Innovation system barriers in orphan drugs development within the Netherlands

an exploratory analysis

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Abstract

With the growth of scientific knowledge about genetic defects and other orphan diseases also the development of orphan drugs for treatment of these diseases has increased also. However, orphan drug development often stops in its pre-clinical stage. Why this happens is the subject of this paper. By analyzing orphan drug development within the Netherlands it is tried to identify the barriers present in the Dutch innovation system of orphan drug development. From the tentative empirical results obtained various barriers can be identified. The identified barriers appear to be quite different in nature (e.g. economic, juridical, medical, etc.) but not independent from one another and to be the responsibility of various actors in the innovation system.

Keywords: orphan drugs, drug innovation process, innovation system barriers

1. Introduction

It is estimated that over 5000 identified rare diseases exist, which altogether affect tens of millions of people worldwide (Binns & Driscoll 2000). However, each of these diseases affects relatively few people. Rare diseases are considered to be life threatening or chronic progressive conditions, which are generally accepted to have a prevalence of less than one case per two thousand people. The combination of these small number of people affected, thus providing only small markets for drugs designed for them, and the high costs associated with drug development generally makes it unprofitable for pharmaceutical companies to develop drugs to treat or prevent these diseases. These diseases or conditions are therefore indicated as ‘orphan’, and the products that could be used to treat or prevent them are commonly known as ‘orphan drugs’. Box 1 gives an example of a well-known orphan disease and the developed orphan drug.

The rapid growth of molecular biological knowledge in the last years and the recent insights from the Human Genome Project lead to new delineations and classifications about disorders and diseases. At the moment, about 7,000 genetic disorders are known being the result of a mistake in the coding of one gene. Many of these genetic disorders fall into the category of orphan disease. For about 1,000 genetic disorders the deviant gene is identified by modern DNA-technology. Another category of orphan diseases includes rare variants of non-rare disorders, such as heart- and vascular diseases, lung diseases, rheumatism, cancer and psychiatric disorders. Because of the increased understanding of these disorders and improved DNA-techniques and DNA-scanning methods the possibilities for diagnosis and therapy may be expected to improve considerably in the next future. When it will be possible to diagnose many hundreds of genetic disorders by usage of biochemistry, further development of biopharmaceutical orphan drugs becomes feasible (Meijer *et al.*, 2001).

Box 1: Case study: Orphan disease: Pompe's disease and alpha-glucosidase production

An example of an *orphan disease* is Pompe's disease. People with Pompe's disease have a genetic defect that causes their bodies to fail to produce a necessary enzyme called alpha-glucosidase, which converts sugar and starch into glycogen. Without alpha-glucosidase, glycogen cannot be broken down and released and the body's cells cannot produce energy. In Pompe's disease, the muscle cells store the glycogen, which quickly leads to rapid deterioration of the muscles. Clinical forms of Pompe's disease vary according to the age of onset and progression of symptoms. The infantile form is diagnosed in the first few months after birth and is characterized by a rapid build-up of glycogen in several tissues, severe muscle weakness, and enlargement of the heart and liver. Complications in the respiratory system and heart complications predominantly lead to an early death in the first or second year of life. The juvenile form develops more slowly and often leads to death by a respiratory failure before the age of 30. Symptoms of the adult form may go undetected until the age of 30 to 50. Here also respiratory problems are the main cause of death.

The bio-pharmaceutical company Pharming N.V. in Leiden, the Netherlands, has succeeded in producing the enzyme human alpha-glucosidase by recombinant DNA techniques at high levels in the milk of transgenic rabbits. A US and European patent has been granted. The enzyme has showed to be active, since glycogen storage decreased and muscle regeneration was observed with the four infantile patients included in the first Phase II clinical trial performed. For the further development and commercialization of the transgenic orphan drug human alpha-glucosidase (so called Pompase®), Pharming formed an alliance with Genzyme. In exchange for investment funds Genzyme acquired the right of free use of Pharming's patent on alpha-glucosidase. But once another American partner of Genzyme proved to be successful in producing alpha-glucosidase in vitro, Pharming's production of the enzyme seems to have become obsolete. Nowadays, Pharming is experiencing economically hard times due to cash flow problems and problems with raising funds for further investments in developing Pompase®.

Because of the serious effects of orphan diseases, it is hard to accept that, in general, almost no orphan drugs are further developed or brought onto the market. It is found that the development of many of these orphan drugs very often entered the pre-clinical stage of drug development, after which, in general, no clear further development trajectory towards registration and market introduction has taken place. The availability of drugs to treat these rare disorders is limited by their weak economic incentive and lack of commercial value. Nevertheless, rare conditions such as Pompe's disease, amyotrophic lateral sclerosis (ALS), Gaucher's disease, and Huntington's chorea affect thousands of people worldwide.

Several regulatory instruments have been developed in order to encourage the development of orphan drugs. The first of these instruments was the 'Orphan Drug Act'[1] that was passed in the USA in 1983. A EU initiative did not follow until December 1999 when the 'European Orphan Drug Regulation'[2] was approved, which gives up to ten years of market exclusivity to orphan

[1] In 1983, the Orphan Drug Act was passed in the USA. Through a system of tax credits, government grants and assistance for clinical research, seven years of marketing exclusivity for orphan indications of approved products and exemptions from drug registration fees, this Act encouraged the development of orphan drugs. By the end of 1997, this resulted in over 150 new orphan drugs being approved, which are currently used by over seven million patients (Binns & Driscoll, 2000).

