of other regimes, but only refer to those rules that are aligned to each other. For example, consumer preferences are rules that apply to consumers, which may be coupled by anticipating them, but which are not part of other regimes. The benefit of this analytical distinction between different regimes is that it creates the possibility to study the (lack of) relations and alignment between them. So, our interest is to develop the notion of a use regime and to study its relation with a technological regime.

How can we define and characterise a use regime? Few studies only mention the concept (Geels, 2004; Kuhlmann and Shapira, 2006; Van den Bergh and Kemp, 2006) and to our knowledge only one study has use regimes as its central object of analysis. Hirschl et al. (2003) assess the potential of a use regime shift from private to collective ownership of washing machines and ski equipment. They define a use regime as "a set of technological, economic, and social elements such as technical infrastructure, attitudes and values, institutional

[2] For an even further broadening of the regime concept in transition research see Holtz et al. (2008).

arrangement, price relations, and symbolic meanings of products that determine consumer behaviour" (Hirschl et al., 2003, p.877).

We emphasise that behaviour is never fully determined. We also emphasise that a regime refers to sets of shared rules. Regime rules are shared in communities of users as distinguished by private rules or idiosyncratic adoption decisions (cf. Franssen, 2002). And, we emphasise that regimes do not cover any 'element' affecting behaviour. Regimes include behavioural regularities such as routines, habits and lifestyles, but only to the extent that rules are incorporated and routine behaviour de facto reproduces these rules (cf. Franssen, 2002). We then define use regimes *as the rule-set or grammar embedded in routines, procedures, artefacts, classifications, and institutions, and shared via infrastructures, that governs people using particular technological artefacts in particular circumstances in particular ways*. Sometimes, rules are deliberately and consciously followed, as in the case of instructions. More often, they are learned and internalised while dealing with them in daily life, like a car driver, who follows rules tacitly. In general, learning to use a technology involves following, sharing, adjusting, and thus producing and reproducing the rules that govern the use of technology. This requires a lot of symbolic work.[3] Use rules emerge only gradually, when innovations are being domesticated and integrated into the worlds of user communities, and hence internalised as routines, skills, habits and lifestyles of people.

Although use regimes consist of rules, they cannot exist without infrastructures for exchange and sharing. Via infrastructures key problems, technologies, problem solving strategies, and meanings associated with technology are exchanged. Physical infrastructures, such as distribution networks for consumer commodities, account for the exchange of rules that are inscribed in or delivered with physical artefacts. Also important are product reviews and online forums on the internet. Communication channels and their associated vocabularies form a condition for sharing rules, experiences and knowledge, which is fundamental for use regimes since users are not organised per se.

[3] See, for example, Silverstone & Hirsch (1992) for a theorisation of the way information and communication technologies are displayed in households, arranged in relation with other objects, and used in order to express values, classifications of gender and age, identifications, and status differences of members of the household as well as their relation with the outside world. The concept of domestication refers to this cultural work involved in learning to use technology.

To elaborate the concept of use regime further we first take a closer look at rules that link particular technologies to particular circumstances and then at rules that suggest how to use and domesticate a particular technology. Thirdly, we turn to the issue of technology assessment and conceptualise the way existing use regime rules influence the reception of new technology.

4.1 Rules for using particular technologies in particular circumstances: key problems and technological interrelatedness

The adoption of technology is not independent of the characteristics of the situation in which it occurs. Use regimes provide rules and guidelines that indicate why a particular technology is appropriate in a particular context or for a particular community of users. We distinguish two related kinds of rules in this respect: key problems and technological interrelatedness.

