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Orphan drugs: Unmet societal need for non-profitable privately supplied new products

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Abstract

Due to the severity of rare diseases, the societal need for biopharmaceutical treatments for these diseases is high, despite low numbers of patients. Therefore, we investigated the barriers currently hindering the willingness to develop orphan drugs in the Netherlands. To this end, a robust, small sample, exploratory analysis of Dutch multi-actor development of orphan drugs was performed. Various factors that were expected to stimulate the adoption of orphan drug development were found to be important barriers. Concerted actions of producers, users, and especially regulators are necessary to overcome these barriers, but the prerequisite of a shared problem definition is lacking.
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1. Introduction

In various instances, market conditions fail to produce incentives for the development and production of products (goods and/or services) that are demanded in Western societies. If such market imperfections occur with respect to generally desired products, such as security, healthcare, housing and environment, then governments often develop policies and measures to sustain the supply of these products. These governmental policies and measures are developed using juridical rules, taxation, subsidies, and public financing, and aim to increase the accessibility of these products for the general public. Decision-making concerning such governmental policies and measures can be analyzed using public-choice theory (Arrow, 1963; Olson, 1966). The dilemma to be solved by public-choice theory is between the efficacy of reaching those societal groups that need but cannot afford these products and the efficiency of putting a (financial) burden on those groups that do not need or want these products in order to produce them. This dilemma becomes more complicated if there is only a (very) small societal need for such products but a large societal moral pressure to provide them, for example, clean air in isolated, heavily polluted industrial areas, and healthcare for rare diseases. This is particularly true when these products must be provided by private enterprises at large costs within networks in which many other interested groups are involved, such as research institutes, governmental agencies, and pressure groups. In these cases, firm behavior is not only dependent on external incentives, such as governmental policies and measures, but is also dependent on the characteristics of

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the network in which these firms operate. In addition, if new products are needed, then the functioning of the network – the product-related innovation system – in which the firms participate becomes particularly important. Also, not only juridical and financial measures determine the functioning of that innovation system but also knowledge production and diffusion, learning, coordination of activities, and demand articulation by organizing consumer demand. Consequently, the successful operation of such an innovation system depends on various characteristics of the actors involved and their linkages. However, all these aspects may also contribute to the barriers that prevent an innovation system from becoming successful in providing publicly desired and privately produced new products.

To identify and analyze such innovation barriers, an exploratory empirical study of orphan drug development in the Netherlands has been conducted. More specifically, this article aims to provide insight into the innovation barriers that influence the dynamics of orphan drug development. Accordingly, the central research question is: *Which barriers in the innovation trajectories of orphan drugs are currently present and hinder the development of orphan drugs in the Netherlands?*

This study is limited to orphan drug development in the Netherlands. The reasons for this empirical limitation are two-fold.

First, during the late 1990s, biotechnology was identified by the Dutch government as an important enabling technology for the development of a national knowledge-based economy, which is regarded as a prerequisite for sustaining societal wealth and welfare in the Netherlands in the future. In 1998, an analysis by the Ministry of Economic Affairs showed that the Dutch biopharmaceutical sector was lagging behind neighboring countries, the main restrictions being that Dutch knowledge institutes lacked a business culture, the results of scientific research were seldom commercialized, there was not enough venture capital available for new life science companies, and there was a shortage of facilities, such as office and laboratory space (Ministry of Economic Affairs, 1999). Therefore, in 2000, the BioPartner Network program was started to stimulate the start-up of biotech firms in the Netherlands. Today, the Dutch life sciences sector is still in an early stage of development and consists of about 160 primarily small, privately held, often loss-making, entrepreneurial companies (BioPartner, 2005). These start-up companies often begin as 'offspring' of Dutch academic research groups trying to commercialize new research findings in the biotechnological field. Dutch policy makers also realize that the failure rate of start-up firms is high, especially in a new technological

field like biotechnology. But, it is expected that the surviving start-up firms will be able to grow and together contribute to the development of a new high-technology, knowledge-based industry within the Netherlands. Biopharmaceutical companies receive special attention in this policy because of their large knowledge content.

Second, only a small number of orphan drugs are developed in the Netherlands, some of them being granted EU orphan designation by the European Medicines Evaluation Agency (EMEA), and none of them have yet left the experimental or clinical phases of drug development and received market approval.[1] But, market approval of orphan drugs is a necessary condition for biopharmaceutical firms to expand their operations. Therefore, insight into the factors and conditions that hinder the development of orphan drugs in the Netherlands is important, especially from the industry policy perspective described above.

As only a small number of orphan drugs have been developed within the Netherlands, and have not yet received market approval, research into their development would only reveal partial information on current barriers to innovation. In particular, information about postponed and suspended decision-making and decision-making with negative outcomes that prevent the development of other orphan drugs or stop further development of orphan drugs will not be gathered. Furthermore, information about barriers to commercialization and use of orphan drugs is missing. Therefore, another approach is adopted in this study by identifying the small number of important, knowledgeable actors involved in the Dutch field of orphan drugs and interviewing them on relevant issues concerning the whole trajectory of orphan drug development.

This article is organized as follows. Section 2 discusses the process of (orphan) drug development and the actors and institutional structures involved in this process. Some of them provide incentives that affect the willingness to develop orphan drugs. Section 3 presents a conceptual model of these incentives and other factors affecting the adoption of orphan drug development. To investigate causal effects in the conceptual model, Section 4 describes the applied research methodology.

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[1] Given the long time frames of drug development and the fact that most dedicated life sciences firms in the Netherlands are less than 10 years old, it is understandable that no drug produced by a Dutch life sciences company has been approved for the market yet. Several companies now have compounds in clinical development. For example, Pharming's recombinant human C1 inhibitor, having an EMEA Orphan Medicinal Product status, is now in clinical phase III, and Pharming expects to submit it for market approval in 2005 (BioPartner, 2005).

Interviews with knowledgeable actors in the field of orphan drug development provided a rather small dataset for analysis. To test the presumed causal effects in the conceptual model, this dataset has been analyzed by means of robust small sample statistical methods. Section 5 presents the results of these analyses together with their managerial and policy implications. These results are discussed in Section 6. Section 7 presents the conclusions drawn from these results, as an answer to the research question stated above.

2. Orphan drug development

2.1. Background

It is estimated that there are between 5000 and 8000 identified rare diseases, which together affect about 55 million people in Europe and the USA alone (Binns and Driscoll, 2000; Rinaldi, 2005). However, each of these diseases affects relatively few people. A rare disease is, according to European definition, a life-threatening or chronically debilitating condition from which not more than one affected person per 2000 citizens in the European Union suffer. As only small numbers of people are affected, there are only small markets for drugs, and the high costs associated with drug development generally makes it unprofitable for pharmaceutical companies to develop drugs for these diseases. The medicinal products intended for the diagnosis, prevention or treatment of rare disorders are commonly known as 'orphan drugs'. Several rare diseases are well described, such as cystic fibrosis, hemophilia, amyotrophic lateral sclerosis (ALS), Huntington's chorea, phenylketonuria (PKU), and severe acute respiratory syndrome (SARS). Box 1 gives an example of a well-known orphan disease, hereditary angioedema (HAE), and the developed orphan drug recombinant human C1 inhibitor.[2] Examples of general not well-described disorders include primary ciliary dyskinesia, Darier disease, Usher syndrome, and alkaptonuria. Examples of groups of rare diseases are neuromuscular diseases, inborn errors of metabolism (such as lysosomal storage disorders, such as Gaucher, Pompe and Fabry), several chromosomal disorders and rare forms of cancer (van Weely and Leufkens, 2004; Orphanet, 2006).

The rapid growth of molecular biological knowledge in the past few years and the recent insights from the Human Genome Project have led to new delineations

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[2] The Dutch firm Pharming Technologies B.V. has developed this recombinant human C1 inhibitor orphan drug.

