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Exploring emerging technologies using metaphors – A study of orphan drugs and pharmacogenomics

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Abstract

Due to uncertainties of several aspects of emerging health technologies, there is a need to anticipate these developments early. A first step would be to gather information and develop future visions about the technology. This paper introduces metaphor analysis as a novel way to do this. Specifically, we study the future of pharmacogenomics by comparing this technology with orphan drugs, which are more established and often act as a model with comparable (economic, research organisation, etc.) characteristics. The analysis consists of describing the dominant metaphors used and structurally exploring (dis)similarities between pharmacogenomics and orphan drugs developments. This comparison leads to lessons that can be learnt for the emerging pharmacogenomics future. We carried out a comprehensive literature review, extracting metaphors in a structured way from different areas of the drug research and development pipeline. The paper argues that (1) there are many similarities between orphan drugs and pharmacogenomics, especially in terms of registration, and social and economic impacts; (2) pharmacogenomics developments are regarded both as a future 'poison' and a 'chance', whereas orphan drugs are seen as a 'gift', and at the same time as a large 'problem'; and (3) metaphor analysis proves to be a tool for creating prospective images of pharmacogenomics and other emerging technologies.

Keywords: Orphan drugs; Pharmacogenomics; Metaphors; Emergent technologies

Introduction

Emerging technologies are technologies in an early phase of development. This implies that several aspects, such as the characteristics of the technology and its context of use or the configuration of the actor network and their related roles are still uncertain and non-specific. For certain technologies, especially those with a disruptive character and a significant influence on society, it is advisable to be aware at an early phase of development of the quality of potential (negative and positive) impacts. This relates to the control dilemma of Collingridge (1981): in the emergent phase it is difficult for stakeholders to specify what they want from the technology, while owing to the fluidity of the technology, the direction of development can be steered more easily. In contrast, in the later phases, demands are clearer but potential options decrease. Learning how to deal with this dilemma can be beneficial in the context of decision-making on emerging technologies.

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This article focuses on assessing *metaphors* representing the future of a technology and exploring possibilities to anticipate future developments. Metaphors describe something in terms of something else; by subsequently bringing these aspects together, the concept described is clarified (Miller, Ahern, Smith, & Harvey, 2006; Wyatt, 2000). A future technology, of which only a few characteristics are known today, can be compared with a more established technology. This helps people engaged in creating and discussing a vision about the future technology. A foremost example of metaphors used in the context of (medical) technology is the gene envisaged as a ''book of life'' (Copland, 2005; Keller, 1995).

This paper focuses on emerging technology in the field of genomics and medicine, referred to as pharmacogenomics. The promise of pharmacogenomics features stratifying the patient population, on the basis of genetic make-up, into smaller groups for which specific treatment can be developed (EMEA, 2003). This could mark the advent of individualised drugs. The Royal Society (2005) report stated that pharmacogenomics could be at least 15–20 years away due to gaps in the understanding of how genetics relates to disease-working mechanisms. Currently, only a few pharmacogenomics products are on the market, and although there is a notion of the ethical, legal and social expectations regarding the future of pharmacogenomics, their quality and impact remain uncertain.

A large range of technology watchers and peers in the health care arena claim that the future of pharmacogenomics might resemble the currently more established orphan drugs. This is not only evident from review articles, but also from explorative interviews conducted among a heterogeneous set of experts, ranging from members of the medical profession, to scientists, industry representatives and patient advocates (see Box 1). Orphan drugs are defined as medicinal products developed for diagnosis, treatment or prevention of rare diseases. Rare diseases are a heterogeneous group of life-threatening or chronically debilitating conditions, from which no more than 5 out of 10,000 inhabitants of the European Union suffer. Examples are Pompe disease, haemophilia, and phenylketonuria. Often, there is no access to effective medicines. Despite the urgent health needs of rare diseases, the drugs are known as 'orphans' because companies are not interested in 'adopting' them.The small number of patients makes the comparison between orphan drugs and the pharmacogenomics future instructive. It is claimed that orphan drugs can act as a model with comparable characteristics, such as economic impacts on businesses and the health system in general, regulation, and the organisation of basic and

Box 1. Quotations on the similarities between pharmacogenomics and orphan drugs

From review articles:

''Pharmacogenomics technology might create an avalanche of new orphan drugs'' (Loughnot, 2005).

''Testing based on pharmacogenomics could 'segregate the population into smaller and smaller pieces', resulting in an 'orphan drug syndrome''' (Larkin, 1998).

''It is anticipated that pharmacogenomics will result in the identification of more 'orphan diseases''(Haffner, Whitley, & Moses, 2002).

From interview statements:

''There is a big chance that indications will be subdivided into smaller ones. The unravelling of the human genome accelerated this division process'' (representative of innovative pharmaceutical industry, 2004).

''There are many similarities in research and application'' (university researcher on rare diseases, 2005).

''There is a chance that we will go towards a future with more 'orphans''' (representative of biotechnology industry, 2005).

''Tailor-made medicine means that 'common diseases' will turn into 'orphan diseases''' (clinician, 2005).

''Everyone will have a rare disease in the future because of pharmacogenomic developments'' (intermediary organisation working on orphan drugs stimulation, 2005).

''Rare diseases can be seen as a model for the future of more personalised medicines'' (policy-maker at the health ministry, 2006).

clinical research and development. If we assume that this comparison between orphan drugs and pharmacogenomics is useful, it might be interesting to increase our understanding of pharmacogenomics. We do this by studying discourses of how actors view developments across the different 'domains' of drug research and development and application pipeline, through the use of metaphors regarding pharmacogenomics and orphan drugs. First, metaphors are identified by systematically reviewing the literature using these domains. Second, orphan drugs and pharmacogenomics are compared following these domains. This sheds light on similarities and dissimilarities between these drug classes. Next, this exploration of the comparison of two drugs classes leads to visions of and lessons for future emerging technologies, such as pharmacogenomics.

Accordingly, the central research question is *what metaphors are used in pharmacogenomics and orphan drugs in the different drug research and development domains; what are the (dis)similarities; and what can we learn from them in the context of the emerging pharmacogenomics future*?