- Some rules are implied in the phrasing and classification of a *key problem* for which the technology is believed to contribute to a solution. For example, bicycles with equally sized wheels did not become very popular until the unsafe aspect of high-wheeled Ordinary bicycles was seen as the key problem (Pinch and Bijker, 1987). Regardless whether the problem initiated the solution or vice versa, once a link between the two is established, problems are perceived, articulated and communicated to assert collective influence on technology choice. A key problem thus provides an orientation at a preferred solution.
- Rules for employing a particular technology are also embedded in the design of related technology. *Technological interrelatedness* refers to complementarities between different hard- and software parts of a technological system making it difficult to substitute one component without the other. For example, typewriters based on QWERTY key arrangement have been preferred by late 19th century business firms, because of the existence of an interrelated market for training in touch typing based on the same arrangement (David, 1985). Technological interrelatedness is thus an important barrier to shifts in a use regime. A shift from private ownership of ski equipment to rental services, for example, is not likely to happen when most skiers already possess expensive ski boxes for packaging and transporting their own equipment (cf. Hirschl et al, 2003).

Clearly, there may be more rules for using a particular technology in particular circumstances than those embedded in key problems and related technologies. We limit ourselves to rules that help understanding non-alignment in our case study.

4.2 Rules for using technologies in particular ways: script and subscription

A second set of rules that constitute use regimes are related to *how* technologies are used. Technologies can be used in different ways. An automobile may alternatively be used as a stationary power source (Kline and Pinch, 1996), a digital camera as a photocopier and a gramophone turntable as a hip-hop music instrument (Faulkner and Runde, 2009). Such examples support the claim from cultural studies that technologies must be culturally appropriated to become meaningful (Oudshoorn and Pinch, 2008; Sørensen, 2004). We argue that use regimes provide rules for cultural appropriation by discussing two complementary kinds of rules: scripts and subscription.

- To some extent, rules are designed into technologies. For example, the play button on music devices tells users to push it in order to listen to the music. From a background in actor network theory, Akrich (1992) has introduced the metaphor of a film *script* to emphasise how technologies define roles for actors and scenes to play. Her example is that of a photovoltaic lighting kit that was assembled using non-standard plugs to ensure that, when broken, users would return it to authorized maintenance services instead of fixing the fragile equipment themselves. The concept of a script thus reflects a set of rules that define and signify the range of possible ways of handling the technology.

- Rules for using technologies in particular ways are not merely designed into technologies. They also reside in their environments. We conceptualise this with another notion from the vocabulary of actor network theory: *subscription* (Akrich and Latour, 1992). For a script to become a performance, users need to subscribe to it. Subscription is governed by social rules applying to communities of users, which provide guidance to the adoption, implementation and use of a technology. These rules include the rules of the market, information about the product, guidelines in user manuals, and rules for troubleshooting and consulting after-sales services. Apart from rules that come together with products as explicit instructions, rules also emerge when users start experimenting with new technology or adjusting old technology to new situations. An example here is the breakbeat-rule for deejays who started using two gramophone turntables to produce non-

stop music in the 1970s. This rule said that either one of two turntables had to be slowed down manually in case the dance beats of the subsequent songs did not exactly correspond (Faulkner and Runde, 2009).

This second set of rules governs the way in which technologies are used. Script refers to rules inscribed in artifacts and subscription to those that accompany their appropriation. In practice, however, especially when artifacts are routinely used, it is impossible to distinguish between them. Only when the object breaks down, when the same object is (ab)used in different ways, or when different objects are used in similar ways, the discrepancy between inscriptions and subscriptions becomes observable (Akrich and Latour, 1992).

4.3 Rules for assessing new technology

A somewhat different category of rules than those linking users to particular technologies in particular circumstances are rules referring to the assessment of new technology. Specifying these rules is crucial to understand why a potentially beneficial celiac disease pill was conceived but not embraced.