[2] Until recently, there has been no concerted European initiative, although some regulatory authorities have granted fee exemptions and reductions for orphan products, and some money has been made available for rare diseases in European Community research programs. In April 1999, however, a four-year program of EU action on rare diseases was finally adopted. This is intended to promote, throughout the EU, further understanding of rare diseases, monitoring and support networks, training of rare-disease experts, and transnational collaborations in this field. Of greater importance for the development of new drugs is the European Orphan Drug Regulation, which was passed in December 1999. This EODR gives up to ten years of market exclusivity to orphan medicinal products, and facilitates their registration by guaranteeing the availability of an EU-wide approval procedure. The EODR defines orphan medicinal products as those for which it can be established that either: (1) they are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five of ten thousand persons in the EU; or (2) they are intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the EU and that, without incentives, they are unlikely to generate sufficient revenues to justify the necessary investments. The second condition allows the orphan drug status to be given to diseases that are relatively prevalent but for which treatments might not be commercially viable. However, if a medicinal product is deemed orphan and if there is a satisfactory alternative then the product must be of significant benefit to patients (Binns & Driscoll, 2000).

drugs, and facilitates their registration. There are, however, still many uncertainties about the effects of these regulatory instruments.

Despite these regulations, not many companies are developing orphan drugs right now. Why does that happen? It seems as if the dynamics of the innovation processes in the field of orphan drugs is rather low and the barriers are very high. This paper, therefore, aims to provide insight into the innovation barriers that diminish the dynamics of orphan drugs development. More specifically, this paper tries to answer the following question.

Which barriers in the innovation trajectories of orphan drugs are currently present and discourage the development of orphan drugs in the Netherlands?

In order to investigate this question in further detail the paper is organized as follows. Section 2 discusses the process of (orphan) drugs development and the actors involved in this process. Some of these actors provide incentives that affect the willingness to develop orphan drugs. Section 3 presents some theoretical notions about innovation characteristics and assumptions affecting the development of orphan drugs. On the basis of these and previously presented insights in orphan drug development and the actors and their relations involved, a conceptual model of the factors affecting the adoption of orphan drug development will be specified. In order to investigate the propositions about the causal effects in the conceptual model, Section 4 describes the applied research methodology. Interviews with most relevant actors in the field of orphan drug development provided data, which are used for further testing of the presumed causal effects in the conceptual model. Section 5 presents the results of these analyses, which also indicate the barriers in the innovation trajectory of orphan drugs. These results are discussed in Section 6. The conclusions to be drawn from these results, as an answer to the research question stated above, will be presented in Section 7.

2. Orphan drugs development

2.1 The development process

This section first focuses on the general innovation process of drugs, and especially with regard to orphan drugs. Next, some theoretical considerations about specific innovation characteristics of (orphan) drugs development are presented, leading to a conceptual model and some general assumptions about orphan drugs development.

The process, which eventually leads to the market introduction of a drug, lasts a long time. In this process various stages can be identified (see figure 2.1)

The first stage in the development of medicinal drugs consists of research into the working mechanism and the pathogenesis of a disease. This information is needed as a basis for the development of therapeutic substances. Therefore, the lack of knowledge about the pathogenesis of orphan diseases, which is caused by a lack of research, is a big problem in the development of orphan drugs.

The next stages in the development of a drug begin with the design of the substance. When a promising (guiding) substance is found (by screening, molecular modification, rational design or serendipity), it will be thoroughly tested in subsequent stages. In these tests the quality, safety and efficacy of this substance must be established. The first series of the tests involves animal experiments. The main objective of animal tests is to obtain an indication of a safe dose for further testing on humans. Animal models, however, are often absent because only little research has

been carried out on the pathogenesis of orphan diseases. Clinical experiments form the next series of tests, which can be categorized into three phases of testing.

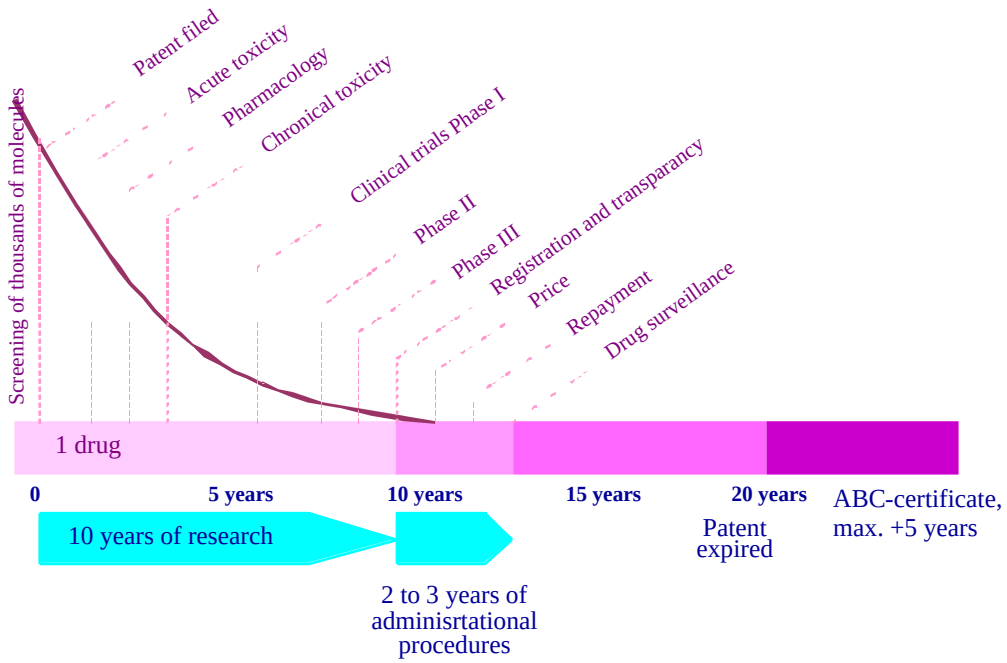

Figure 2.1: Different stages of drug development (Kleijwegt & Schuttelaar, 2001)

In the first clinical phase I the substance is administered to a small number of healthy volunteers. The purpose of these experiments is to collect more data on the safety of the drug in humans. In the experiments conducted during phase II of the clinical research only patients are involved. Furthermore, the experiments involve a larger group of subjects. The main goal of this research is to establish the short-term single dose efficacy. The last phase III involves a still larger group of patients taking part in randomized controlled, double blind, trials in order to establish both the short- and long-term efficacy. But in case of orphan diseases, it is difficult to get sufficient patients for these clinical trials. In some cases all patients within one or even more countries have to be included in order to carry out a statistically sound experiment. Only when phases I to III have been successfully concluded, the pharmaceutical substance is eligible for market registration. When the drug is registered, it can be introduced to the market. After this introduction, the effects of the drug will still be monitored and evaluated. This is usually indicated as the post-marketing phase IV of the clinical trials (Otten & Vermeulen, 2001).