This paper supports the idea that learning about the (dis)similarities between the two drug classes might contribute to a better understanding of pharmacogenomics innovations among policy-makers and managers by creating prospective images of emerging technologies, and in turn assist them to overcome the Collingridge dilemma. For example, they can decide which characteristics of orphan drugs to include in their vision of pharmacogenomics, and they can learn more about both orphan drugs and pharmacogenomics because the metaphors accentuate their characteristics. More importantly, this analysis adds to the existing literature and methodology on technology future analysis and metaphor assessment, and might prove to be applicable to other emerging technologies as well.

Studying the future using metaphors deals with the theory on metaphors and its use as a future analysis method. Methodology presents the methodology used, while the subsequent sections deal with the results, the conclusions and discussion.

Studying the future using metaphors

Assessing technologies in their ''embryonic state'' (Mambrey & Tepper, 1999) is the premise of a large array of technology futures studies (Porter et al., 2004). One way of analysing the future is through the prospective and desirable images shared by numerous actors, i.e. images that steer stakeholders' actions and interactions (Grin et al., 1999). They include visions, 'Leitbilder', expectations and promises. Methods investigating this type of future include vision assessment, science fiction analysis and metaphor assessment.

A metaphor is described as ''a conceptual system that allows us to understand and experience one type of thing in terms of another'' (Miller et al., 2006). Several authors have contributed to theories of metaphors ranging from Aristotle and his substitution theory to Lakoff and Johnson (1980) and their cognitive theory. In the latter, a metaphor is defined as ''a cross-domain mapping between the source (secondary) and the target (primary) domains'' (Hellsten, 2002). This mapping process treats these two domains as holistic, abstract concepts, in which some – but not all – features of the source are used to highlight some of the features of the target. An emerging technology, for example, will consist of a combination of known and new features.

Metaphors describe situations that people involved in the public debate are expected to be familiar with, and by doing this reduce the complexity of issues. In this way, they function as communication devices. At the same time, metaphors have a normative and even political quality (Miller et al., 2006). The normative character of metaphors lies in the fact that people put their wishes, needs, values and assumptions in the metaphors they use: ''different social groups use different metaphors to capture and promote their own interests and desires for the future'' (Wyatt, 2004). Metaphors can, therefore, become shared and might have the same functions as visions and expectations in guiding technological development (Brown, Rappert, & Webster, 2000). The political use of metaphors ties in with the fact that they are mostly formed as a result of an interactive discourse in which different stakeholders – sometimes strategically (Berkhout, 2006) – use different metaphors or the same metaphor with different meanings. Meanings of metaphors are heterogeneous and sometimes ambiguous but as the debate goes along, closure is expected and the use and meaning becomes solidified.

Using metaphors in the context of science and technology has two functions (Hellsten, 2002). First, they help in elucidating science and technology for the general public, while facilitating science communication, knowledge transfer, and promoting science. Second, it has a stimulating effect on scientific development itself, by making ideas more concrete, generating new ideas, helping to communicate complex matters or interests between scientists, and by legitimising the research projects to financial backers.

Accordingly, metaphors take shape in an interactive discourse, have a strong normative quality, and while representing the desired state of a currently emerging technology, could drum up strong guidance for these technologies. Few authors have already contributed to such technology future analysis based on metaphors, and nearly all of them focused on studying metaphors within a discourse around a technology. Examples include a so-called 'metaphor analysis' (Miller et al., 2006) in which scientific journal editorials are screened for opinions about and metaphorical imagery of the future of human genetics. Other authors use different classes of metaphors (hyperboles, analogy, contrast, etc.), dissecting metaphors in different elements or as members of a same domain (Mambrey & Tepper, 1999). Additionally, Wyatt (2004) screened magazines to uncover metaphors that were used during the development of the Internet. The next section shows how metaphors are studied within the discourses of orphan drugs and pharmacogenomics.

Methodology

To elucidate the metaphors used in the context of orphan and pharmacogenomics drugs, we investigate the similarities and dissimilarities between the characteristics of these two drug classes as found in literature. We restricted our search to international review articles and reports published in the period 1997 up to the beginning of 2006. The starting point of this period was marked by the arrival of the term pharmacogenomics in scientific papers (Hedgecoe, 2003), which coincides with the growing interest for structural and functional genomics aspects in the context of the Human Genome Project. These review articles and reports produce a wide range of characteristics of orphan drugs and pharmacogenomics.

The articles and reports on both pharmacogenomics (Baker, 2005; Bartfai, 2004; Boulnois, 2000; Dean, Zanders, & Bailey, 2001; ESHG & IPTS, 2004; Evans & Relling, 1999; Evans & Relling, 2004; Fierz, 2004; Ginsburg & McCarthy, 2001; Hall, 2003; Hedgecoe, 2004; Hedgecoe & Martin, 2003; Kirchheiner, Fuhr, & Brockmöller, 2005; Lindpaintner, 2001; Lindpaintner, 2002; Loughnot, 2005; Noble, 2003; PriceWaterhouseCoopers, 2005; Reiss, 2001; Roses, 2000; Royal Society, 2005; Rubinstein & Roy, 2005; Shastry, 2005; Tribut, Lessard, Reymann, Allain, & Bentue-Ferrer, 2002; Van Delden, Bolt, Kalis, Derijks, & Leufkens, 2004; Webster, Martin, Lewis, & Smart, 2004; Weinshilboum & Wong, 2004) and orphan drugs (Alcimed, 2004; Anand, 2005; Aronson, 2006; Bosanquet, 2003; Clarke, 2006; Daina, 1994; EMEA, 2005; FDA Consumer, 2003; Haffner, Whitley, & Moses, 2002; Hollis, 2006; Joppi, Bertele, & Garattini, 2006; Loughnot, 2005; Lunn & Stockwell, 2005; Maeder, 2003; Milne, 2002; NICE, 2004; Rai, 2002; Rinaldi, 2005; Service, 2004; Shah, 2003; Smith, 2005; Stolk, Willemen, & Leufkens, 2005; Visser, 2006; van Weely & Leufkens, 2004; Zitter, 2005) were collected by searching two publication and conference paper abstract databases, i.e. the Science Citation Index (via ISI Web of Science) and PubMed. We interviewed three genomics scientists and three Dutch scientists and policy-makers engaged in work on rare diseases. They provided us with keywords that cover the technological fields as complete as possible. The experts on pharmacogenomics and orphan drugs were identified through consulting, respectively, the Netherlands Genomics Initiative and the Dutch Steering Committee on Orphan drugs. These keywords were then used in structurally searching the databases; taking into account the time-period (1997 to early 2006) and the classification of articles as 'review articles'.