According to the diffusion theory of Rogers (1962) users decide to adopt new technology after assessing five of its innovation attributes: relative advantage, compatibility, trialability, observability and complexity, the first being the most important (Völlink et al., 2006). Attributes of new technologies are assessed in comparison with the attributes of technologies currently in use. The main assumption underlying this theory is that attributes like relative advantage are clear to potential adopters in advance. While we do not want to dispute whether this holds true for mature technologies, in case of emerging technologies it seems to be problematic. Social constructivist scholars like Pinch and Bijker (1987), Bijker (1995) and Kline and Pinch (1996) emphasise that the assessment of emerging technologies takes place under the condition of ‘interpretive flexibility’, meaning that there are different possibilities for users to make sense of them in the context of existing rules, routines and key problems in these groups. In other words, attributes of emerging technologies are not given, but constructed within a range of possibilities in a process of technology assessment.

In analogy with ‘user representation’ (Akrich, 1995), we propose the notion of *technology representation* as a heuristic for technology assessment in use regimes. A technology representation is a vision of or narrative about what a technology can do, how it fits in existing practices, how it impacts on these practices, in what circumstances it might be appropriate to

give it a try, etc. The attributes of technology representations thus reflect Rogers attributes of technologies, but in a more imaginary and discursive way. They nevertheless provide rules and orientations to users for following the development of new technology with curiosity or scepticism; or even for engaging with developers in a constructive interaction (e.g. Veen, Gremmen, et al., 2011). When particular representations are shared widely, they may exert considerable force on innovation processes.

Rules of a use regime suggest when and how it is appropriate to make use of particular technologies. These rules usually remain implicit in the routines of everyday life. However, when new innovative opportunities are presented, users are invited to reflect on these rules and make more informed decisions. These reflections and decisions will be made against the background of old routines.

5 Case part 2: the gluten free use regime

We followed a single case study approach to the gluten-free use regime in order to identify use regime rules of celiac disease patients. In a qualitative way we elaborated use regime rules by focusing on 1) rules that link particular technologies to particular circumstances, 2) rules suggesting how to use a technology in particular ways, and 3) rules for assessing new technology. Data were primarily gathered by studying infrastructures that CD patients use for sharing problems, interests, knowledge and experiences. Online support and internet forums are main source. Such a digital infrastructure delivers two types of support: emotional support (i.e. 'lotgenotencontact' in Dutch) and informational support about disease conditions, diagnosis, treatment, gluten-free diets etc. (Lazarus and DeLongis, 1983). Various information sites for celiac disease patients exist, such as www.celiac.org, (slogan: Celiacs do it gluten free), www.celiac.com, an online support group: www.glutenfreeforum.com, and in the Netherlands www.glutenvrij.nl. Furthermore, such online infrastructures promote disease awareness and build a supportive community for CD patients, families and healthcare professionals. The website www.celiac.org poses "10 ways to raise awareness everyday" (CDF, 2012). Since 1987, October has been celebrated as Celiac Disease Awareness Month in the US and Canada (www.csaceliacs.org/month.php). Another example is the celiac patient organisation NCV, a Dutch companions group for people with celiac disease, consisting of more than 9000 members. It offers an infrastructure for knowledge and CD practices sharing. Especially the website of patient organization NCV, www.glutenvrij.nl, provides a common identity for CD patients.

See for example their slogan: ‘Glutenvrij hoort erbij’ (e.g. NCV, 2012). For this research, information was mainly collected from the NCV (www.glutenvrij.nl) and reactions of patients on their internet support forum (www.glutenfreeforum.com).

In addition, we studied international review articles and reports, interviewed the science representative of the NCV (the organization that was also involved in the Celiac Disease Consortium) and consulted guidelines of healthcare professionals for diagnosis of celiac disease, and guidelines for gluten-free labeling. These sources enable a description of the dominant use regime of celiac disease patients.