Box 1. Pharming and the development of C1 inhibitor orphan drug for hereditary angioedema treatment

Background and prevalence: Hereditary angioedema (HAE) is a genetic disorder that causes shortage of a protein called C1 inhibitor. Patients suffer from recurrent attacks of oedema, causing swellings in the soft tissues of the body. This swelling can be extremely painful. When misdiagnosed it can lead to unnecessary surgical interference and costly hospital care. The disease can even be lethal if attacks in the throat area lead to asphyxiation. The prevalence of HAE is from 1 in 10,000 to 1 in 150,000, with an average of 1 in 30,000, which means that in the Western world some 22,000 patients suffer from it.

Treatment: Androgens can help to prevent attacks of HAE but may cause serious side effects, such as excessive hair growth in women, menstrual disorders, infertility, hepatitis, and, in rare cases, liver cancer. Attacks are also treated with anti-fibrinolytics or plasma C1 inhibitor. Anti-fibrinolytics are associated with side effects such as nausea, abdominal pain, diarrhea, and even thrombosis. In addition, the presently available C1 inhibitor protein is obtained from blood plasma. This implies a risk of transmission of pathogenic viruses and its availability is limited since human donor blood is scarce.

Pharming has developed a recombinant human C1 inhibitor (rhC1INH) that is obtained from the milk of transgenic rabbits. Pharming is a Dutch life sciences company developing innovative protein therapeutics for unmet medical needs. The company's products include potential treatments for genetic disorders, medical, and specialty products for surgical indications, and intermediates for various applications.

The transgenic rabbit DNA contains an extra bovine-milk-specific promoter sequence (alpha-S1 casein) functionally

linked to the gene encoding human C1 inhibitor. This makes them produce rhC1INH in their milk. This is a relative easy, quick and clean production method of human C1 inhibitor in large quantities.

Project status: Pharming is nearing the end of the development program for rhC1INH. Almost all safety tests in laboratory animals have been completed, and control tests have been developed. The product is now in phase III of clinical testing in humans. Submission for market approval is expected in 2005.

To enhance development speed, Pharming had a patient register developed, which contains unique patient data, enabling faster recruitment of patients for clinical trials and facilitating various opportunities for further scientific research. Once marketing approval has been obtained, the register ensures faster market penetration of the product.

Orphan drug designation: Pharming obtained an orphan drug designation for rhC1INH in both prophylaxis and acute treatment of hereditary and acquired angioedema from the US Food and Drug Administration (FDA). In addition, the EMEA granted an Orphan Medicinal Product status for prophylactic and acute treatment. These designations provide several advantages like certain market exclusivity, various financial incentives, and a well-defined regulatory approval path.

Sources: Pharming (2005) and Lareb (2005).

and classifications of disorders and diseases. At present, about 7000 genetic disorders are known to be the result of a mistake in the coding of one gene. Many of these genetic disorders are categorized as rare diseases.

About 80% of the identified rare diseases have a genetic origin (Rinaldi, 2005). Another category of rare diseases include rare variants of non-rare disorders, such as heart and vascular diseases, lung diseases, rheumatism, cancer, and psychiatric disorders. Owing to increased understanding of these disorders and improved DNA techniques and DNA-scanning methods, the pos-

sibilities for diagnosis and therapy may be expected to improve considerably in the future.[3] If it becomes possible to diagnose many hundreds of genetic disorders, then further development of biopharmaceutical orphan drugs becomes feasible (Meijer et al., 2001; Zitter, 2005).

Despite all the progress made over the past decades, for many of the rare diseases there is still no effective and safe treatment available. Various barriers related to the development of orphan drugs can be identified, such as the small number of patients, the debate about choosing appropriate trial methodology and outcome parameters, and a lack of knowledge about the natural course of the disease, all of which hamper positioning of orphan drugs in clinical practices (Haffner et al., 2002; van Weely and Leufkens, 2004).

Affordability of orphan drugs has become a major issue and creates tensions between the various stakeholders involved (van Weely and Leufkens, 2004; Stolk et al., 2005). Owing to the severe symptoms of rare diseases, it is hard to accept that, in general, only few drugs for rare diseases are going to be further developed or brought onto the market. The development of many orphan drugs often entered the preclinical stage, after which there was no clear further development towards registration and market introduction. The availability of orphan drugs is limited by their weak economic incentive and lack of commercial value. Nevertheless, rare conditions such as hereditary angioedema (HAE), amyotrophic lateral sclerosis (ALS), Gaucher's disease, and Huntington's chorea affect thousands of people worldwide.

Several regulatory instruments have been developed to encourage the development of orphan drugs. The first of these instruments was the Orphan Drug Act (ODA) that was passed in the USA in 1983. The ODA offers significant incentives for (bio)pharmaceutical firms to develop drugs for rare diseases. These benefits include quick review by the US Food and Drug Administration (FDA), a short approval time, tax credits, 7 years of market exclusivity for orphan indications of approved products and exemptions from drug registration fees for a company willing to develop an orphan drug. Furthermore, the FDA Office of Orphan Products Development (OOPD) has awarded research grants to both private and public parties to support clinical trials of orphan drugs. To qualify for these incentives, potential medicines first receive 'orphan designation'

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[3] Right now, for one-third of the people with a rare disease, getting an accurate diagnosis can take 1–5 years. These rare diseases are difficult to diagnose because in their early stages, symptoms may be absent or masked, misunderstood, or confused with other diseases.
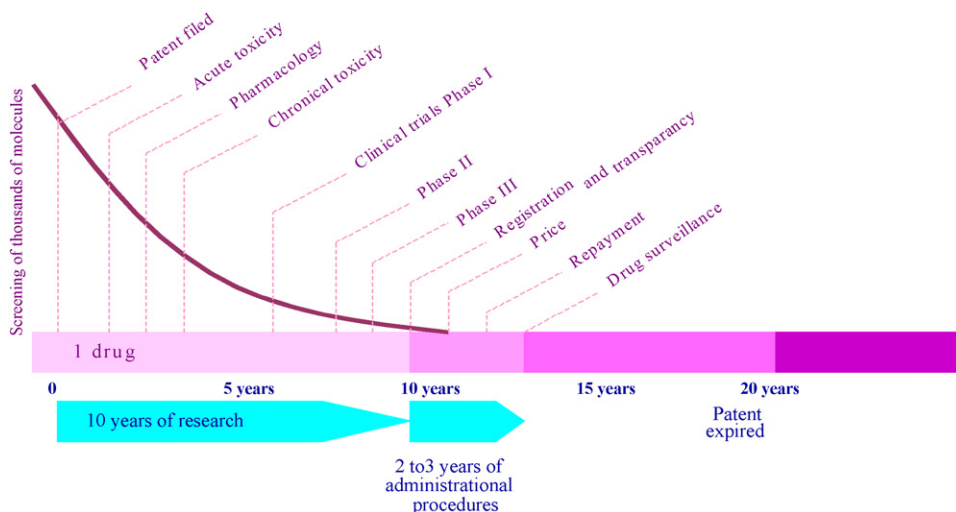
Fig. 1. Different stages of the common drug development process (EMEA, 2001).

from the OOPD, and then go through the normal evaluation process for safety and efficacy (Haffner et al., 2002; Maeder, 2003). Since the ODA came into effect, its impact on the development of orphan drugs has been tremendous. From 1983 to April 2005, a total of 269 orphan drugs received market approval in the USA and 1449 orphan designations were accepted (FDA, 2005). Together, these 269 new drugs now provide help for more than 11 million people in the USA alone (Rinaldi, 2005). An EU legislative framework did not follow until December 1999, when the European Orphan Drug Regulation (EODR) was approved by the European Parliament (EU Regulation 141/2000; Binns and Driscoll, 2000; Sinnema, 2001). The EODR incentives include 10 years' market exclusivity to orphan drugs, exemption from registration fees, technical assistance for development of the application file, and accelerated marketing procedures. Other provisions, such as tax breaks and grants towards clinical research costs were largely delegated to the member states (Rinaldi, 2005). So far, approximately 270 drugs have been granted EU orphan designation, and about 23 of these have reached the market in 2005 (Pharmacos, 2005).