The resulting set of articles contained 688 articles on pharmacogenomics and 63 on orphan drugs. From this database, we selected those articles that were cited at least 10 times in other articles. This might have led to a bias towards older articles but this consideration was outweighed by the need for 'authoritative' articles, especially because the emergent, undefined character of pharmacogenomics calls for a deliberate set of views.

We also included reports on orphan drugs and pharmacogenomics, published by leading regulatory institutes such as EMEA, FDA and NICE. These reports featured most often in the lists of references of these articles. After reading through the resulting 57 pharmacogenomics and 39 orphan drugs publications, it appeared that only 27, respectively 25, would be of use for our analysis (some were too scientific/technical or contained duplications). The review articles are internationally oriented although we acknowledge that the reports have a strong European focus. This bias is caused by the way we selected the reports: mostly European reports were cited because during 1997–2006, the EU was trying to redress its lacking orphan drug regulation compared to the United States (EU orphan drug regulation came in place in 2000). These European reports still reflect a pan-European perspective because they constantly make comparisons with the situation in the United States.

Subsequently, we undertook a literature review and metaphor analysis consisting of three stages. First

of all, we analysed the articles and reports using a so-called 'domains' heuristic consistent with Miller et al. (2006). We read the texts, extracting quotes and concepts that are important for an understanding of the orphan drugs context and the pharmacogenomics future. To structure the search results, we labelled the texts into predefined domains that form salient aspects of drug research and development, following the drug research and development pipeline, marketing, and utilisation (Gassmann, Reepmeyer, & Zedtwitz, 2004). Fig. 1 illustrates the different search domains used.

The second step dealt with constructing concise summaries and reading eye-catching metaphors that were representative of the different domains in the two drugs classes. We took the texts with the same labels together, making sure that these summaries contained all different metaphors, especially the ones that were mentioned most often, in this way reflecting relevant issues of all topics. Both steps, i.e. extracting texts from the articles and reports, and summarising, were done taking into account interrater reliability. Two raters studied all the publications and made summaries independently, which were then discussed. Especially, the question of what could be regarded as a metaphor was discussed thoroughly. For a start, a phrase should comply with the definition of a metaphor. When uncertainties remained, we searched the aforementioned literature databases and investigated in which context these phrases were used in other articles. The uniform list of summaries and notable metaphors is presented in the next section.

The final step was to compare the most important issues per domain. This implies focusing on the metaphors used in the discourses of orphan drugs and pharmacogenomics to obtain a better understanding of the problems and solutions, as well as their underlying assumptions and values. The level of importance of the metaphors found could not be quantified. This would suggest that metaphors and their meanings could be added up, which proved difficult because of nuances in the metaphors used. Nevertheless, we used a qualitative analysis in which both raters discussed which metaphors were comparable and would form a major discourse within one domain. Analogously, the analysis of similarities and dissimilarities between the different drug classes on each domain was done based on discussions between the raters. Table 1 in Conclusions and discussion illustrates this comparison.

Results

This section outlines the findings following the presented domains structure (Fig. 1).

Basic research and clinical trials

The orphan drug publications emphasise the lack of understanding of the pathogenesis of rare diseases (''health orphans'' Aronson, 2006; Daina, 1994), available animal models, and current treatments: 'the absence of treatment for many rare diseases constitutes a ''clear pharmacological gap''' (van Weely & Leufkens, 2004). The barrier to prevention, diagnosis, and treatment is a 'lack of mechanistic knowledge about the disease' (Stolk et al., 2005). On the other hand, orphan drugs act as ''model systems'' (van Weely & Leufkens, 2004) for research of more prevalent disease. The clinical trials prove difficult to organise because of the low number of patients with a specific rare disease. Therefore, complying with clinical trial standards as used for more prevalent diseases is complex: 'It is next to impossible to gather enough patients to achieve sufficient statistical power

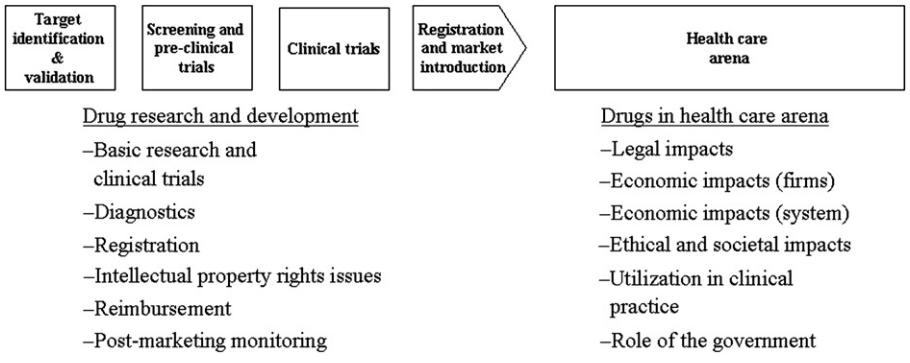

Fig. 1. Domains used in the context of the drug research and development pipeline.