It is obvious that the research and development process of orphan drugs face some specific problems. An important difference with conventional drug development is the fact that only little research into the pathogenesis of orphan drugs has been conducted. Another main problem is the small number of patients that are available for the clinical trials (Leufkens, 2001; Lang & Wood, 1999).

2.2 Actors involved in the development of orphan drugs

Various actors play an important role in the development of orphan drugs, namely universities and research institutes, academic hospitals, pharmaceutical companies, patients' organizations, and

governmental institutions (i.e. the 'government' in figure 2.2). The role of each of these actors will be described below.

Universities and research institutes play a rather important role in the first stage of drug development, namely the research into the working mechanisms underlying an orphan disease. This research is very often performed in collaboration with academic hospitals, which can provide clinical data. It is less common that universities play a significant role in the development of an actual pharmaceutical substance. More often, universities cooperate with pharmaceutical companies providing data on the pathogenesis of the disease, while leaving the actual development process of the drug to the pharmaceutical industry. Sometimes, universities do play a role in subsequent stages of the drug development process, but this is mostly as a subcontractor conducting, for example, animal experiments for pharmaceutical firms.

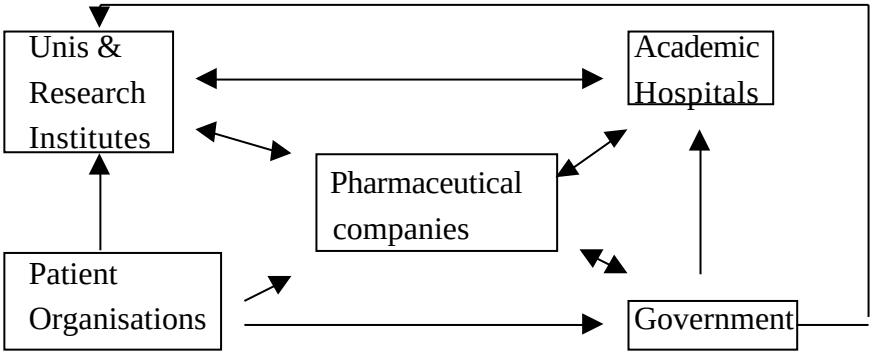

Figure 2.2: Network of actors involved in the development of orphan drugs

Academic hospitals also play an important role in the drug development process via their research into the pathogenesis as well as via providing clinical data to universities and other actors for further research into the pathogenesis. Furthermore, academic hospitals often take an important role in the clinical testing of drugs. Because of the high costs of testing and registration, an academic hospital does this in cooperation with pharmaceutical companies.

Pharmaceutical companies are the most important players in the development of pharmaceutical drugs. They participate in every stage of the development process. Some firms do their own research into the pathogenesis of diseases. But most firms obtain this kind of information from research by universities, research institutes and academic hospitals as this kind of fundamental research is not very profitable for pharmaceutical firms. They focus especially on the development of specific pharmaceutical substances. In the next phase of drug development, some firms do their own animal experiments although it is not uncommon for firms to subcontract those experiments to universities and research institutes. Phases I and II in the clinical trials are mostly done in-house by the pharmaceutical firms. Because of the larger patient groups involved in the later phases of clinical testing cooperation with academic hospitals is common use. For registration of the developed drug, the pharmaceutical firm has to deliver adequate data on the safety, efficacy and quality of the drug. After registration and market introduction of a drug, the pharmaceutical firm is responsible for the evaluation of its effects on patients, who use the developed drug (so called post-marketing surveillance). Some other actor groups also play an important role during the post-marketing stage; especially the hospitals, physicians, pharmacists, patients and patients' organizations, because they may give feedback on the use and effects of the drug. Many

pharmaceutical firms increasingly cooperate with patients' organizations in the drug development process (Meijer *et al*. 2001).

Patients' organizations have mostly not a very direct influence on the development of a drug. They are, however, very important to increase the awareness of a certain disease (Lang & Wood, 1999). This is especially important in the case of orphan diseases. The inventory done by patients' organizations led to the preparation of an extensive list of orphan diseases. Furthermore, these organizations indicated the importance of further development of diagnostics, the collection of reliable data on the prevalence of orphan diseases, the further development of treatment methods based on genetic knowledge, and the mobilization of sufficiently large patient groups in studies to establish the efficacy of orphan drugs. In addition, they collect information on regulations as well as sources of financial support. They also play an important role in initiating and stimulating the cooperation between scientific researchers and the industry (RGO, 1998). Furthermore, patients' organizations promote and stimulate the development of orphan drugs and they are continuously trying to persuade the government and pharmaceutical companies to invest in orphan drugs development.

The *government* is also an actor in the drug development process. Although it doesn't play a direct role in the development process, except for the registration phase (via 'College ter Beoordeling van Geneesmiddelen' and EMEA), its indirect influence on the other development stages is not negligible. The government is responsible for policies regarding medical knowledge, industry and public health (RGO, 1998). The ways chosen by the government to stimulate research and development of orphan drugs is of great importance for the outcome of the innovation process. The government can influence the development of orphan drugs in several ways by applying the EODR. The European Orphan Drugs Regulation is based on the American Orphan Drug Act, which uses tax benefits, subsidies, support for clinical trials and seven-year market exclusivity as important instruments. The European Orphan Drugs Regulation expands on this act by facilitating registration and providing ten-year market exclusivity. However, European laws do not provide possibilities of tax benefits for pharmaceutical companies involved in orphan drug development (Binns & Driscoll 2000; Directive No. 1295/1999/EG; Otten & Vermeulen, 2001).