Since orphan drug regulations have been in place in various countries (including USA, EU, Japan, Australia, Singapore, and Canada), patients, clinicians, policy makers, and industry have recognized their huge impact on the development of new drugs (Bosanquet et al., 2003; Stolk et al., 2005). There are, however, two main concerns regarding orphan drugs. First, many orphan drugs are (very) expensive. Second, certain drugs that were originally approved in the USA as orphan drugs later became top sellers, either because the once rare condi-

tion they were intended to treat increased in frequency, such as AZT to block HIV replication, or because the drugs, such as epoetin-alfa (EPO), proved effective against more common disorders (Lawton, 1992; Maeder, 2003).

2.2. The development process

Drug development takes, on average, 10–12 years and involves various stages (Fig. 1). The first stage in the development of medicinal drugs consists of research into the mechanism and the pathogenesis of the particular 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 is a big problem in the development of orphan drugs. Basic molecular understanding of the disease and identification of possible pharmacological targets (valid biomarkers) is often lacking for many of the rare mono- and polygenic disorders (Maeder, 2003; Stolk et al., 2005).

The next stage in the development of a drug begins with the design of the substance. When a promising (guiding) substance is found (by screening, molecular modification, rational design, or serendipity), it is tested for its quality, safety, and efficacy. The first series of the tests involves animal experiments. Animal-experimental models are used to replicate a disease or a partial aspect of a disease in humans (Drews, 1999). Animal models for rare diseases, however, are often absent or rarely available because only little research has been carried out on the pathogenesis of rare diseases and valid biomarkers are often lacking.

Clinical experiments form the next series of tests, which can be categorized into three phases of testing. In clinical phase I the substance is administered to a small number of healthy volunteers. The purpose of these experiments is to collect data on the safety of the drug in humans. In experiments conducted during phase II of the clinical research only patients are involved.

Furthermore, the experiments involve larger groups of subjects. The main goal of this research is to establish the short-term single-dose efficacy. In orphan drug development, phase I and II studies are often combined, and the registration authorities have accepted these exceptional circumstances.

Phase III studies involve large groups of patients in randomized, controlled, double-blind trials to establish both the short- and long-term efficacy. But in the case of rare diseases, it is difficult to recruit sufficient patients for these clinical trials. In some cases, all patients in one or even several countries have to be included to carry out a statistically reliable experiment. Only when phases I–III have successfully been concluded, the pharmaceutical substance becomes eligible for market registration. The pharmaceutical firm has to submit a registration dossier containing adequate data on the safety, efficacy, and quality of the drug. When the drug is approved, it can be introduced to the market. After registration and market introduction of a drug, the pharmaceutical firm is responsible for the monitoring and evaluation of its prolonged effects on patients (so-called post-marketing surveillance) (Buurma et al., 1999).

2.3. Actors involved in the development of orphan drugs

Various actors have important roles in the development of (orphan) drugs, namely universities and research institutes, academic hospitals, pharmaceutical companies, patients' organizations, and governmental institutions (the 'government' in Fig. 2).
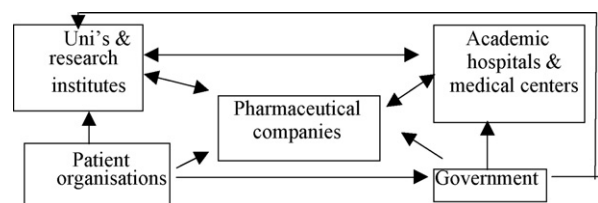

Fig. 2. Network of actors involved in the development of orphan drugs. Single-arrowed lines represent uni-directional causal effect of incentives of certain actors, while double-arrowed lines represent bi-directional effects or interactions between actors.

Universities and research institutes have important roles in the first stage of drug development because they perform the research into the mechanisms underlying a rare disease. Various university groups, including (bio)chemical, pharmaceutical, and molecular biology departments, are involved in the drug discovery processes. Research collaboration with academic hospitals, which can provide clinical data, is frequent. Relative to other countries, the Netherlands has shown ample scientific interest in rare diseases, the underlying molecular mechanisms, and possible therapeutic approaches. In particular, the Dutch research community has gained international recognition in the field of lysosomal storage disorders (Gaucher, Pompe, Fabry), other inheritable diseases (such as hemophilia), rare disorders in children (such as neurological diseases), and neonatal diseases (Leufkens and van Weely, 2005). University departments often cooperate with pharmaceutical companies by providing data on the pathogenesis of the disease, while leaving the actual development process of the drug to the pharmaceutical industry. Sometimes, universities have 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. Furthermore, university medical centers often cooperate with academic hospitals in clinical trials. Thus, the first stages of orphan drugs development often take place within universities and academic hospitals.

Academic hospitals also have important roles in the drug development process via their study of the pathogenesis of the rare disorder and providing the clinical data. Furthermore, academic hospitals have important roles in the clinical trials. These are often carried out in cooperation with pharmaceutical companies due to the high costs associated with testing large groups of patients and expensive registration procedures. In the Netherlands, more than 10 different research laboratories, university departments, and academic hospitals are active in orphan drug development (Orphanet, 2006).[4]

[4] These departments and laboratories include the Academic Medical Center of the University of Amsterdam, the Department of Human Genetics of University Medical Centre Nijmegen, Rudolf Magnus Institute of Neuroscience of Utrecht University Medical Center, Department of Pediatric Cardiology of University Hospital Rotterdam/Erasmus MC-Sophia, Department of Rehabilitation Medicine of VU University Medical Center Amsterdam, Departments of Neurology of University Medical Center Rotterdam, Department of Neurology of the Academic Medical Centre Amsterdam, Children's Hospital of University Hospital Nijmegen, the Institute of Ophthalmology of University Hospital Nijmegen, Pharming Technologies Leiden and Genzyme Therapeutics Naarden (Orphanet, 2006).

Pharmaceutical companies have the most important roles in the development of medicinal drugs, often participating in every stage of the development process. Some companies study the pathogenesis of diseases themselves, but most firms obtain this knowledge from research institutes, university research, and academic hospitals, as this type of fundamental research is not very profitable for pharmaceutical firms. Most firms focus only on the development of specific pharmaceutical substances. In the next phase of drug development, some firms perform their own animal experiments, although it is not uncommon for firms to subcontract these experiments to universities and research institutes. Generally, phase I and II clinical trials are contracted out. For orphan drug development, phase I and II clinical trials often take place in academic hospitals because the hospitals are more familiar with the patients, often via specialized rare diseases centers. Many pharmaceutical firms also increasingly cooperate with patients' organizations (Meijer et al., 2001). The pharmaceutical firms then use the know-how of these clinical centers and patient organizations for further development of the orphan drugs. So far, only two Dutch orphan drug projects have been granted an orphan drug designation, one project of Pharming Technologies (see Box 1) and one project of AMT, a "spin-off" company of the Academic Medical Center Amsterdam.[5]

Patients' organizations are particularly important in increasing the awareness of a certain disease, especially in the case of orphan diseases (Lang and Wood, 1999). An inventory done by patients' organizations within the Netherlands in 1994 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 groups of patient in studies to establish the efficacy of orphan drugs. In addition, these organizations collect information on regulation as well as sources of financial support. They also have important roles 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 drug development. The Vereniging Samenwerkende Ouder-en Patientorganisaties (VSOP) is the Dutch Genetic Alliance, and is an umbrella organization of about 60 national, disease-linked, parent and patient organizations, most of which are concerned with genetic and/or congenital disorders. Rare disorders is a central field of interest (VSOP, 2005). Examples of Dutch orphan-disease-related patient organizations are the Dutch Cystic Fibrosis Foundation (Nederlandse Cystische Fibrosis Stichting), the Dutch Fabry Support and Information Group (Fabry Support & Informatie Groep Nederland), the Dutch Gaucher Association (Gaucher Vereniging Nederland), and the Dutch Muscular Diseases Association (Vereniging Spierziekten Nederland). The European Platform for Patients' Organizations, Science and Industry (EPPOSI, 2005) is an EU patient-led partnership between patients, industry, and academic science institutes focusing on the treatment and prevention of serious diseases.