5.1 Rules for using particular technologies in particular circumstances

Why do CD patients follow a strict diet? Rules are implied in the phrasing and classification of the *key problem* for which the diet is believed to be the best solution. CD patients share a condition consisting of a pattern of various chronic, sickening symptoms in the digestive system and in the rest of the body. In the 1950s, Dutch pediatrician Dicke recognized that the disease was caused by the ingestion of wheat proteins and related cereals (gluten) (Dicke et al., 1953). The discovery of gluten intolerance as the key problem of CD patients marked the emergence of a rule stating that a lifelong, strict gluten-free diet is the most appropriate remedy to celiac disease. This rule serves to interpret which symptoms are associated with gluten intake and can thus be attributed to celiac disease. Although the interpretation of CD is relatively stable, minor modifications are possible. For example, in May 2009, the National Institute for Health and Clinical Excellence (NICE) in the UK issued a new guideline to improve the recognition and diagnosis of celiac disease. This guideline provides a clear set of symptoms, signs, and types of presentation or conditions that should alert healthcare professionals in the CD use regime to consider the presence of celiac disease.

As soon as somebody is diagnosed as a celiac disease patient, the rule to follow a strict gluten free diet applies. However, this rule immediately raises a number of other problems and concerns shared by CD patients for which practical rules are continuously discussed on forums. Firstly, gluten are ubiquitous, being widespread in western diets. Many daily food products contain gluten (e.g. in wheat, barley, rye) and often these gluten are ‘hidden’ at a first glance. Gluten is often used as a food additive, for example adding protein content inexpensively and giving dough its elasticity and stickiness, which helps in manufacturing. Thus, given the omnipresence of wheat in foods, cross contamination is a continuous key concern, shared by

CD patients. Secondly, CD patients share important concerns regarding finding their way towards the gluten-free foodstuffs, as a very small amount of wheat can cause severe symptoms. The challenge then is how to obtain better, more appetizing, gluten free food, as non-gluten products generally do not taste very well. Thirdly, manufacturers often reveal on their labels that a product "may or may not" contain wheat, rye etc. While this is satisfactory to the legal community, this vagueness of rules is frustrating to CD patients. The FDA defines the term 'gluten-free' for voluntary use in the labeling of foods. So, a problem for CD patients is the inadequacy of current food labels for identifying hidden gluten in food products.

The key problem of serious sickening symptoms together with associated problems defines a particular identity of the 'celiac disease patient' that does not only include medical aspects, but social ones as well. To this patient, the rule to follow a gluten-free diet applies. Giving shape to such a diet is a continuous struggle, for which practical coping rules are actively discussed.

Technological interrelatedness refers to complementarities between different hard- and software parts of a technological system (i.e. a gluten-free diet for CD patients) making it difficult to substitute one component without also substituting the other. The rule that CD patients should follow a gluten-free diet is strongly related to a celiac disease diagnosis. This relation becomes manifest in the guidelines or rules for health care professionals. A step-by-step procedure was approved in 1970 by a panel of experts of the European Society for Pediatric Gastroenterology (known today as ESPGHAN). Physicians were urged not to diagnose celiac disease until it could be proven that gluten was really the cause of the damage. A first biopsy would show damage to the small intestine. A second biopsy after a complete, gluten-free diet would reveal a healed intestine. And a third biopsy, after reintroduction of gluten into the diet would show reoccurrence of the damage. During the next 20 years, this was the only acceptable way to diagnose CD (Meeuwisse, 1970). In the 1980s, it became clearer that CD could be associated with other conditions, mostly autoimmune disorders. In 1989, an Italian multi-centered study showed that a correct diagnosis of CD could be reached in 95% of cases by doing a single biopsy (Guandalini et al., 1989). Since 1990 diagnostic guidelines do not require gluten reintroduction and a second and third biopsy anymore (Anonymous, 1990). In 2008, the Dutch Society of Gastro-Enterologists formulated a guideline for Coeliakie and Dermatitis Herpetiformis. In addition to the diagnosis guideline, they formulated the following treatment rules for physicians: A gluten-free diet is both for children and adults the proper treatment and the physician should clearly explain its importance. Treatment and follow-up by a

dietician is recommended, who is familiar with CD and who can explain the gluten-free diet and the labels on food products. Treatment guidelines for dieticians have been made available (Guideline, 2011). It is recommended to evaluate the diet compliance after one year. Furthermore, the costs of the gluten-free diet should be reimbursed and CD patients should be referred to the Dutch patient organization Nederlandse Coeliakie Vereniging (NCV) by the physician or dietician (Guideline, 2008).