Despite the stimulating measures taken by European governments and the efforts made by patients' organizations, the current situation in the Netherlands is that orphan drug development in the pre-clinical stage has increased without being followed up in later stages of clinical trials, registration and market introduction. In order to acquire more insight into the barriers of orphan drugs development, the next section presents some theoretical notions leading to a conceptual model of the willingness to develop orphan drugs to be investigated empirically.

3. Theoretical considerations

In general, drug development represents a science based innovation trajectory initiated by demand-pull conditions (cf. Tidd *et al*. 2001). These demand-pull conditions are reflected in expected innovation (i.e. drug) adoption and diffusion among potential customers (i.e. patients). If expected drug adoption by patients is high on a large scale then the willingness to develop such a drug will be large for reasons of competitive advantage and returns on investments. Consequently, we apply the conceptual model of innovation adoption and diffusion developed in various successive innovation studies (cf. Tornatzky & Klein, 1982; Moore & Benbasat, 1991; Rogers, 1995; Tidd *et al*. 2001). For the purpose of this study, actual innovation adoption and diffusion in this model has been replaced by expected innovation adoption and diffusion among

customers to be measured on the willingness to develop orphan drugs (see figure 3.1). By analyzing this conceptual model for various actor groups involved in different stages of orphan drug development, the multi-actor perspective will be taken into account.

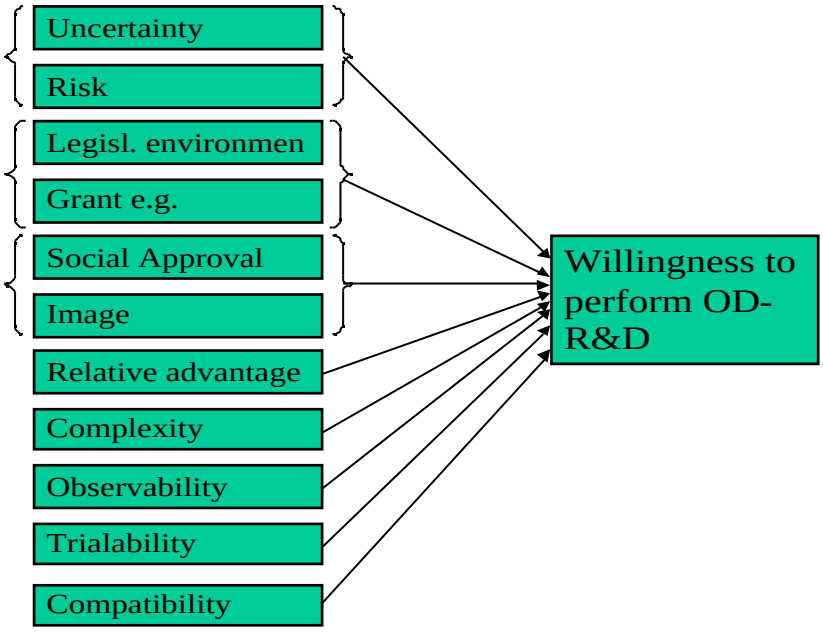

Figure 3.1 Potential independent variables influencing willingness to develop orphan drugs (Kleijwegt & Schuttelaar, 2001)

Depending on the value taken, each independent variable in figure 3.1 may contribute to the willingness to develop orphan drugs or may represent a barrier to this willingness. The most important barriers will be briefly described below.

There are various *uncertainty* factors, which provide pharmaceutical companies with additional risk. A new drug has to be pharmaceutically possible, therapeutically needed and financially profitable to be developed. Orphan drugs are therapeutically necessary. Although not much people suffer from orphan diseases, they do suffer much. Pharmaceutical companies have to cope with a great uncertainty about whether they will receive sufficient revenues after market introduction to cover the initial R&D costs of orphan drug development. A government may try to reduce this uncertainty by imposing tax credits, clinical research assistance and market exclusivity. Uncertainty is thus highly correlated with financial *risk*. Pharmaceutical companies are not different from other firms in trying to avoid such risk as much as possible. Consequently, they are inclined to select (the most) profitable opportunities. As uncertainty factors are closely related to risk, we include only the independent variable *risk* in our final conceptual model.

The *legislative context* for orphan drug development could provide a stimulating effect, in the form of grants, tax fees, support with application/registration and clinical trials and market exclusivity. The European Orphan Drug Regulation provides a current example of such stimulating legislative environment. The question remains, however, whether or not such measures taken by the government will be sufficient for orphan drug development to take place.

Two closely related variables are *social approval* and *image*. According to Tornatzky & Klein (1982), “social approval refers to status gained in one’s reference group as a function of adopting a particular innovation.” And image is defined as: “the degree to which use of an innovation is

perceived to enhance one's image or status in one's social system" (Moore & Benbasat, 1991). To prevent the data gathered in the interviews from multicollinearity, only one of these closely related variables is included in our conceptual model, i.e. *image*, with social approval being an associated dimension. The development of an orphan drug by a pharmaceutical company can, if well communicated to the outside world, be expected to have a positive influence on its image.

The specific features of innovation processes also provide another set of variables affecting these innovation characteristics. These characteristics are, amongst others: complexity, compatibility, relative advantages, observability and trialability, etc. (Tornatzky & Klein, 1982; Rogers, 1995). These characteristics will be discussed not from the perspective of customers (i.e. patients) but from the perspective of developers/producers. The reason for this orientation is that the objective of this study is not the adoption of a product innovation by customers but the adoption of a product-process innovation by developers/producers.

The first additional characteristic is *relative advantage*, which is defined as "the degree to which an innovation is perceived as being better than its predecessor." (Moore & Benbasat 1991). In our study, the advantage is not relative to the predecessor, but relative to the development and adoption of conventional drugs. The most important differences are provided by the Orphan Drug status (the so called OD-status) and the benefits it provides, the small production scale and the improvement of image both leading to a competitive advantage. For some pharmaceutical companies, the OD-status may provide a very stimulating incentive for image improvement, especially when proper funding and a profound knowledge base are lacking. For small companies, the small scale of production of orphan drugs can be very attractive.