The government has a role in the process by which the developed medicinal drug gains authorization via the Dutch Medicine Evaluation Board (College ter Beoordeling van Geneesmiddelen [CBG]) and the EMEA. Furthermore, the government is responsible for policies regarding medical knowledge, industry, and public health (RGO, 1998). The government can influence the development of orphan drugs in several ways by applying the European Orphan Drugs Regulation (EODR), which allows the provision of market exclusivity, scientific advice, and regulatory guidance (Binns and Driscoll, 2000; Maeder, 2003).

2.4. Institutional structure regarding orphan drug development in the Netherlands

In the Netherlands, several initiatives have been undertaken to encourage scientists in public knowledge institutes (such as universities and academic hospitals) to start up their own biotechnology company, for example, the above-mentioned BioPartner programme initiated by the Ministry of Economic Affairs (BioPartner, 2005). However, at the end of 2004, only three small companies with a business plan for treatment of a specific rare disease had started in this way.

The European Parliament and the Council of the European Union have also shown a clear interest in orphan diseases during the past few years. The adop-

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[5] Two Dutch projects have been granted with an orphan drug designation, being the C1 inhibitor for HAE treatment of Pharming (designation date 11/05/2001, see Box 1) and an Adeno-associated viral vector expressing lipoprotein lipase for lipoprotein lipase deficiency of AMT, a spin-off company of the Academic Medical Centre Amsterdam (designation date: 08/03/2004). Furthermore, the Belgian company Henogen S.A. has recently got a designation for its ricin A chain fusion protein for graft versus host disease (26/08/05). This product has been taken from Immunotoko, a Dutch spin-off company of the UMC Hospital Nijmegen (van Weely, 2005).

tion of the Programme of Community Action on Rare Diseases (1999–2003) and the Regulation No. 141/2000 on Orphan Medicinal Products are examples of this increased interest. In 2000, an European Committee for Orphan Medicinal Products (COMP) was created as part of the EMEA, supporting the registration procedure of orphan drugs. In 1997, the former Minister of Health, Welfare and Sports (VWS) asked the Dutch Advisory Council on Health Research (RGO) to provide advice regarding the coordination, priority, and stimulation of research in the Netherlands with respect to orphan drugs. In 1998, the RGO advised the building of a national structure on orphan drugs. Therefore, the Steering Committee on Orphan Drugs (Stuurgroep Weesgeneesmiddelen) was appointed by the Minister of VWS in April 2001 for a period of at least 4 years. This committee is an independent organization and consists of 10 members and one observer. The members are representatives of patient organizations, pharmaceutical companies, physicians, hospital pharmacists, scientists, a representative of the Dutch Medicine Evaluation Board and a representative of the Dutch Health Insurance Board (WGM, 2005). In January 2003, the Dutch Health Care Insurance Board (CVZ) compiled requirements regarding the reimbursement for orphan drugs (CVZ, 2003). In the Netherlands, the Minister of Health, Welfare and Sports, advised by the Health Care Insurance Board (CVZ), decides whether a new product will be included in the National Health Insurance System. New drugs aiming for intramural treatment (treatment within the hospital), such as most orphan drugs, should be paid from the hospitals budgets. Orphan drugs often do not fit within these budgets, being expensive, often biotechnologically made products. Therefore, two Dutch policy measures have been introduced for the intramural use of drugs (one for expensive drugs and one for orphan drugs). In the case of expensive drugs in hospitals, 80% of the drug costs will be reimbursed. In the case of orphan drugs in academic hospitals, 95% of the drug costs will be reimbursed. When the Minister of VWS comes to decide on these policy measures, the Dutch 'College Tarieven Gezondheidszorg/Zorgauthoriteit i.o.' (CTG/Zaio) is the executive organization responsible for the policy measures for expensive drugs and orphan drugs.[6] Drugs for treatment outside the hospital (extramural) can be reimbursed by means of the Dutch Drugs

Reimbursement System, called the 'Geneesmiddelen-vergoedingssysteem' (GVS). Since 1 January 2006, a subsidy of 11 million euros has been allocated for the costs of European registered extramural orphan drugs for use in the Netherlands (CTG/Zaio, 2006).[7]

Despite the measures described above, the current situation in the Netherlands is that, although orphan drug development in the preclinical stage has increased, only the Dutch firm Pharming has a drug with orphan designation in the last phase of clinical trials (see Box 1). Phase III of clinical trials is still a barrier to market introduction for many orphan drugs. This is due to the small number of patients involved and the fact that most orphan drugs are developed by start-up firms. The small number of patients involved requires the cooperation of patients in many countries in a phase III clinical trial. But start-up firms are not very well connected to the international market and often experience severe difficulties organizing phase III clinical trials. Consequently, the development of orphan drugs can get stuck at the stage of phase III clinical trials. One solution to this problem is for the start-up firms to cooperate with large (foreign) pharmaceutical firms, which already have access to the international market. But such cooperation is not free and often results in mergers and take-overs of start-up firms by large pharmaceutical firms. Loss of independence and identity are then the unattractive consequences for the start-up firm.

To avoid these problems with phase III clinical trials in orphan drug development, which also threaten the development of a high-technology, knowledge-based biopharmaceutical industry within the Netherlands, the Dutch government should take a more active role in organizing access to international patient groups with rare diseases via the European Union or even the World Health Organization.

To acquire a more comprehensive insight into the barriers to orphan drug development, the next section presents some theoretical notions leading to a conceptual model of the willingness to develop orphan drugs. Later, this model will be investigated empirically.

3. Conceptualization of the willingness to develop orphan drugs

In general, drug development represents a science-based innovation trajectory, carried out by a network of

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[6] *Policy regulation Expensive Drugs*: 20% of the costs of medicinal drugs to be paid by the hospital itself and 80% reimbursed by the policy rule. *Policy regulation Orphan Drugs*: 5% of the costs of drugs to be paid by the academic hospital itself and 95% reimbursed by the policy measure (CTG/Zaio, 2006).

[7] The annual cost of treatment of orphan diseases (€6000 to >€300,000) is beyond the possibilities of most households (Alcimed, 2004).

interrelated actors, such as research institutes, producers, government, and patient organizations, and based on demand-driven conditions, such as unmet medical needs (Tidd et al., 2001). These conditions are reflected in expectations about potential customers (i.e. patients) and drug innovation, adoption, and diffusion. If large-scale drug adoption by patients is expected to be high, 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 (Tornatzky and Klein, 1982; Moore and 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[8] innovation adoption and diffusion among customers, which is reflected in the producer's willingness to develop orphan drugs. By analyzing this conceptual model for various actor groups involved in different stages of orphan drug development, a multi-actor perspective is chosen. In orphan drug development, three important actor groups can be identified: producers, regulators, and consumers.