To conclude, a gluten-free diet has been the standard therapy for CD patients. This treatment has been strongly linked to CD diagnosis since the 1960s and it has been formalized in the CD use regime via shared rules (guidelines) for healthcare professionals (pediatricians, doctors, dieticians) for adequate recognition and diagnosis of CD and with general definitions of the term 'gluten-free' to be used in the labeling of foods.

5.2 Rules for using technologies in particular ways

To study how a diet is given shape in the CD use regime, the concepts of *script* and *subscription* are helpful.[4] The *script* concept reflects a set of rules that define and signify the range of possible ways of giving shape to the technology. There is a whole set of rules implied in the script of a 'gluten-free diet'. The labeling of gluten-free products should be very distinct in supermarkets and food shops. Today, gluten-free foodshops and webshops exist and general shops have corners with gluten-free products. Alternative wheat and breads bakeries have been established. Restaurants introduced gluten-free dining possibilities. Furthermore, celiac disease patients often have a gluten-free house or gluten-free corner in the house, with for example a separate toaster for gluten-free bread to avoid cross-contamination. Specific non-gluten-free food products, such as bread, cookies or cereals, are separately stored in the house. So the arrangement of a gluten-free dining room/corner at home is a solution for CD patients to cope with their disease. In the USA, a national magazine "Gluten-Free Living" supports people with CD, sharing ideas and tips how to live gluten-free. For CD patients, the script of a gluten-free diet is inscribed in the entire gluten-free food value chain by various necessary rules, such as adequate labeling of gluten-free products, manifold presences of specialized gluten-free food shops, possibilities to gluten-free dining in restaurants and a gluten-free house.

[4] As a gluten-free diet is more a practice than an artifact, the concepts of script and subscription are partly intertwined.

The *subscription* concept refers to those rules that accompany the appropriation of rules inscribed in the gluten-free food value chain. These rules suggest practical solutions for the kind of problems CD patients are typically confronted with, such as the ubiquity of gluten, the continuous threat of contamination, and the indistinctness of labels. For example, rules exist that help determining whether CD patients tolerate a particular product or meal, such as the available norms and information on labels, and the label reading routines. Patients in the celiac community are devoted 'label readers'. Labeling products really gluten-free does make a difference for them, making it easier to shop for products they need to eat and enjoy life (FDA, 2007). So, the rule guiding label reading is that CD patients should eliminate all foods derived from wheat, barley, rye and oats from their diet. CD patients were 'thrilled' when food labeling in the USA via the Food Safety norms in the Codex Alimentaris was improved because it would save them time reading labels and researching ingredients, reduce frustration and provide a measure of confidence that they and their family are eating foods that are safe. The Codex Alimentarius Commission of the WHO and FAO distinguishes 'gluten-free foods' as those consisting of ingredients with a gluten level of <20 ppm or those which have been 'rendered gluten-free' with a gluten level of <200 ppm (Gallagher et al., 2004).

The dietary compliance is a general problem, as following a gluten-free diet requires a lot of discipline and is very challenging, given the problems related to cross-contamination, lack of clear food labeling policies, and poor information on minimal toxic amounts of prolamins in CD patients (Angelis et al., 2006). Patients are really concerned about cross-contaminations in their diet. A food item labeled gluten-free should have no trace amounts of detectable gluten. There is a lot of information out there that seems to have been put forward on basis of no evidence. People not always understand what certain ingredients are, such as malt coming from barley. The improved information on labels and label reading routines are shared rules helping CD patients to subscribe to a gluten-free diet. Still, dietary compliance and misinformation about their gluten-free diet remains a major concern and subscription rules have to be followed very consciously.