The second additional innovation characteristic is *complexity*, which is defined as "the degree to which an innovation is perceived as being difficult to use. " (Moore & Benbasat 1991). Orphan drugs development is more complex than the development of conventional drugs because of several differences. The absence of detailed pharmacological information is one of them. Usually not much research into orphan diseases has been carried out. Furthermore, there are more technical and organizational difficulties involved since orphan diseases often have a genetic background, lack suitable animal models are require more collaboration with other institutes than conventional drug development.

The third additional innovation characteristic is *observability*, which is defined as "the degree to which the results of an innovation are observable to others." (Moore & Benbasat, 1991). It could be stated that because of the difficulties mentioned above the advancement of research into orphan drugs is less observable. This is not considered to be a very important influence on the willingness to develop orphan drugs because it will depend on the difficulties creating complexity.

Trialability, the fourth additional characteristic, is defined as "the degree to which an innovation may be experimented with before adoption." (Moore & Benbasat, 1991). The trialability of orphan drugs suffers from the difficulties that arise during the clinical trials stage, when sufficient patients with a particular orphan disease are needed. Patients' organizations can then very helpful for finding these people.

The last additional innovation characteristic represented in figure 3.1 is *compatibility*. "Compatibility is the degree to which an innovation is perceived as being consistent with the existing values, past experiences, and needs of potential adopters." (Moore & Benbasat, 1991). The compatibility is high when the research or development fit the company or research institute well. In principal, the development of orphan drugs is not different from the development of conventional drugs. Therefore, compatibility is not considered to be a large barrier in the development of orphan drugs.

In sum, the following conceptual model has been constructed, which indicates the causes of the willingness to develop orphan drugs (Figure 3.2):

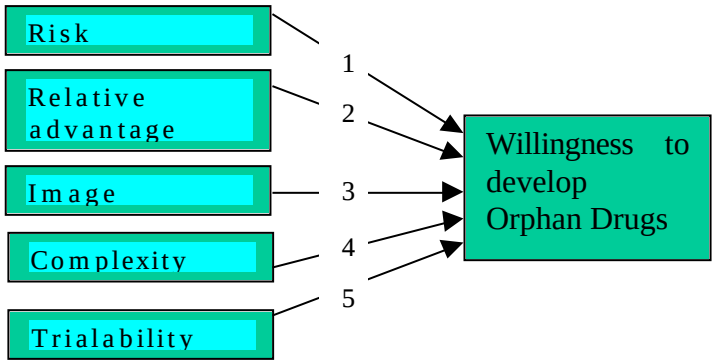

Figure 3.2: conceptual model (Kleijwegt & Schuttelaar, 2001)

The following propositions about the effects of the independent concepts on the willingness to develop orphan drugs depicted in figure 3.2 can be formulated:

1. If the risk decreases then the willingness to develop orphan drugs will increase.
2. If the relative advantages are perceived to be lower then the willingness to develop orphan drugs will decrease.
3. If image is an important factor for a research institute or pharmaceutical company then the willingness to develop orphan drugs will increase.
4. If research and development on orphan drugs is more complex then the willingness to develop orphan drugs will decrease.
5. If the trialability of developing orphan drugs increases then the willingness to develop orphan drugs will increase.

These propositions apply especially to that actor group, which is directly involved in orphan drug development, namely pharmaceutical companies in collaboration with research institutes, academic hospitals and universities called hereafter 'producers'. Various other actors within a country like the Ministry of Public Health and various (public and private) medical and health organizations, physicians and patients and their organizations affect the magnitudes of the independent variables in the conceptual model. These other actors are classified into two additional actor groups, namely legislative and regulatory organizations called hereafter 'regulators', and organizations of physicians and patients called hereafter 'consumers'. Regulators may influence the prevailing values of *risk*, *complexity* and *trialability* by taking (enhanced) financial, legislative and regulatory measures based on the European Orphan Drug Regulation. Consumers may improve the prevailing values of *complexity* and *trialability* by participating in the development of the pathogenesis of orphan diseases and the development of orphan drugs. But regulators and consumers will only be inclined to contribute to diminishing the barriers in orphan drug development if they are aware of these barriers. And only if all three actor groups have a shared view on the barriers in the orphan drug development trajectory the willingness to conduct concerted actions may be expected to increase. Then concerted action may be designed and planned that may facilitate orphan drug development. In order to assess and compare the perceptions of these barriers among producers, regulators and consumers, the conceptual model in figure 3.2 will be operationalized in the next section.

4. Research methodology

4.1 Operationalization of concepts

The concepts in figure 3.2 have been operationalized by representing them as various empirical variables.

Risk is related to financial risk, which is indicated by the costs of research into the pathogenesis of an orphan disease, costs of developing an orphan drug (drug design, drug production, animal models, pre-clinical and clinical tests, registration and monitoring), expected revenues (number of patients, insurance payments of costs of use) and expected profitability (returns on investments). Another indicator of risk concerns the realization of the juridical benefits allowed by the EODR, namely achieving the OD-status.

Relative advantage has been operationalized by two sets of indicators. The first set of indicators concerns the degree of correspondence between orphan drug development and conventional drug development by pharmaceutical companies, namely the scale of production and servicing market niches. The second set of indicators concerns the stimulating activities induced by the government, namely providing clinical research assistance, facilitating registration and granting market exclusivity.

Image is conceived to be indicated by actual orphan drug development by pharmaceutical companies and their cooperation on orphan drug development with academic hospitals, patients' organizations and the regulators.

Complexity is indicated by the degree of available knowledge about the pathogenesis of orphan diseases, available animal models, measures for financial support and registration procedures, together with the degree of sharing this knowledge among the three actor groups producers, consumers and regulators.

Trialability is measured on the possibilities to conduct clinical trials and the cooperation of patients' organizations in these trials.

Willingness to develop orphan drugs is indicated by various stages in the policy process regarding orphan drug development, namely: nothing done, policy goals defined, policy measures planned, policy instruments developed, and policy instruments implemented.