The actor group of producers comprises organizations that are directly involved in orphan drug development, namely pharmaceutical companies in collaboration with research institutes, academic hospitals, and universities, such as the Dutch firms Pharming and AMT. The actor group of regulators includes various public and private medical and health organizations, including the Dutch Ministry of Health, Welfare and Sports, the Medicine Evaluation Board, the Health Care Insurance Board, and the CTG/Zaio, which represent the institutional infrastructure of orphan drugs and some of whom are involved in the reimbursement of treatment of orphan diseases. The actor group of consumers represents patients, patient groups, and also physicians and (hospital) pharmacists who prescribe the orphan drugs.

The willingness to develop orphan drugs and its causal factors apply mainly to the actor group of producers. In addition, the influence of both other actor groups on the adoption of research and development activities into orphan drugs consists of affecting its causal factors. By focusing on the perceptions and behaviors of the three actor groups identified, the structuralistic and functionalistic approaches of (innovation) systems can be integrated into a system dynamics framework. The structuralistic approach considers system dynamics as a function of the structure of the system, which is made up of its institutional environment and (the perceptions of) their regulations and rules imposed on it. The functionalistic approach of systems conceives system dynamics as a function of interactions among its constituent subsystems and system elements. By linking the perceptions of regulations, rules, and other causes of (adoption) behavior to interactions among the three actor groups, the structuralistic and functionalistic perspectives on system dynamics become integrated. Effective system dynamics regarding the adoption of R&D activities necessary for orphan drug development can then be seen to depend on the degree of concerted actions among the three actor groups involved, which in turn depends on a shared view regarding how to develop orphan drugs. The shared view consists of the degree of agreement among the three actor groups about whether to develop orphan drugs and the extent to which the causal factors have a positive or negative effect. Concerted action then consists of adaptations of current behaviors of the actor groups to stimulate the willingness to develop orphan drugs of the producers. However, disagreement among the actor groups involved over the effects and relations of the causal factors will be conceived as innovation barriers in the development of orphan drugs. To identify such barriers to orphan drug development, these causal factors and their effects and relations are briefly described below.

The clinical success of a drug is measured in terms of the adoption rate. Adoption is defined as "a decision to make full use of an innovation as the best course of action available" (Rogers, 1995). According to Rogers' diffusion theory, the adoption of innovations, in this case orphan drugs, by individuals or social entities takes place through the innovation-decision process. The different stages of this process are dominated by the goal to reduce uncertainty about the attributes of a new product through information gathering. Rogers (1995) mentions several key innovation characteristics relevant to the process of (expected) adoption (so called 'adoption factors') or, in the context of this study, the degree of willingness to develop orphan drugs: (1) relative advantage; (2) compatibility; (3) complexity; (4) trialability; and (5) observability.

Relative advantage is the degree to which an innovation is perceived as better than its predecessor. This attribute depends on the number of alternatives and the added value of the new drug compared with the standard therapy. The added value is measured in terms of economic benefits, including financial risk and non-financial benefits (for example, business factors and legislative measures), and social prestige (image).

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[8] 'Expected' because (1) the focus is on ex ante analysis, not ex post, and (2) too little case study material is available for comparative analyses. Consult further Section 4.3.

In general, drug development is associated with several uncertainties. A new drug has to be evidence-based, therapeutically needed and financially profitable to be developed. Orphan drugs are therapeutically necessary. Pharmaceutical companies have to cope with considerable financial uncertainties about whether they will receive sufficient revenues after market introduction to cover the initial R&D costs of orphan drug development. A government can try to reduce these financial uncertainties by imposing tax credits, clinical research assistance, and market exclusivity. This uncertainty is thus highly correlated with financial risk. Pharmaceutical companies are no different from other firms in trying to avoid such risk as much as possible. Consequently, they are inclined to select (the most) profitable opportunities. In this study, the relative advantage is not relative to the predecessor, but relative to the development and adoption of conventional drugs. The most important non-financial benefits are provided by legislative measures for orphan drug development, which are expected to have a stimulating effect on the willingness to develop such drugs. Both the American Orphan Drug Act and the European Orphan Drug Regulation are examples of legislative measures aimed at increasing the financial benefits of orphan drug development (for example, market exclusivity, scientific advice, and regulatory guidance).[9] For some pharmaceutical companies, an orphan drug designation may provide a powerful incentive for image improvement, particularly when proper funding and a profound knowledge base are lacking. For dedicated life sciences companies, the small production scale for orphan drugs can be attractive. Consequently, legislative measures are conceived to be contained in the concept of non-financial benefits. In addition to relative advantage, we included the independent variable financial risk in our conceptual model and expected it to have a negative effect on the willingness of producers, and more specifically of pharmaceutical companies, to develop orphan drugs.

Social prestige and image are closely related. 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 and Benbasat, 1991). The image of developing an orphan drug (that is, helping the 'orphans') would be expected to have a positive influence on the willingness to develop such a drug.

Compatibility is the degree to which an innovation is perceived as being consistent with the existing values, past experiences, and needs of potential adopters (Rogers, 1995; Moore and Benbasat, 1991). Compatibility is high when the research or development involved fit the company or research institute well. In principle, the development trajectory of orphan drugs is no different from the development of conventional drugs, as it involves preclinical, clinical, and registration phases. Therefore, compatibility is not considered to be a large barrier in the development of orphan drugs and is therefore excluded from our conceptual model.

Complexity is defined as "the degree to which an innovation is perceived as being difficult to use" (Moore and Benbasat, 1991). As mentioned in Section 2, orphan drug development is relatively complex compared with the development of conventional drugs due to a lack of mechanistic knowledge about the disease, a lack of valid biomarkers, inappropriate diagnostics, and small patient groups for clinical trials. Rare diseases often have a genetic element, lack suitable animal models, and require more collaboration with other institutes than conventional drug development. Together, these factors indicate highly complex development processes and form a barrier to orphan drug development.

Trialability is defined as "the degree to which an innovation may be experimented with before adoption" (Moore and Benbasat, 1991). Regarding drug adoption, the trialability of a drug depends on the overall clinical experience with the specific drug. 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 for testing. Patients' organizations can then be very helpful in finding suitable patients. We expect a positive effect of trialability on the willingness to develop orphan drugs.

Observability is defined as "the degree to which the results of an innovation are observable to others" (Rogers, 1995; Moore and Benbasat, 1991). It could be stated that the advancement of research into orphan drugs is less observable, due to the lack of information at each stage of development. This is due to the complexity of orphan drug development. These variables are therefore closely related, which makes it difficult to distinguish their effects on the willingness to develop orphan drugs. Therefore, only one of them is included in the conceptual model, namely, complexity leaving out observability as the associated dimension.

In summary, the following conceptual model has been derived, which indicates a set of factors influencing the willingness to develop orphan drugs. These factors can be conceived as stimuli but also as barriers to innovation (Fig. 3).

The following propositions about the effects of the independent concepts on the willingness to develop

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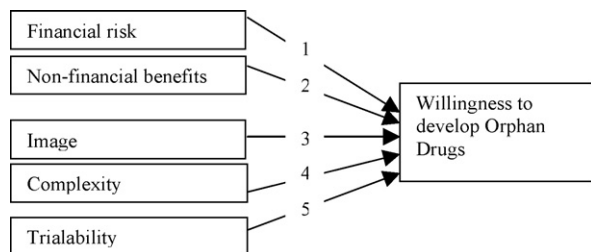[9] Legislative measures are correlated with risk via financial aspects.

Fig. 3. Conceptual model of the willingness to develop orphan drugs.

orphan drugs can now be formulated:

1. If the financial risk decreases, then the willingness to develop orphan drugs will increase.
2. If the non-financial benefits 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 of 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 the actor group of producers. From their perspective, high financial risk, low non-financial benefits, poor image, high complexity, and low trialability represent important barriers to orphan drug development. From the multi-actor perspective of orphan drug development described above, the regulator and consumer actor groups will affect the independent concepts in Fig. 3, and may try to lower these barriers in the following ways. Regulators can influence the prevailing values of financial risk, non-financial benefits, complexity, and trialability by taking (enhanced) financial, legislative, and regulatory measures, for example, based on the European Orphan Drug Regulation (EODR). Consumers can improve the prevailing values of complexity and trialability by participating in the study of rare diseases and the development process of orphan drugs (such as diagnosis, pathogenesis (animal) models, ways of treatment, and number of patients involved in clinical trials).