5.3 Rules for assessing new technology

Technology representation is a vision or narrative about what a new technology (the CD pill) can do, how it fits in existing practices (gluten-free diet of CD patients) and how it impacts these practices. In other words it is a heuristic for technology assessment in use regimes. With

the development of an AN-PEP based celiac disease pill by the Dutch Celiac Disease Consortium CD patients are confronted with a new technology as a potential solution for their disease.

The CDC consortium regards this pill as a general supplement or food additive, relieving patients from the consequences of their condition. CD patients do not unconditionally accept this representation. During the last ten years, the gluten-free diet practice has been increasingly improved, and the gluten-free food market is so vast regarding various ingredients and alternative wheat/breads bakeries that some CD patients do not regard living a gluten-free lifestyle could be considered "suffering" to the point that they are in need of a pill to avoid it. In addition, the latest EU regulation concerning labeling of foodstuff for CD patients in 2009 has improved gluten-free labeling and facilitates the appropriation of a gluten-free diet (EC, 2009). In addition, for many CD patients gluten-free has become a way of living. They are afraid of therapy unfaithfulness and they do not want to be medicalised by pills of the pharma industry: "You can either be mindful of what you put into your mouth or be brain dead and let the drug companies decide for you" (Aviles, 2003). So these CD patients represent the celiac disease pill as a threat to their current gluten-free diet routines. Their fear is that a pill would pressure the availability of gluten-free products on the market (Veen, 2011; Veen, Gremmen, et al., 2011; Veen et al., 2010; Veen, te Molder, et al., 2011). They regard the pill at best as an emergency kit that protects highly sensitive patients against 'hidden gluten' (NCV iv, 2007). These kinds of reservations are also observed in other studies. Veen et al. (2010) found that CD patients reject quitting the diet as a valid option. Instead they 'construct a 'diet world' in which dietary transgression is presented as an integrated part of everyday life'. Te Molder et al. (forthcoming) also confirm that CD patients assess the pill as a potential technological solution in such a way as to protect and maintain their current identity.

These negative technology representations have their point of reference in a firmly established gluten-free diet regime, with which the celiac disease pill is poorly reconcilable. We conclude that this tension forms the second part of the explanation for the lack of constructive interaction between patient organization NCV and research partners in the first years of the Celiac Disease Consortium. The NCV as a spokesperson of CD patients was strongly inclined to propagate the rules of a gluten-free diet regime.

6 Discussion

While both users and producers can benefit from knowledge exchange and dialogue about desired directions of technology development, it proves hard to organise effective interaction. This research proposes two explanations from a regime perspective.

First, a technological regime consists of rules and heuristics that guide the decisions by actors involved in R&D. If these rules allow R&D actors to routinely acquire relevant information about users and the market, then they will be less inclined to actually interact with representatives of users. We have shown how the knowledge base at DSM Food Specialties about the fungus *Aspergillus niger* offered a focusing device for researchers in the embryonic phase of the Celiac Disease Consortium. Once the potential of an enzyme derived from the fungus (AN-PEP) to develop a food additive for celiac disease patients was recognised, this focusing device turned into a technical model specifying the various aspects of such a food additive that required further research, development and testing. At the same time, the potential of a food additive was coupled to representations of users defining a potential market, based on imagination and on personal contacts with patients in a clinical setting. These user representations suggested the commercial viability of the invention. Whereas the technical model specified the research agenda in terms of content, a technological roadmap specified the path to be followed from R&D to market. These four kinds of heuristics address issues that could have been dealt with in cooperation with users, but that were mainly treated internally.