4.2 Data acquisition

The indicators are measured on the perceptions of their relative importance/influence held by selected key-role actors in the field of orphan drug development within the Netherlands to be expressed on a 5-point Likert scale (1 = no importance / strongly negative, …, 5 = most important / strongly positive). Five key-role actors within every distinguished actor group have been interviewed (cf. Kleijwegt & Schuttelaar, 2001; Mastbergen & van der Valk, 2001; Otten & Vermeulen, 2001). These key-role actors are:

1) the head of a research team within an academic childern's hospital managing research into the pathogenesis of orphan diseases, an university professor specialized in biopharmaceuticals and pharmacotherapy concerning orphan diseases, the director of a biopharmaceutical company, the organization of pharmaceutical enterprises, and the chairman of the scientific council on orphan drug development for the group of producers;
2) the ministry responsible for public health, the council for the admittance of drugs, the organization of health insurance companies, the advisory council on public health, and the organization for research into public health for the group of regulators; and
3) two patients' organizations on orphan diseases, the organization of physicians, a medical specialist working within an orphan disease department of an academic children's hospital, and the organization of medical hospital specialists for the group of consumers.

As these key-role actors are well-informed about orphan drug development they have been interviewed in order to improve the reliability of the data analyzed. Statistical analyses based on random samples of respondents from the three actor groups are not feasible because orphan diseases are not common diseases, which are also very different from each other with respect to their pathogenesis, so that the actual number of people within each actor group involved is very limited.

4.3 Method of analysis

Analysis of data obtained from only 5 respondents within each actor group by means of statistical methods will result in inherently unreliable results due to small sample sizes. Therefore, the results of data analysis are based on a combination of majority counts and average scores.

In case of a Likert scale whereon 1 represents 'strongly negative' and 5 represents 'strongly positive', if the majority and the average of the scores on each indicator is below or above the neutral scale value of 3 then the coincidence of the indicator with the concept it represents is interpreted as negative or positive, respectively.

In case of a Likert scale whereon 1 represents 'no influence' and 5 represents a 'very strong influence', if the majority and the average of the scores is between 0 and 1.5, 1.5 and 3.5, or 3.5 and 5 then the coincidence of the indicator with the concept it represents is interpreted as none, weakly positive or very positive, respectively.

In both cases, if the average score of an indicator does not coincide with the majority of all scores then the coincidence of that indicator with the concept it represents is interpreted as nonexistent because it is generated by outliers.

The scores on every indicator are thus reduced to one out of three possible categories of coincidence with the concept represented by that indicator, namely **-/0**/+ or **0**/+/++. The correlation of every pair of indicators is derived from their combination of categories of coincidence with the concepts they represent (see Figure 4.1)

	-	0	+
-	+	0	-
0	0	0	0
+	-	0	+

	0	+	++
-	0	-	-
0	0	0	0
+	0	+	+

	0	+	++
0	0	0	0
+	0	+	+
++	0	+	+

Figure 4.1 Correlations between indicators derived from 27 combinations of possible categories of coincidence with the concepts they represent

5. Results

Applying the methods of analysis to the data obtained on the indicators mentioned, as described in the previous section, gives the results summarized in table 5.1.

Table 5.1 Perceived coincidence of indicators with the concepts they represent

concept	indicator	coincidence for producers	regulators	consumers
risk	- costs of development		+	+
	- expected revenues	-	-	
	- Orphan Drug status	-		-
relative advantage	- scale of production	-		+
	- servicing market niches	-		
	- subsidies	+		+
	- facilitating registration	+	+	+
	- granting market exclusivity	+	+	+
	- enhanced patent period			+
image	- developing orphan drugs	+		+
	- coop. with patients' organizations	+		+
	- coop. with medical institutions	+		+
	- coop. with public health organizations	+		
complexity	- knowledge of pathogenesis	-	-	-
	- knowledge of animal models	-	-	
	- knowledge of financial support measures	-	-	
	- knowledge of registration procedures	-	-	
	- knowledge sharing	+	-	+
trialability	- clinical trials	+	+	+
	- participation of patients' org.	+		
willingness to contribute to orphan drug development		+	+	0

The willingness to contribute to orphan drug development within the groups of producers and regulators is just a little positive reflecting rather intentions than actions. This willingness is expected to be influenced positively by the relative advantage and the image of and the trialability during orphan drug development. The (financial) risks and complexity of orphan drug development are expected to influence this willingness negatively. As can be seen in table 5.1, all distinguished actor groups share only four perceived barriers to orphan drug development. And even though, they still differ in the importance assigned to most of these shared barriers.

The *risk* of orphan drug development is thought by the regulators and the consumers to consist of the enormous amount of costs of development involved. Producers think quite different about that. They are acquainted with the relatively large costs of any drug development. What bothers them more are the expected little revenues from such a drug and the uncertainties surrounding obtaining the OD-status on which a EU-market exclusivity for such a drug may be grounded.

The *relative advantage* of orphan drug development is perceived by the producers to be negatively affected by its relatively small scale of production and the extra efforts needed to service its small market niches. Consumers think that the small scale of production improves the relative advantage

of orphan drug development because they will mostly be produced by small biopharmaceutical enterprises. But most of these enterprises lack the financial resources to boost production and to develop market niches to maximum extent in order to generate profitable economies of scale.

Both producers and consumers stress the importance of getting help from governmental agencies in the form of facilitating registration of and granting market exclusivity for orphan drugs based on the OD-status under the EODR. The regulators agree with the significance of these measures but perceive their contribution as less important.

The improvement of the *image* of pharmaceutical companies due to actual orphan drug development and their cooperation with patients' organizations and medical (research) institutions in order to gain societal support for burden sharing are perceived as important by the producers and consumers of orphan drugs but not by the regulators.

The *complexity* of orphan drug development is rather high according to the producers and regulators because of a lack of knowledge about their pathogenesis and suitable animal models. Consumers think less negative about this complexity because they can contribute actively to the knowledge base concerning orphan diseases.