But regulators and consumers will only be inclined to contribute to lowering the barriers to orphan drug development if they are aware of these barriers, and only when all the three groups have a shared view on the barriers and their mutual relations in the orphan drug development

trajectory. Then, the willingness to conduct concerted actions may be expected to increase to facilitate orphan drug development. This is the key theme to be elaborated in order to lower the innovation system barriers to orphan drug development. For the assessment and comparison of the perceptions of these barriers among producers, regulators, and consumers, the conceptual model in Fig. 3 will be operationalized in the next section.

4. Research methodology

4.1. Operationalization of concepts

The concepts in Fig. 3 have been operationalized according to their empirical facets discussed in Section 3.

Financial risk applies to producers, which is related to their uncertainty about the economic profitability of orphan drug development (Rogers, 1995). This uncertainty arises from the huge costs of orphan drug development and the relative small target population to which the drug can be marketed, thereby creating revenues. Therefore, financial risk is indicated by the costs of orphan drug development and their expected revenues.

Non-financial benefits are indicated by variables that provide incentives for orphan drug development relative to conventional drug development by reducing the costs and improving the expected revenues from orphan drug development. These incentives comprise the small scale of production and marketing needed, and the governmental measures that provide juridical benefits and financial support allowed by the EODR via the orphan drug designation, providing scientific advice in clinical trials, regulatory guidance at registration and granting market exclusivity. In this study, non-financial benefits (for example, business factors and legislative measures), are expected to reduce the financial risk (Rogers, 1995).

Image is indicated by actual orphan drug development by pharmaceutical companies and cooperation in orphan drug development with academic hospitals, patients' organizations and the regulatory authorities. This operationalization refers to the efforts of pharmaceutical companies to satisfy societal need to tackle (particular) orphan diseases. By doing so, the social prestige of these companies increases, thereby increasing the likelihood of the public to favor other products in their portfolios (Rogers, 1995).

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 shared knowledge concerning these issues among

the producer, regulator and consumer actor groups. Little knowledge of each of these issues and a lack of shared knowledge increases the complexity of orphan drug development considerably (Rogers, 1995).

Trialability refers to the possibility of testing an innovative product in reality (Rogers, 1995). Here, it is measured by the ability to conduct clinical trials and the cooperation of patients' organizations in these trials.

Willingness to develop orphan drugs is indicated by the various stages in the orphan drug development policy process, 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 held by selected key actors in the field of orphan drug development within the Netherlands, and are expressed on a five-point Likert scale (1—no importance/strongly negative, 5—most important/strongly positive). The key actors have been selected according to the following criteria. Academic experts in the field of rare diseases and biopharmaceuticals at Dutch universities were asked to suggest knowledgeable fieldworkers. Individuals who were mentioned at least twice by different academic experts were invited for an interview. Therefore, the selection of respondents in this study is based on their reputation in the field of rare diseases and orphan drug development in the Netherlands. The key actors within each main actor group were interviewed in September 2001 (Kleijwegt and Schuttelaar, 2001; van Mastbergen and van der Valk, 2001; Otten and Vermeulen, 2001). These key actors included:

(1) For the producer group, a university professor who specializes in biopharmaceuticals and pharmacotherapy concerning orphan diseases, the head of a research team at an academic children's hospital who is responsible for managing research into the pathogenesis of orphan diseases, the chairman and secretary of the scientific council on orphan drug development, the director and managers of three (bio)pharmaceutical companies, and a member of the organization of pharmaceutical enterprises ($N = 7$).
(2) For the regulator group, two representatives of the ministries responsible for public health and economic affairs, a member of the Medicines Evaluation Board, a member of the organization for health insurance companies, and a representative of the advisory council on public health ($N = 5$).
(3) For the consumer group, three representatives of patients' organizations on orphan diseases, a member of the committee for orphan medicinal products, the secretary of the scientific council on orphan drug development, two medical specialists working at an orphan disease department of an academic children's hospital, and a head pharmacist in a hospital ($N = 8$).

As these key actors are well informed about orphan drug development they were interviewed to improve the reliability of the data analyzed. Because orphan diseases are not common diseases and are also markedly different from each other with respect to their pathogenesis, the actual number of people in each actor group involved is limited. Consequently, statistical analyses based on random samples of respondents from the three actor groups are not feasible.

4.3. Method of analysis

Statistical analysis of data obtained from only five to eight respondents within each actor group will result in inherently unreliable results due to the effects of outliers in small samples. Consequently, the challenge of the current multi-actor research is to develop a robust method of data analysis for small samples. These small samples are due to the relative young age of the technological field of biopharmaceuticals and the rareness of the area of orphan diseases, which together result in only a limited number of specialists and patients involved and only a few well-informed individuals.

The method of data analysis that was developed and applied is based on the combination of majority counts and average scores, thereby eliminating the effects of outliers in the data on the results.

Case 1: A Likert scale in which "1" represents "strongly negative" and "5" represents "strongly positive". If the majority and the average of the scores for each indicator are 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. The neutral value of 3 is assigned 0 for this coincidence. In this case, the association between an indicator and the concept its represents is indicated as −, 0, or +.
Case 2: A Likert scale in which "1" represents "no influence" and "5" represents a "very strong influence". If the majority and the average of the scores are 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 non-existent, weakly positive, or

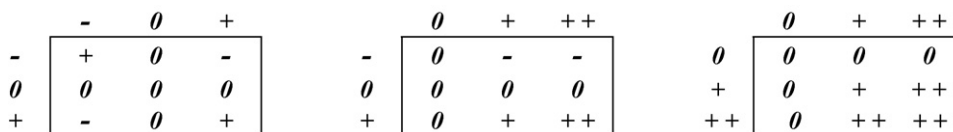|	-	0	+			0	+	++			0	+	++
-	+	0	-		-	0	-	-		0	0	0	0
0	0	0	0		0	0	0	0		+	0	+	++
+	-	0	+		+	0	+	++		++	0	++	++

Fig. 4. Correlations between indicators derived from 27 combinations of possible categories of coincidence with the concepts they represent.

very positive, respectively. In this case, the association between an indicator and the concept its represents is indicated as 0, +, or ++.

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 non-existent because it is generated by outliers. Such non-existence of the coincidence of an indicator with the concept it represents is also assigned 0 for their relationship.

To investigate the nature of the relation among the independent concepts, positive, negative or no correlations among their indicators are assessed as follows. The sign of the correlation of each pair of indicators is derived from their combination of categories of coincidence with the concepts represented by them.