Table 1
Comparison of pharmacogenomics and orphan drugs per domain

	Pharmacogenomics	Orphan drugs
Similarities		
Basic research and clinical trials	Uncovering underlying disease pathways	''Model systems'' for more common diseases
Diagnostics	Diagnostics are essential to pharmacogenomics concept (''tandem'')	Diagnostic tools are important (but currently lacking)
Registration	Small populations (''genotypically enriched populations'')	Small populations (''salami slicing'')
	Speeding up process (''fast-tracked'')	Speeding up process (''first-in-class'', ''fast-tracked'')
	Change organisation of process (''safe harbours'', ''voluntary submission'')	Change organisation of process (''collegial relationship'')
Economic impacts (firms)	Stratification leads to smaller, uninteresting markets	Small markets are uninteresting (''ultra-orphans'')
	Niche markets beneficial through high market penetration (''minibusters'', ''niche franchises'', ''best-in-segment'')	Niche markets beneficial (''therapeutic Gold Coast'')
Economic impacts (system)	(Uncertainty over) growing expenditure	(Uncertainty over) growing expenditure
Ethical and social impacts	Equity (''dispossess subgroups of patients''), and patient involvement and education (''informed consent'')	Equity (''ignorance seriousness rare diseases''), and expectations (''hope'')
	Genetics-specific: confidentiality, ''genetic reductionism'', ''genocide weapons''	–
Utilisation in clinical practice	Importance of awareness medical professionals (''genomics education'')	Importance of awareness medical professionals
	Experiences and expectations on smaller patient populations (''individualisation'', ''tailor-made'', ''customisation'')	Experiences and expectations on smaller patient populations (''stratification'')
Dissimilarities		
Basic research and clinical trials	''Rescue strategy''	''Lack of mechanistic knowledge about…''
	Insufficient safety	''Clear pharmacological gap''
Post-marketing monitoring	Chance and important	Problem, but important
Legal impacts	Legal responsibility	Abuse of regulation (''balkanization'', ''game the system'')
Economic impacts (firms)	Low development costs	High development costs
Role of government	Market chance: no support of research	Market failure: support research with orphan drug regulations (''African-like development'')
No clear distinction: IPR issues, reimbursement		

to demonstrate significant clinical benefits of a therapy' (EMEA, 2005). The same goes for the ''uncontrolled'' phase II studies (Joppi et al., 2006): there are no markers to follow the treatment, and the natural history of the genetic orphan disease is often unknown (Lunn & Stockwell, 2005).

The pharmacogenomics documents focus on the subdivision of patient groups providing opportunities for adequate data on efficacy and safety. This might increase efficiency and chances of success for the innovation process with efficacy and safety data resulting in ''early decisions'' (Kirchheiner et al., 2005) and 'a paradigm shift from a linear process to an integrated and heuristic one' (Ginsburg & McCarthy, 2001). Also, the imminence of a rescue strategy is put forward. Drugs that have shown insufficient efficacy or safety levels in the general population can now be approved for smaller subgroups of patients. Basic research might benefit from the discovery of similar underlying patterns or pathways between diseases.

To conclude, in the domain of basic and clinical research we see a difference in perspective between the two classes of drugs. Patients see orphan drugs as a gift, whereas searching for new orphan drugs is seen as a problem. Conversely, companies and others see pharmacogenomics as a chance or opportunity,

while it is stressed that developments should be kept under control because of the fear that such drugs might turn into a poison. Moreover, the problems stated in the orphan drugs articles are more specific, while those in pharmacogenomics articles are not.

Diagnostics

The major concern in orphan drugs articles is the lack of appropriate diagnostic tools, which leads to limitations on orphan drug development and recognition of rare diseases. Regarding pharmacogenomics, advantages include facilitating market definition for businesses and the fact that genetic test results are valid for a lifetime, while disadvantages concern fears about test accuracy, genetic determinism and consumers using these tools without medical supervision. Many authors see diagnostics as an essential part of pharmacogenomics because it concerns the combination of diagnostics and therapy or the ''personalised diagnostic-therapeutic tandem combination'' (Fierz, 2004). This goes for drugs that are on the market, and also for those that are still part of clinical trials. After all, patient populations will have to be stratified by conducting genetic tests. Businesses can choose to follow three strategies: co-development of therapy and diagnostic testing, first developing diagnostics then therapy, or first therapy then diagnostics. As it is not in the interest of pharmaceutical companies to stratify or reduce their ''one-dose-fits-all'' market (Kirchheiner et al., 2005), they will hesitate to follow these strategies, whereas diagnostic companies might be less irresolute.

Registration

Similarities are observed within the registration domain. Both classes pertain to small populations in clinical development and in the market phase. 'The lack of reliable methods for evaluating the effect of drugs on small numbers of patients is partly responsible for the generally poor quality of the dossiers' (Joppi et al., 2006). Both mention phrases like ''stratification'' (Hollis, 2006), ''salami slicing'' (Maeder, 2003) and ''genotypically enriched populations'' (Bartfai, 2004; Roses, 2000). Second, a speeding up of the drug development process is expected in both instances, leading to faster registration, because these small populations are genetically characterised in the case of pharmacogenomics. For rare diseases, new drugs are often ''first-in-class'' (Haffner et al., 2002) and thus obtain ''fast-track'' approval (Shah, 2003) more easily. 'Less stringent criteria are acceptable for orphan drugs' (Joppi et al., 2006), also in the light of the novel and lifesaving aspects of these drugs. Third, pharmacogenomics and orphan drugs change the way the drug development process is organised. Interaction with pharmaceutical companies is induced through 'voluntary submission of pharmacogenetic analyses' (Kirchheiner et al., 2005). These data are then discussed in so-called ''safe harbours'' (Royal Society, 2005), i.e. the results of the discussions will not influence the FDA's approval decision. It is simply a way of experimenting and learning in a niche. Also, for orphan drugs a ''collegial relationship'' (Loughnot, 2005) exists between the FDA and drug sponsors.

Thus, orphan drugs are ''fast-tracked'' to approval due to the life-threatening nature of the disease, the lack of alternative effective treatments and a reduced clinical trial size required to license a drug. For pharmacogenomics, a drug shown to be more effective for a serious disease in a defined subpopulation has many characteristics in common with traditional orphan drugs.

Intellectual property right issues

Patents are deemed to add time to market exclusivity, and attempts to appropriate genes and gene manifestations are uncertain. Moreover, pharmacogenomics might lead to 'new claims for old products' (ESHG & IPTS, 2004) ('recovering ''lost'' drugs' Shah, 2003). This domain does not provide a clear view about the similarities between the two drug classes.

Reimbursement

In the context of orphan drugs, reimbursement is seen as a major hurdle to market introduction and a cause of inflated prices. This applies especially to Europe, where companies have to cope with different reimbursement procedures in different member states. Nevertheless, organising reimbursement is important 'because orphan products address considerable unmet needs for relatively small patient groups for which care would otherwise be extremely expensive' (Milne, 2002). For pharmacogenomics, little was found on this issue in the review articles.

Post-marketing monitoring

For both drug classes, an emphasis is put on the importance of post-marketing surveillance because of the fast-track procedures these drugs are supposed to be going through. This implies the obligation to produce

safety and efficacy data after market introduction to show that the drugs have been approved with good reason.