The regulators think that the available knowledge about financial support measures and registration procedures are widely spread and shared although the producers are less optimistic about that. Additionally, producers and consumers both think that knowledge about orphan drug development is shared on a moderate but increasing scale. The regulators think, however, that this knowledge sharing hardly occurs and needs to be stimulated.

All actor groups involved in orphan drug development perceive the *trialability* of orphan drugs to depend on the possibilities to conduct clinical trials. Additionally, producers stress the importance of the participation of patients' organizations in these trials. But patients' organizations have not foreseen such a role in orphan drug development yet.

All these coincidences of indicators with the concepts they represent are presented in figure 5.1 as fat arrows together with their sign of coincidence. The thin arrows in figure 5.1 represent non-zero correlations between the indicators, which are obtained as described in Section 4.3. In figure 5.1 the admittance of a drug is added although it is not investigated as an indicator of one of the concepts. It is added because it is the outcome of registration procedures based on the results of clinical trials and represents a necessary condition for generating revenues from drug development. A few other coincidences of indicators with the concepts they represent and associated non-zero correlations among indicators are not presented in figure 5.1 and are discussed below.

The contradictory perceptions of the indicator 'knowledge sharing' are not presented. Producers and consumers already participating in the development trajectory of orphan drugs perceive knowledge sharing to increase the problem of complexity. Probably they foresee that knowledge sharing will further complicate the organization of orphan drug development with a negative marginal improvement of the development trajectory. Regulators think quite differently about this. They perceive a lack of knowledge about orphan diseases and orphan drug development within pharmaceutical companies. As if those companies are not already cooperating and sharing knowledge with academic hospitals and research institutes.

Also the positive coincidences of cooperation with medical institutions and public health organizations are not presented in figure 5.1. The first type of cooperation is implicitly taken into account by putting medical institions into the category of producers due to their tight relationships with universities, research institutes and pharmaceutical companies.

The second form of cooperation is not taken into account because the regulator driven effects in figure 5.1 imply this cooperation.

The final results of the analyses depicted in figure 5.1 show that the willingness to develop orphan drugs at the level of intentions instead of actions depends on:

1) A high financial *risk* due to large development costs, expected little revenues and no realized admittance of orphan drugs. The costs of orphan drug development are that large due to the small scale of production, small market niches to be serviced and little subsidiary payments of research costs by the regulators (i.e. the government). Expected little revenues are perceived to be caused by uncertainty about granting market exclusivity and the absence of an agreement about subsidiary payments by the regulators (i.e. insurance companies) to consumers in order to reduce the costs of use. Furthermore, no orphan drug has been admitted yet by public health organizations due to problems concerning their registration.
2) The perception of a small *relative advantage* of developing orphan drugs because of a required scale of production that is smaller than and different from conventional drug production, the need to service market niches, which differs from servicing a large consumer market for conventional drugs, and the prevailing uncertainties concerning registration, market exclusivity and subsidiary payments for research.
3) A lack of *image* improvement because there has no admittance of orphan drugs taken place yet, which in its turn is due to problems of registration. Furthermore, *image* and *willingness*, which represents actual drug development by its highest score, are mutually reinforcing.
4) A high degree of *complexity* concerning orphan drug development because of a lack of knowledge about the pathogenesis of orphan diseases, suitable animal models and sufficient clinical trials. These unfavorable conditions prevail without an extra high rate of participation of patients, extra subsidiary payments for research and help with the registration of orphan drugs.
5) A low level of *trialability* results from insufficient possibilities to conduct statistically valid clinical trials, which in their turn result from the conditions mentioned above.

These unfavorable conditions for orphan drug development represent barriers in the Dutch innovation system of orphan drug development. As the characteristics of producing and marketing orphan drugs are rather stiff because of the nature and prevalence of orphan diseases, these barriers can only be lowered by improving the conditions under control of the regulators and consumers. Only then the willingness to develop orphan drugs can rise from the level of good intentions to the level of (concerted) actions.

6. Discussion

The results on the variables and concepts affecting the willingness to develop orphan drugs within the Netherlands presented in figure 5.1 are hardly surprising. But these results should be regarded as tentative for the following reasons.

First, by adapting the conceptual model of actual innovation adoption to a conceptual model of expected innovation adoption the theoretical foundation of the model should be reassessed.

Secondly, the selected respondents, who are rather well informed about orphan diseases and orphan drug development, may represent biased samples from their actor groups. Random samples of respondents in the distinguished actor groups should be obtained as soon as the population of the actors in each group has been defined.

Thirdly, various empirical indicators of the explanatory concepts still represent multiple observable aspects. This applies especially to the indicators '(knowledge of) subsidiary payments for research and use', which contains at least 4 observable aspects, and '(knowledge of)

facilitating registration', which contains at least 2 observable aspects. Ergo, the operationalizations of the explanatory concepts should become further detailed.

Fourthly, instead of applying descriptive statistics and combinations thereof proper statistical methods based on probability theory should be applied. These methods will allow us to test the face validity of the operationalizations derived from the concepts and the construct validity of the relationships between the concepts specified in the conceptual model on the estimated relationships among their operationalizations (cf. Riley, 1963). Knowledge about these validities is necessary to improve confidence in the conceptual model of the willingness to develop orphan drugs and the obtained results concerning this conceptual model as derived in this study.

In sum, various possible theoretical and methodological uncertainties contained in the results obtained must be further investigated in future research.

With regard to the content of the tentative results presented some interesting options for facilitating orphan drug development can be derived. From figure 5.1 it becomes clear that the actor group of regulators may affect the concepts influencing the willingness to develop orphan drugs directly or indirectly to an extent that is much less possible with conventional drug development. The EODR provides the legislative foundation to do so. If the measures related to the OD-status granted to pharmaceutical enterprises are backed up with coordinated subsidiary payments of costs of research by the government and costs of use by insurance companies then the barriers to orphan drug development may be overcome. But that requires another focus on orphan drug development to be adopted by the regulators than the one held now. The current focus of the regulators on orphan drug development is on sharing knowledge about orphan diseases and orphan drug development among the various actors contained in the distinguished actor groups in order to promote learning by and cooperation between them. The actor groups of producers and consumers do not support this view of the regulators. They require them to assume a much more active role in orphan drug development by promoting and facilitating the achievement of the OD-status by pharmaceutical enterprises and to support this achievement with subsidiary payments of research into and use of orphan drugs. Additionally, coordination and planning of the activities to be conducted by the various actors involved in orphan drug development should lead to concerted action programs for specific orphan drug developments wherein the actors' contributions and liabilities are matched and defined. Such programs should prevent the adoption of free rider behavior by one or more actors involved.