If one indicator coincides positively with its concept, which implies that the overall score of the respondents on that indicator is relatively high (see above), and another indicator coincides negatively with its concept, which implies that the overall score of the respondents is relatively low (see above), then the indicators are considered to be negatively associated and their concepts also. If two indicators coincide negatively with the concepts they represent, then the indicators are considered to be positively associated and accordingly, the concepts are also considered to be positively associated. If one indicator of each pair of indicators does not coincide with the concept it represents, then the association between both indicators and, accordingly, between the concepts represented by them, is considered to be zero. All possible associations between the coincidences of two indicators with the concepts

Table 1
Perceived coincidences of empirical indicators with the concepts they represent

Concept	Indicator (scale of coincidence)	Coincidence for		
		Producers	Regulators	Consumers
Financial risk	Costs of development (−/+)	0	+	+
	Expected revenues (−/+)	−	−	0
Non-financial benefits	Scale of production (−/+)	−	0	+
	Servicing market niches (−/+)	−	0	0
	Orphan Drug status (−/+)	+	0	+
	Subsidies (0/++)	+	++	0
	Facilitating registration (0/++)	++	+	++
	Granting market exclusivity (0/++)	++	+	++
	Enhanced patent period (0/++)	0	0	++
Image	Developing orphan drugs (0/++)	++	0	+
	Cooperate with patients' organizations (0/++)	++	0	++
	Cooperate with medical institutions (0/++)	+	0	++
	Cooperate with public health organizations (0/++)	+	0	0
Complexity	Knowledge of pathogenesis (−/+)	−	−	−
	Knowledge of animal models (−/+)	−	−	0
	Knowledge of financial support measures (−/+)	−	−	0
	Knowledge of registration procedures (−/+)	−	−	0
	Knowledge sharing (−/+)	+	−	+
Trialability	Clinical trials (0/++)	++	+	++
	Participation of patients' organizations (0/++)	+	0	0
Willingness to contribute to orphan drug development (0/++)		+	+	0

they represent derived in this study are shown in Fig. 4.

5. Results and implications

5.1. Results

The methods of analysis have been applied to the data obtained on the observed indicators as described in the previous section. These methods produce positive, negative, and non-existent coincidences of observed indicators with the concepts represented by them for each of the investigated actor groups involved in orphan drug development (Table 1). Comparison of the reported coincidences of an indicator with the concept it represents between the actor groups involved provides insight into the degree of consensus about the prevalence of the coincidence of that indicator with the concept it represents. After making such comparisons for all observed indicators, it is possible to determine the shared view of all actor groups to the barriers in the development of orphan drugs.

In theory (Fig. 3), the willingness to contribute to orphan drug development is expected to be influenced positively by non-financial benefits, image, and trialability of orphan drug development. The financial risks and complexity of orphan drug development are expected to negatively influence this willingness. Consequently, these five causal concepts become barriers to orphan drug development if non-financial benefits, image, and trialability have relatively low scores and financial risk and complexity have relatively high scores. Owing to the multi-faceted empirical appearances of these causal concepts depending on the context of technology or technological field investigated, these five concepts have been operationalized in this study according to the 20 empirical indicators reported in Table 1. Consequently, 20 potential barriers are indicated in this study of orphan drug development in the Netherlands.

As can be seen in Table 1, all actor groups share only four perceived barriers to orphan drug development: facilitating registration, granting market exclusivity, knowledge of pathogenesis, and clinical trials. However, they still differ in the importance assigned to most of these shared barriers. Regarding the sixteen other barriers, the three groups do not have a shared view on their existence. In addition, with respect to the knowledge-sharing barrier there is a marked difference in perceptions of its existence and effects on the complexity of orphan drug development between the producers and consumers on one hand and the regulators

on the other hand. A more detailed account of these results is given below.

The lack of a shared view on 80% of the empirical barriers to orphan drug development represents a superseding barrier for this willingness to develop orphan drugs. Without a shared view on (the majority of) the barriers for increasing the willingness to contribute to orphan drug development, concerted actions to overcome these barriers by the three actor groups are unlikely to be jointly undertaken. This makes a further discussion of the effectiveness of such concerted actions to diminish the barriers obsolete.

The *willingness to contribute to orphan drug development* within the producer and regulator groups is just a little positive reflecting intentions rather than actions. Within the consumer group there is disagreement about the willingness to contribute to orphan drug development.

The regulators and consumers consider the *financial risk* of orphan drug development to be an enormous amount of the development costs. However, producers think quite different: they are acquainted with the relatively large costs of any drug development, but the small revenues that are expected from orphan drugs is more of a concern.

The *non-financial benefits* of orphan drug development are considered to be negatively affected by the relatively small scale of production and the extra efforts needed to service its small market niches by the producers. Consumers think that the small scale of production improves the non-financial benefits 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 a maximum to generate profitable economies of scale.

Both producers and consumers stress the importance of getting help from governmental agencies in the form of achieving orphan drug status under the EODR and subsequently facilitating registration of and granting market exclusivity for orphan drugs.

The regulators agree with the significance of the latter two measures but consider their contribution to be less important. This may be attributed to the fact that the regulators do not fully recognize the urgency of achieving the orphan drug status, which is perceived by producers as a necessary condition for developing orphan drugs, as a crucial non-financial benefit stimulating the willingness to develop orphan drugs.

The improvement of the *image* of pharmaceutical companies due to actual orphan drug development and their cooperation with patients' organizations and medi-

cal (research) institutions 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 owing to a lack of knowledge about their pathogenesis and a lack of suitable animal models. Consumers think less negatively 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 widespread and shared, although the producers are less optimistic about this.

With respect to knowledge sharing regarding orphan drug development, producers and consumers both think that this happens on a moderate but increasing scale, indicating the complexity of orphan drug development. Producers and consumers already participating in the development trajectory of orphan drugs also 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 and think that knowledge sharing needs to be stimulated to reduce the complexity of orphan drug development. As if those companies are not already cooperating and sharing knowledge with academic hospitals and research institutes.

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

What can now be concluded about the perceptions of barriers to orphan drug development in the Netherlands that are held and shared among the three actor groups involved? Barriers perceived by the producers are: little expected revenues from an orphan drug due to serving only market niches by means of small-scale production; little support from the regulators in realizing these small expected revenues by helping the producers with achieving the orphan drug status, thereby subsidizing research and development costs, facilitating the registration of the drug, granting market exclusivity for the drug and subsi-

dizing the use of the drug; little image improvement due to the small number of orphan drug approvals by 2005; little knowledge of the pathogenesis of orphan diseases and, subsequently, of suitable animal models in clinical trials; and low participation of patients and patients' organizations in clinical trials. The barrier of the financial risk of non-profitable orphan drugs is also recognized by the regulators as being due to little expected revenues of an orphan drug. The regulator-related barrier of producers requiring help to secure the small revenues from an orphan drug is not recognized as such by the regulators. In addition, the regulator-related barrier of image improvement due to the approval of orphan drugs is not sufficiently recognized as a barrier by the regulators. With respect to the knowledge- and testing-related barriers, all actor groups agree on their existence and the need for increased patient participation to lower these barriers. But regulators and consumers are not yet convinced that patients' organizations have a crucial role in promoting and continuing patient participation in knowledge creation and drug testing.

In summary, the presented results indicate that especially lowering the barriers related to the regulators and consumers could help to secure and improve expected revenues from orphan drug development by producers.

The derived causal order between the indicators of the innovation barriers derived from the adoption factors related to orphan drug development as argued above could be tested. This is done by assessing the correlations between these indicators according to the derived causal order as path coefficients in the causal sense. The assessment of correlations between indicators has been carried out as described in Section 4.3. The resulting path coefficients are presented in Fig. 5 as causal effects indicated by thin arrows accompanied by their sign. Via their coherence with the concept they represent, which is indicated by the thick arrows and the associated signs in Fig. 5, the causal effects of the indicators of innovation barriers on the willingness to develop orphan drugs can be assessed. In addition, the actor groups most concerned with particular subsets of barriers are also indicated in Fig. 5. Although it was not investigated as an indicator of one of the concepts, the approval of a drug is included as an indicator to Fig. 5. It is included because it is the outcome of registration procedures based on the results of clinical trials and represents a necessary condition for generating revenue from drug development.