Apart from this similarity, pharmacogenomics technology is seen as a way to improve the monitoring system, while for orphan drugs the lack of epidemiologic, efficacy, and safety data is stressed, just as knowledge on the natural course of the disease. Many authors claim that the setting up of a data monitoring system, centres of expertise, and better diagnostics should contribute to the collection of these data. Again, the contrast of 'chance' versus 'problem' is evident in this domain.

Legal impacts

Not many legal impacts are mentioned for pharmacogenomics. Only the issue of physicians' responsibilities associated with genetic tests were found as medico-legal implications. Legal issues surrounding orphan drugs focus on the Orphan Drug Act in the United States (since 1983) and the EU Orphan Drug Regulation (since 2000). Drugs can obtain an Orphan Drug Designation that guarantees ''appropriate incentives'' (Clarke, 2006; Stolk et al., 2005), such as market exclusivity and protocol assistance. Beneficial effects are discussed: 'the […] orphan regulation provides hope' (Anand, 2005; EMEA, 2005). On the other hand, some authors stress the abuse of orphan drug regulation (e.g. Loughnot, 2005; Smith, 2005). 'Had the Orphan Drug Act been co-opted as a Biotechnology Promotion Act?' (Maeder, 2003). Orphan drug regulation encourages businesses to ''game the system'' (Hollis, 2006) by identifying subgroups of diseases as new diseases in order to qualify for orphan drug status, also called ''balkanization'' (Hollis, 2006) or ''stratification'' (Hollis, 2006), since common diseases are split up into many rare diseases. Moreover, medicines that have already been approved under the Act can become blockbusters because of unintended proven effectiveness against common disorders, or because the indication area is suddenly expanding, e.g. in the case of AZT to block HIV replication. Consequently, legitimacy questions are asked constantly about this so-called ''unreasonably profitability'' (Maeder, 2003). Concluding, the orphan drugs legal impacts are more concrete, but potential abuse for pharmacogenomics could become a major issue.

Economic impacts for businesses

Statements made on economic impacts for businesses partially show similarities between both orphan and pharmacogenomics drugs. Both classes imply smaller markets (''ultra-orphans'' NICE, 2004), which are not attractive for pharmaceutical companies: 'the more personalised the medicine, the less interesting the business' (Hall, 2003). Disease stratification would decrease the market size for an individual drug. At the same time, smaller, niche markets are still interesting for companies, mostly smaller ones. While stratifying the patient population a drug might position itself in an exclusive, monopolistic way within the market: 'a particular drug could fully command 10% of the huge depression market and that would be a blockbuster [… in an] exclusive market without having to fear generic competition' (ESHG & IPTS, 2004). Drugs can then turn into ''minibusters'' (Hedgecoe & Martin, 2003), ''niche franchises''(PriceWaterhouseCoopers, 2005), or ''best-in-segment'' (PriceWaterhouseCoopers, 2005) medicines: promising drugs that work for a portion of the population, whereby patients are pre-selected based on their genetic profiles.

Accordingly, the economics of orphan drug development could be favourable: entry barriers are lower and markets, although smaller, are predictable and profitable, plus patients are chronically ill and thus for a long time dependent on a particular product. This could be a ''therapeutic Gold Coast'' (Milne, 2002). Market exclusivity provides protection against 'me-too' competitors, and the small markets for orphan drugs dissuade generic competition. Furthermore, marketing costs are smaller as knowledgeable medical specialists could be fast-reached.

Nevertheless, there is a difference in expected costs in drugs research and development. Thanks to more efficient clinical trials, and target and lead discovery, it is foreseen that pharmacogenomics will lower development costs. This decrease in costs is not foreseen for orphan drugs, which are inflated through the anticipated small markets.

Economic impacts for the health care system

The high prices cause problems for the financing and affordability of orphan drugs through (national) reimbursement schemes. The absence of competition adds to this problem, which is propagated by legislation that ensures market exclusivity for a drug treating a specific rare disease. The reasoning that it encourages pharmaceutical companies to back the development of drugs with small markets legitimises this measure (Alcimed, 2004). The same goes for pharmacogenomics drugs: 'sponsors likely demand a higher price for them' (PriceWaterhouseCoopers,

2005) as these drugs are innovative, high-quality drugs on a monopolistic market. Nevertheless, it is uncertain how the overall balance of costs and benefits will turn out. Some authors claim that higher efficacy and safety results in cheaper clinical practice, e.g. through less adverse drug effects, less trial-and-error treatment, reducing hospitalisation. Others emphasise the uncertainty regarding financing the accompanying diagnostics.

Ethical and social impacts

For pharmacogenomics, a lot of ethical and social impacts are proposed. They include public trust in general, as well as questions on privacy protection, equity, confidentially and discrimination (Rai, 2002). The latter not only includes neglecting persons in their relation with health insurance companies and employers, but also includes concerns about the development of drugs only for certain subgroups (''dispossess subgroups of patients'' Hall, 2003, ''splinter groups'' Hall, 2003, and ''genetic exceptionalism'' Royal Society, 2005), especially those that live in developing countries. Other risks include ignoring non-genetic aspects of drug response and disease susceptibility (''genetic reductionism'' ESHG & IPTS, 2004), and risks concerning a whole country (developing ''genocide weapon[s]'' Bartfai, 2004). Lastly, the need for patient participation and education in clinical trials and genetic testing is stressed, mostly with respect to getting patient's ''informed consent'' before they participate (ESHG & IPTS, 2004; Fierz, 2004).

Orphan drugs do not share the genetics-specific ethical and social issues. One issue deals with the lack of interest of society in general, whereas rare disease patients are heavily engaged. As one patient said: 'orphan diseases are not important unless you happen to have one' (Daina, 1994). There is a societal 'ignorance of the seriousness of rare diseases' (Bosanquet, 2003). Dissemination of information is important for patients and professionals in order to prevent misdiagnoses, but there is a lack of infrastructure and proper exchange of information. Especially regarding rare diseases, patient advocacy groups have shown to have a major influence on drug innovations because these patients are highly involved and there is much to be gained (''hope'' for a new future Rinaldi, 2005). The equity issue (Bosanquet, 2003; FDA Consumer, 2003) is also in agreement with the one presented in the pharmacogenomics context: there are fears of unequal access to therapy, e.g. because of registration and reimbursement, and unequal attention paid to certain diseases in drug research and development.