7. Conclusions

In this article it is tried to identify the barriers in the innovation system of orphan drug development within the EU. On the basis of the conceptual model of the adoption of innovations (cf. Tornatzky & Klein, 1982; Rogers, 1995; Tidd *et al*., 2001) and by operationalizing the concepts in this model for three different groups of actors involved in orphan drug development, i.e. producers, regulators and consumers, a multi-actor approach of analysis is adopted in this study. The data derived from interviews with 5 key-role actors in every actor groups have been analyzed by means of simple descriptive statistics only because of the small samples sizes. The results of the analyses are reflected in the empirical relationships among the indicators and between the indicators and the concepts they represent contained in figure 5.1, which also indicate the conditions, that is the (ordinal) values of indicators, which hamper the willingness to develop orphan drugs to rise from the level of good intentions to the level of active involvement. These conditions act as barriers in the innovation system of orphan drug development, namely: omissions in the knowledge about the pathogenesis of orphan diseases; a lack of suitable animal models; problems with conducting sufficient clinical trials; problems with the registration of

orphan drugs; the uncertainty about achieving the orphan drug status; the enormous costs of orphan drug development; and the expected little revenues from orphan drug use.

The results presented in this article are only tentative due to the exploratory nature of the research carried out. Further research utilizing random samples of respondents taken from the distinguished actor groups and appropriate statistical tests grounded in probability theory is needed in order to test the validity of these results.

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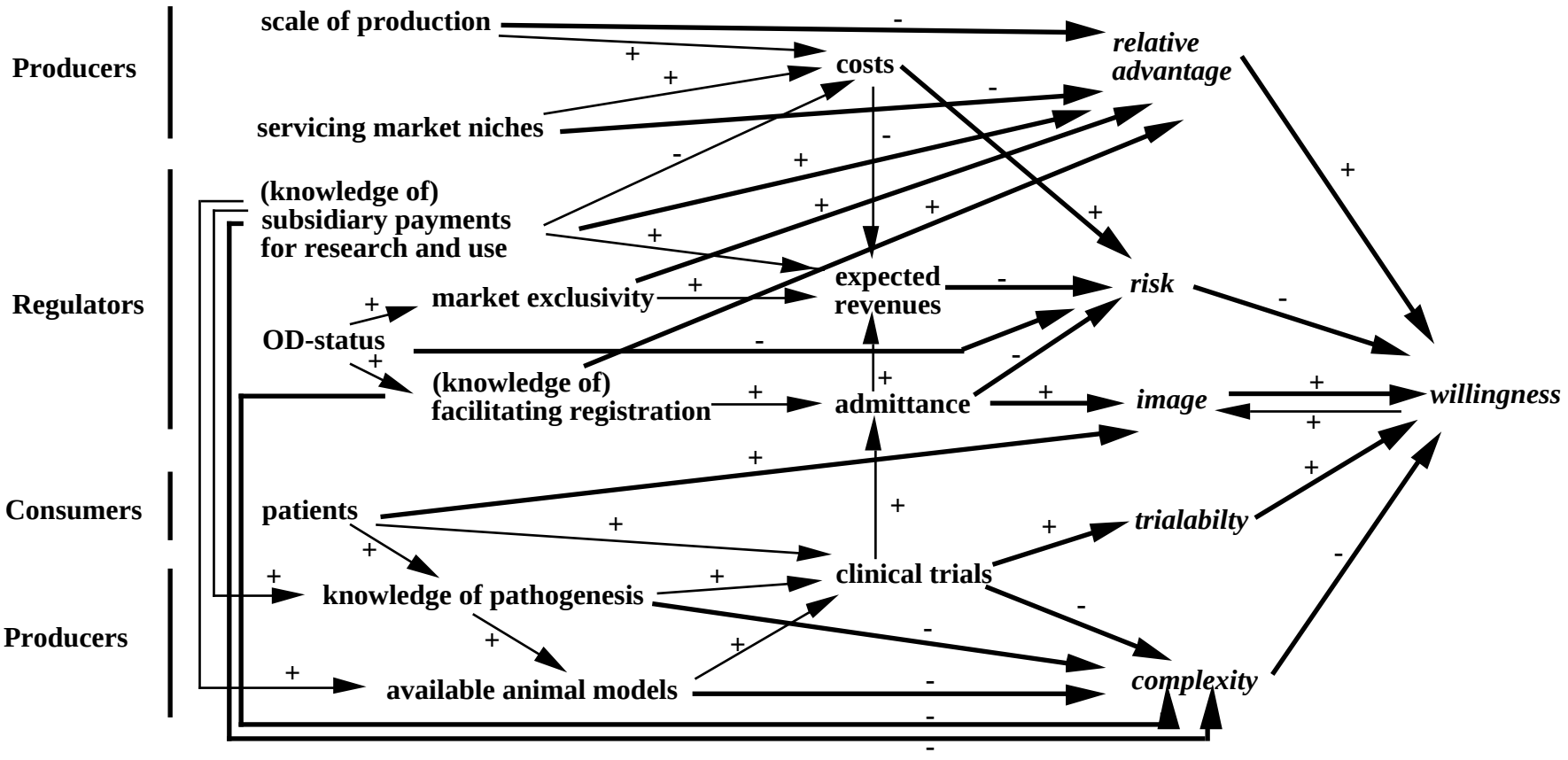

Figure 5.1 Tentative results on the barriers in orphan drug development within the Netherlands