The patient organisation of celiac disease patients did not play an active role in this R&D process. But it did not manifest itself as a stakeholder either. This lack of interest begs for another explanation, which we found by developing and applying the concept of a use regime. A use regime is the rule-set that governs people using particular technological artefacts in particular circumstances in particular ways. It appears that such a use regime indeed exists for gluten-free diets. A celiac disease diagnosis is the formalisation of a particular explanatory model, which at the same time contains a solution: the rule to adhere to a strict gluten-free diet throughout the patient's lifetime. This rule is embedded in guidelines for practitioners. For a variety of associated practical problems coping rules exist, and the exchange of experiences is facilitated via the internet. Rule sharing contributes to the collective identity of celiac disease patients that does not only include medical aspects, but social ones as well. This identity is one effect of the diet-based use regime. Another is the representation of the gluten degrading food additive as it is developed in the Celiac Disease Consortium. The celiac disease 'pill' is at best

represented as an ‘emergency kit’ but as worst as a heteronomous way of coping with the disease and a threat to the availability of gluten-free products, hence as an attack to the social identity of celiac disease patients central to the gluten-free diet regime. This explains why the Dutch patient organization NCV, being a prominent protagonist of the diet regime, initially was very reserved against co-operation in the R&D of the Celiac Disease Consortium.

Our analysis might suggest that there is no future for a celiac disease pill. However, having been engaged with the ambitions and efforts of actors in the consortium, we find this stance too radical. In the final part we therefore want to speculate on three scenarios in which the AN-PEP enzyme may still find a way to the market.

First, use regimes consist of shared rules for applying and using technology. If these rules are followed then particular regularities in the behavior of users emerge. But a scenario in which rules are ignored or breached is also plausible. This explains why the Leiden University Medical Centre had no difficulty in recruiting sufficient celiac disease patients for clinical trials, even though this implied the possibility to be in the control group and to become very sick (the control group is asked to consume gluten, but will get a placebo instead of AN-PEP). When old rules are breached, new rules may emerge. Those patients willing to experiment with a pill could form a niche with the potential to modify the diet-based regime, or in an extreme case even displace it, analogue to previously studied niches for sustainable technology (Schot and Geels, 2008). For the use regime concept this implies that rules cannot solely account for the stability and development of a use regime. Rules form a structuring element in use practices, but whether users conform to rules also depends on other factors, such as users’ agency, power disparities and external pressures on the regime.

A second scenario is based on two co-existing use regimes. The use regime investigated in this research is mainly based on articulations by patients and the patient organisation. These may very well represent the severely reacting extreme of the range of patients. There could also be a market consisting of people that are not diagnosed, but whose vague feelings of discomfort may be associated with gluten intake, perhaps related to changing food patterns (e.g. more bread and pasta and less potato). To illustrate, the disease is believed to be present in up to 1 in 100 of the population, but only about 10–15% of those are clinically diagnosed (Hamer, 2005; Sollid and

Khosla, 2005).[5] Many of the remainder may feel sick at times or suffer more vaguely. Inasmuch as the remainder is at the less severe end of the spectrum, they might constitute a market for a food additive/ dietary enzyme supplement. A pill-based use regime can thus emerge, not within, but next to the diet-based use regime.

A third scenario is one in which AN-PEP may find its way within the existing gluten-free diet regime. In this scenario the enzyme is not made available as a food-additive, but as a process innovation in the wheat starch industry to reduce gluten content to 0 ppm in 'gluten-free' labeled products. We think this scenario is less plausible than the others. An application in processing industry is less exclusive and commercially attractive than a food additive. Our interview at DSM, who owns the patent, did not reveal this scenario. The idea came from a spokesperson of the patient organization, who referred to problems with the norms in the Codex Alimentaris for international trade, according to which products officially labeled 'gluten-free' still may contain a small fraction of gluten. These small fractions can still do much harm to some patients. In this scenario, AN-PEP could even play an important role if the diet-based use regime would continue to dominate.

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[5] Attempts are made to include these patients in the existing regime via guidelines to make proper diagnoses. The National Institute for Health and Clinical Excellence (NICE) in the UK has recently (May 2009) issued such a guideline, which provides a clear set of symptoms, signs, and types of presentation or conditions that should alert healthcare professionals to consider the presence of celiac disease.

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