Utilisation in clinical practice

For both rare diseases and pharmacogenomics, the importance of awareness of medical professionals is mentioned. For pharmacogenomics, there is a need for ''genomic education'' (ESHG & IPTS, 2004; Shastry, 2005), the trial-and-error and evidence paradigms will be changing, the distribution of workload and responsibility might shift, and the role of information technology might also change. Application of pharmacogenomics in the health care setting necessitates physicians and specialists to adjust to prescribing drugs on molecular profiles. They could be resistant to disease (re) classification at a genetic or genomic level as they are trained to diagnose on the basis of symptoms and morphology. Additionally, what is the degree to which insurers will limit physicians' prescribing flexibility?

Furthermore, the expectations of patients are stressed, and the consequences of smaller patient populations (''one size fits all mentality'' ESHG & IPTS, 2004, ''individualisation'' ESHG & IPTS, 2004; Fierz, 2004, ''personalisation'' Fierz, 2004, ''customisation of drugs'' Loughnot, 2005) are sketched in a far more abstract way than in the orphan drug context. The term personalised medicine is often used in the context of pharmacogenomics. It conveys the most extreme vision of what the pharmacogenomics future might bring, namely separate treatment for every person. At the same time, this term caused debates about its use as a metaphor because scientists think that pharmacogenomics means that patient populations will rather be stratified into groups for which certain treatments work efficaciously or safely. In this way, it leads to ''tailor-made'' rather than personalised medicine (Hedgecoe, 2004).

Role of government

For orphan drugs, ideas and needs for the role of the government are rather spelled out. They include tax credits, simplification of marketing authorisation procedures, extended market exclusivity, scientific research programmes, clinical trials set-up support, pan-European networks of excellence, and support for medical education and training for health professionals. Compared to pharmacogenomics, there is a difference in the legitimisation and scope of public intervention. Research on orphan drugs should be

supported because it is a problem that has its roots in failing markets, whereas the government should not necessarily sponsor research on pharmacogenomics while it is regarded as a chance that the market will and should take up themselves. The government should only pay more attention to those patient populations the pharmaceutical companies are unwilling to invest in, in order to avoid ''an African-like development'' (Bartfai, 2004). Moreover, research on rare diseases can function as a scientific model system for other more prevalent diseases. Studying these models then works like performing basic scientific research for which public support is more common.

Conclusions and discussion

The introductory section assumed a further understanding of the emerging pharmacogenomics future by studying and comparing discourses of how actors look at developments across different domains of drug research, development and application in both orphan drugs and pharmacogenomics developments. This paper, therefore, focused on *what metaphors are used in pharmacogenomics and orphan drugs in the different drug research and development domains, what are the (dis)similarities, and what can we learn from them in the context of the emerging pharmacogenomics future*?

Pharmacogenomics is an emerging technology with many uncertainties. Its premise is that patients can be stratified by diagnostic tests into smaller, genetically homogeneous groups that respond favourably to certain drugs or are susceptible to a certain disease. This subdivision of the patient population into smaller groups makes comparison with orphan drugs possible. Table 1 summarises the most important similarities and dissimilarities between orphan drugs and pharmacogenomics in the various domains, including the major metaphors used.

Concerning the discourses within the different domains, we identified that the orphan drugs metaphors and statements used were more specific regarding concrete outcome (e.g. 'ultra orphans', 'clear pharmacological gap'), whereas with pharmacogenomics the content remained more fluid, more an expectation or promise than something concrete (e.g. 'safe harbours', 'customisation', 'genetic reductionism'). This is a consequence of the emerging character of pharmacogenomics. Although orphan drug development is already quite specific, with more than 23 years of acquired experience since the introduction of the first Orphan Drug Act in 1983, pharmacogenomics really took off after completion of the Human Genome Project in 2000.

A difference was also found in observed assumptions and values related to orphan drugs and pharmacogenomics. Table 1 showed different valuing of orphan drugs and pharmacogenomics with metaphors used such as 'African-like developments' for orphan drugs and 'genotypically enriched populations' for pharmacogenomics. Probably these values differ due to the stage of technology development, but also due to the inherent difference between the more general 'gift' versus 'poison' metaphor (or 'chance' versus 'problem').[1]

To compare orphan and pharmacogenomics drugs in order to anticipate the emerging pharmacogenomics future, Table 1 shows a distribution of the similarities and dissimilarities over the domains. Only on certain aspects can orphan drugs be seen as a model for the pharmacogenomics future. These include similarities such as 'first-in-class' and 'salami slicing'. This is in line with what we saw in the metaphors literature; not all elements of the source need to correspond with the target.

Answering the question what we can learn about the pharmacogenomics future, we see that there is a need to emphasise the positive aspects for different actors, e.g. companies can focus on smaller but at the same time monopolistic niche markets, and their registration processes profit from this smaller-scale, more tentative testing. Scientists can position rare idiosyncratic diseases as a model system that might appear beneficial for and spread out to 'neighbouring indications'. Finally, society at large might take advantage and should be preparing for more individualised therapy, considering increased efficacy and lowering adverse drug reactions. Besides these positive outcomes, the potential negative impacts should also be acknowledged and prepared for, i.e. equity issues and costs for the health system (society at large), small market revenues (companies), and an educational and knowledge backlog (clinicians).

The methodology used for comparing a current with an emerging technology class might be useful in learning about discourses in drug classes and about how a future emerging technology could be envisioned. Refinements include deepening the metaphor analysis within the discourse of the domains, and differentiating between problems and solutions, and the underlying norms and values. To contextualize the future vision, these norms and values could also be attributed to

[1] Derrida (1981) discusses Plato's use of 'pharmakon' that, interestingly, means both remedy and poison.

different kinds of stakeholders. In addition, the assessment of the importance of various metaphors extracted from the publications could be enhanced by interviewing actors and also by taking into account differences in actor perspectives when assessing the metaphors used. Furthermore, a drawback of the analysis is that a comparison calls for both classes to state their problems, solutions, etc., on every domain. In this case, for example, regarding pharmacogenomics the IPR and reimbursement issues were not articulated at all, and no statements on the ethical and social impacts regarding genetic-specific issues of orphan drugs were found. A subdivision of domains might ameliorate this.

Concerning the choice for orphan drugs as a 'comparing partner' to pharmacogenomics we should add that it has two drawbacks: (1) the premise of this comparison lies heavily on the small patient populations characteristics. The question could be raised whether the focus on small patient groups and the comparison with orphan drugs is the major discourse (as compared to others, such as the convergence of food and health). This discourse choice is based on reviewing the articles and reports, but this has not systematically been tested; (2) although we introduced pharmacogenomics as a technology that will take at least 10 years to emerge, its principles can also prove to be crucial in treating and diagnosing rare diseases. In the future, the two classes might overlap making a clear-cut comparison conceptually more difficult.

Exploring emerging technologies using a metaphor assessment gives policy-makers, managers and researchers more contextualised prospective images of the future pharmacogenomics (and the current orphan drugs) developments. More importantly, we believe that metaphor analysis is a novel way to analysing (other) emerging technologies.

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References

Berkhout, F. (2006). Normative expectations in systems innovations. *Technology Analysis & Strategic Management, 18*(3/4), 299–311.

Brown, N., Rappert, B., & Webster, A. (2000). *Contested futures: A sociology of prospective techno-science*. Aldershot: Ashgate.

Collingridge, D. (1981). *The social control of technology*. Milton Keynes, UK: Open University Press.

Copland, P. (2005). The book of life. *Journal of Medical Ethics, 31*, 278–279.

Derrida, J. (1981). *Dissemination*. Chicago: Chicago University Press.

EMEA. (2003). *Position paper on terminology in pharmacogenetics*. London: European Agency for the Evaluation of Medicinal Products.

Gassmann, O., Reepmeyer, G., & Zedtwitzv, M. (2004). *Leading pharmaceutical innovation*. Berlin: Springer.

Grin, J., Grunwald, A., Decker, M., Mambrey, P., Reuzel, R., & Van der Wilt, G. (1999). The lessons we learnt: first outline of strategy and a methodical repertoire for vision assessment. In J. Grin, & A. Grunwald (Eds.), *Vision assessment: Shaping technology in 21st century society – towards a repertoire for technology assessment* (pp. 169–189). Berlin: Springer.

Haffner, M. E., Whitley, J., & Moses, M. (2002). Two decades of orphan product development. *Nature Reviews Drug Discovery, 1*(10), 821–825.

Hedgecoe, A. M. (2003). Terminology and the construction of scientific disciplines: the case of pharmacogenomics. *Science, Technology & Human Values, 28*(4), 513–537.

Hellsten, I. (2002). *The politics of metaphor – biotechnology and biodiversity in the media*. Tampere: Tampere University Press.

Keller, E. F. (1995). *Refiguring life: Metaphors of twentieth-century biology*. New York: Columbia University Press.

Lakoff, G., & Johnson, M. (1980). *Metaphors we live by*. Chicago: University of Chicago Press.

Larkin, M. (1998). "Personalised" drug therapy could be near. *The Lancet, 351*(9120), 1937.

Loughnot, D. (2005). Potential interactions of the orphan drug act and pharmacogenomics: a flood of orphan drugs and abuses? *American Journal of Law & Medicine, 31*, 365–380.

Mambrey, P., & Tepper, A. (1999). Technology assessment as metaphor assessment. Visions guiding the development of information and communications. In J. Grin, & A. Grunwald (Eds.), *Vision assessment: Shaping technology in 21st century society – towards a repertoire for technology assessment*. Berlin: Springer.

Miller, F. A., Ahern, C., Smith, C. A., & Harvey, E. A. (2006). Understanding the new human genetics: a review of scientific editorials. *Social Science & Medicine, 62*, 2373–2385.

Porter, A. L., Ashton, W. B., Clar, G., Coates, J. F., Cuhls, K., & Cunningham, S. W., et al. (2004). Technology futures analysis: toward integration of the field & new methods. *Technological Forecasting and Social Change, 71*(3), 287–303.

Royal Society. (2005). *Personalised medicine: Hopes and realities*. London: The Royal Society.

Wyatt, S. (2000). Talking about the future: metaphors of the Internet. In N. Brown, B. Rappert, & A. Webster (Eds.), *Contested futures: A sociology of prospective techno-science* (pp. 109–126). Aldershot: Ashgate.

Wyatt, S. (2004). Danger! metaphors at work in economics, geophysiology, and the Internet. *Science, Technology & Human Values, 29*(2), 242–261.

Pharmacogenomics references

Baker, M. (2005). In biomarkers we trust? *Nature Biotechnology, 23*(3), 297–304.

Bartfai, T. (2004). Pharmacogenomics in drug development: societal and technical aspects. *The Pharmacogenomics Journal, 4*, 226–232.

Boulnois, G. J. (2000). Drug discovery in the new millennium: the pivotal role of biotechnology. *Trends in Biotechnology, 18*, 31–33.

Dean, P. M., Zanders, E. D., & Bailey, D. S. (2001). Industrial-scale, genomics-based drug design and discovery. *Trends in Biotechnology, 19*(8), 288–292.

ESHG, & IPTS. (2004). *Polymorphic sequence variants in medicine: Technical, social, legal and ethical issues: pharmacogenetics as an example*. Seville: ESHG, IPTS.

Evans, W. E., & Relling, M. V. (1999). Pharmacogenomics: translating functional genomics into rational therapeutics. *Science, 286*(5439), 487–491.

Evans, W. E., & Relling, M. V. (2004). Moving towards individualized medicine with pharmacogenomics. *Nature, 429*(6990), 464–468.

Fierz, W. (2004). Challenge of personalized health care: to what extent is medicine already individualized and what are the future trends? *Medical Science Monitor, 10*(5), 111–123.

Ginsburg, G. S., & McCarthy, J. J. (2001). Personalized medicine: revolutionizing drug discovery and patient care. *Trends in Biotechnology, 19*(12), 491–496.

Hall, S. S. (February 2003). Personalized medicine's bitter pill. *Technology Review*.

Hedgecoe, A. (2004). *The politics of personalised medicine*. Cambridge: Cambridge University Press.

Hedgecoe, A., & Martin, P. (2003). The drugs don't work: expectations and the shaping of pharmacogenetics. *Social Studies of Science, 33*(3), 327–364.

Kirchheiner, J., Fuhr, U., & Brockmöller, J. (2005). Pharmacogenetics-based therapeutic recommendations – ready for clinical practice? *Nature Reviews Drug Discovery, 4*(August), 639–647.

Lindpaintner, K. (2001). Pharmacogenomics and the future of medical practice: conceptual considerations. *The Pharmacogenomics Journal, 1*, 23–26.

Lindpaintner, K. (2002). The impact of pharmacogenetics and pharmacogenomics on drug discovery. *Nature Reviews Drugs Discovery, 1*(June), 463–469.

Loughnot, D. (2005). Potential interactions of the orphan drug act and pharmacogenomics: a flood of orphan drugs and abuses? *American Journal of Law & Medicine, 31*, 365–380.

Noble, D. (2003). Will genomics revolutionise pharmaceutical research and development? *Trends in Biotechnology, 21*(8), 333–337.

PriceWaterhouseCoopers. (2005). *Personalized medicine: The emerging pharmacogenomics revolution*. PriceWaterhouseCoopers – Global technology centre – Health research institute.

Reiss, T. (2001). Drug discovery of the future: the implications of the human genome project. *Trends in Biotechnology, 19*(12), 496–499.

Roses, A. D. (2000). Pharmacogenetics and the practice of medicine. *Nature, 405*, 857–865.

Royal Society. (2005). *Personalised medicine: Hopes and realities*. London: The Royal Society.

Rubinstein, W. S., & Roy, H. K. (2005). Practicing medicine at the front lines of the genomic revolution. *Archives of Internal Medicine, 165*(September 12), 1815–1817.

Shastry, B. S. (2005). Genetic diversity and new therapeutic concepts. *Journal of Human Genetics, 50*, 321–328.

Tribut, O., Lessard, Y., Reymann, J., Allain, H., & Bentue-Ferrer, D. (2002). Pharmacogenomics. *Medical Science Monitor, 8*(7), 152–163.

Van Delden, J., Bolt, I., Kalis, A., Derijks, J., & Leufkens, H. (2004). Tailor-made pharmacotherapy: future developments and ethical challenges in the field of pharmacogenomics. *Bioethics, 18*(4), 303–321.

Webster, A., Martin, P., Lewis, G., & Smart, A. (2004). Integrating pharmacogenetics into society: in search of a model. *Nature Reviews Genetics, 5*(9), 663–669.

Weinshilboum, R., & Wong, L. (2004). Pharmacogenomics: bench to bedside. *Nature Reviews Drug Discovery, 3*, 739–748.

Orphan drugs references

Alcimed. (2004). *Study on orphan drugs. Phase I. Overview of the conditions for marketing orphan drugs in Europe*. Paris: Alcimed.

Anand, G. (November 16, 2005). Orphan drugs hold out a lifeline. *The Wall Street Journal*.

Aronson. (2006). Rare diseases and orphan drugs. *British Journal of Clinical Pharmacology, 61*(3), 243–245.

Bosanquet, N. (2003). Equity, access and economic evaluation in rare diseases. The impact of orphan drug legislation on health policy and patient care. *Pharmaceutical Development and Regulation, 1*(3), 51–157.

Clarke, J. T. R. (2006). Is the current approach to reviewing new drugs condemning the victims of rare diseases to death? A call for a national orphan drug review policy. *Canadian Medical Association Journal, 174*(2), 89–190.

Daina, E. (1994). Rare diseases and orphan drugs. *The Lancet, 343*(8912), 1560–1561.

EMEA. (2005). *COMP report to the commission in relation to article 10 of Regulation 141/2000 on orphan medicinal products*. London: EMEA.

FDA Consumer. (2003). Orphan products: hope for people with rare diseases. *FDA Consumer, 37*(6), 10–15.

Haffner, M. E., Whitley, J., & Moses, M. (2002). Two decades of orphan product development. *Nature Reviews Drug Discovery, 1*(10), 821–825.

Hollis, A. (2006). Drugs for rare diseases: paying for innovation. In C. M. Beach (Ed.), *Health services restructuring in Canada: New evidence and new directions* (pp. 155–177). Montreal: McGill-Queen's University Press.

Joppi, R., Bertele, V., & Garattini, S. (2006). Orphan drug development is progressing too slowly. *British Journal of Clinical Pharmacology, 61*(3), 355–360.

Loughnot, D. (2005). Potential interaction of the Orphan Drug Act and pharmacogenomics: a flood of orphan drugs and abuses? *American Journal of Law & Medicine, 31*(2-3), 365–380.

Lunn, M. R., & Stockwell, B. R. (2005). Chemical genetics and orphan genetic diseases. *Chemistry & Biology, 12*(10), 1063–1073.

Maeder, T. (2003). The orphan drug backlash. *Scientific American, 288*(5), 80–87.

Milne, C. P. (2002). Orphan products – pain relief for clinical development headaches. *Nature Biotechnology, 20*(8), 780–784.

NICE. (2004). *Nice citizens council report ultra orphan drugs*. London: NICE.

Rai, A. K. (2002). Pharmacogenetic interventions, orphan drugs, and distributive justice: the role of cost-benefit analysis. *Social Philosophy & Policy, 19*(2), 246–270.

Rinaldi, A. (2005). Adopting an orphan. Incentives to develop drugs for rare disorders raise hopes and controversy. *EMBO Reports, 6*(6), 507–510.

Service, R. F. (2004). Orphan drugs of the future? *Science, 303*(5665), 1798.

Shah, J. (2003). Economic and regulatory considerations in pharmacogenomics for drug licensing and healthcare. *Nature Biotechnology, 21*(7), 747–753.

Smith, A. (2005). From orphan to blockbuster? CNNMoney.com (Accessed 28.06.06).

Stolk, P., Willemen, M., & Leufkens, H. G. M. (2005). *Rare essentials? Drugs for rare diseased on the Essential Medicines List*. Discussion paper for the WHO Expert Committee on the Selection and Use of Essential Medicines. Geneva: WHO.

de Visserde, M. (2006). Neuromuscular disorders: orphan diseases deserve attention. *The Lancet Neurology, 5*(1), 13–14.

van Weely, S., & Leufkens, H. G. M. (2004). Orphan diseases. In: *Priority medicines for Europe and the world. A public health approach to innovation*. Geneva: WHO.

Zitter, M. (2005). Managing drugs for rare genetic diseases. Trends and insights. *Managed Care, 14*(2), 52–67.