A few other coincidences of indicators with the concepts they represent (as mentioned in Table 1) and associated non-zero correlations among indicators are not presented in Fig. 5. These concern the non-coincidence of a prolonged patent period and
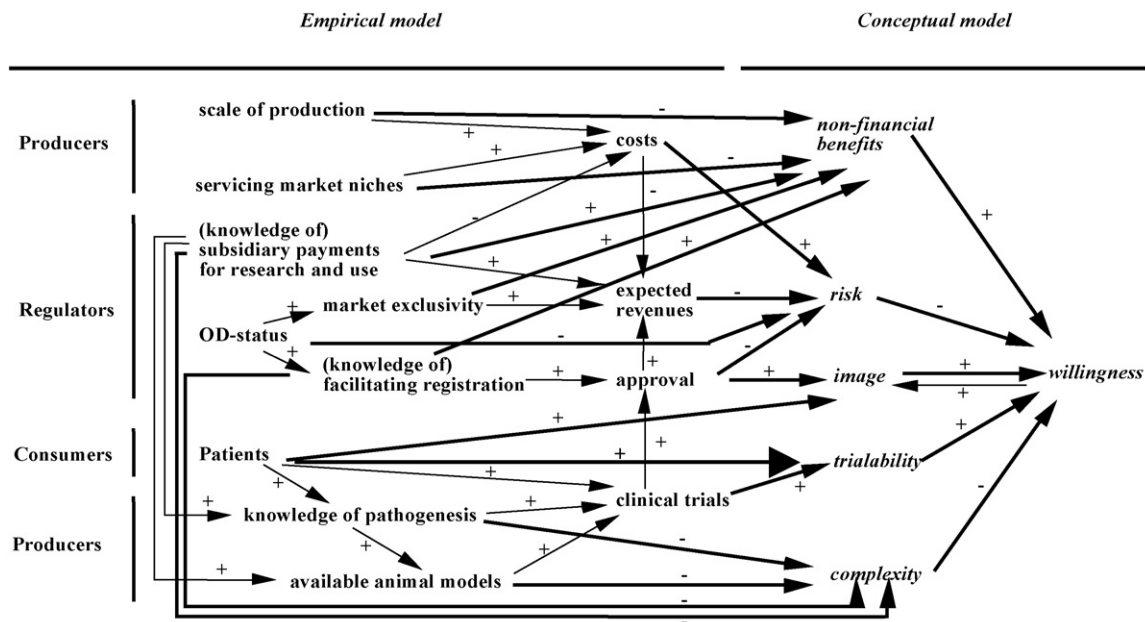
Fig. 5. Results on the barriers in orphan drug development within the Netherlands.

the non-financial benefits for producers, the positive coincidences of image and cooperation with medical institutions and public health organizations, and the coincidence of knowledge sharing and complexity for which there was disagreement. The cooperation between producers and medical institutions is implicitly taken into account by putting medical institutions into the category of producers due to their tight relationships with universities, research institutes, and pharmaceutical companies. The cooperation between knowledge sharing and complexity is not taken into account because the regulator-driven effects in Fig. 5 imply this cooperation.

The results shown in Fig. 5 support the derived causal ordering of the barriers to increasing willingness to develop orphan drugs from good intentions to actions, namely:

(1) A high *financial risk* due to large development costs, small expected revenues and no realized approval of orphan drugs. The costs of orphan drug development are large due to the small scale of production, small market niches to be served and little subsidiary payments of research costs by the regulators (i.e. the government). Small expected revenues are perceived to be due to uncertainty about granting market exclusivity and the absence of an agreement until 2003 about subsidiary payments by the regulators (i.e. insurance companies) to consumers to reduce

the costs of use.[10] Furthermore, until 2004, only a few orphan drugs had been approved by public health organizations. This is mostly due to problems concerning their registration.

(2) The perception of small *non-financial benefits* from developing orphan drugs because of a required scale of production that is smaller than and different from conventional drug production, the need to serve market niches, which differs from serving 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, in Europe, few orphan drugs have been approved compared with the USA.[11] Furthermore, *image* and *willingness* (representing actual drug development by its highest score) are mutually reinforcing.

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[10] In January 2003 the Dutch Health Care Insurance Board (CVZ) has drawn up requirements on orphan drugs reimbursement in the Netherlands (CVZ, 2003). Since January 2006, two policy regulations on expensive and orphan drugs are waiting in the wings to be implemented in the Dutch health care system (CTG/Zaio, 2006).

[11] From 1983 to April 2005, orphan designation was accepted for about 1450 products in the USA and about 270 of these orphan drugs really received market approval. Since 2000, within the EU 270 products have an orphan designation, of which about 23 received market approval (Pharmacos, 2005).

(4) A high degree of *complexity* concerning orphan drug development owing to a lack of knowledge about the pathogenesis of orphan diseases, suitable animal models and patient participation in clinical trials (e.g. 10 versus 10,000 patients). Furthermore, orphan drug development takes place in an international setting, due to the relatively few internationally oriented pharmaceutical companies and start-ups actually involved in orphan drugs development (e.g. Genzyme (USA), Novartis (Switzerland), Bayer Healthcare (Germany), Amgen (USA), Pfizer (USA), Actelion (UK)), thereby further increasing the complexity of orphan drug development.

(5) A low level of *trialability* resulting from insufficient possibilities to conduct statistically valid clinical trials, which in turn result from the conditions mentioned above.

Concerted actions to improve these unfavorable conditions and subsequently to increase the willingness to contribute to orphan drug development remain unlikely as long as there is no shared view of the importance of the regulator- and consumer-related barriers among all three actor groups involved.

5.2. Managerial and policy implications

With regard to the content of the tentative results presented, some interesting options for facilitating orphan drug development can be derived. From Fig. 5 it becomes clear that the regulator actor group may affect the concepts influencing the willingness to develop orphan drugs directly or indirectly and to a larger extent than with conventional drug development. The EODR provides the legislative foundation for this to occur.

If the measures related to the orphan designation granted to pharmaceutical firms are supported by research subsidiary payments by the government and reimbursement by insurance companies, the barriers to orphan drug development and market approval may be overcome. However, this requires the regulators to adopt another focus on orphan drug development. The current focus of the regulators of orphan drug development is on sharing knowledge about orphan diseases and orphan drug development among the various actor groups to promote learning and cooperation between them. The producer and consumer actor groups do not support this action. Due to the poor regulatory infrastructure, they stress the importance of support from governmental agencies in the form of achieving the orphan designation under the EODR, and subsequently facilitating registration of and granting market exclusivity

for orphan drugs. They require them to assume a more active role in orphan drug development by promoting and facilitating achievement of the orphan designation by pharmaceutical enterprises and to support this achievement with subsidiary payments of (clinical) research into orphan drugs, which in turn would lead to more approved orphan drugs within the European Union. This implies that the regulators should also help with organizing phase III clinical trials of orphan drugs by mobilizing patients in other countries to participate in these trials via the European Union or the World Health Organization. This should be achieved by governmental agencies in cooperation with patient organizations. It should be a priority for governmental agencies to adopt such a role, to stimulate coordination and planning of the actions of the various actor groups involved in orphan drug development. This should lead to a shared vision and, consequently, more concerted action programs for specific orphan drug development in which the contributions and liabilities of each actor are matched and defined. In this respect, international programs such as the Sixth and Seventh Framework Programs of the European Union may have important roles.

6. Discussion

The results presented in Fig. 5 on the variables and concepts influencing the willingness to develop orphan drugs in the Netherlands are new but should be considered tentative. This is due to the current nature of orphan drug development and the limited opportunities to conduct empirical research. As most biopharmaceutical orphan drug development is based on only recently acquired insights into the human genome and related DNA technology, the field is relatively new, which leads to three problems.

First, only a few distinct orphan drugs have been developed and approved so far. So, a comparison between successful and unsuccessful orphan drug development trajectories is not yet possible. For this reason, the concept of actual orphan drug development has been replaced by the concept of the willingness to develop orphan drugs. This conceptualization turns out to be very useful in identifying barriers in the innovation system of orphan drug development. The results obtained from the interviews support this conceptualization.

Second, identification of good indicators of the concepts defined in the conceptual model is problematic due to large varieties in a small number of contexts wherein the phenomenon can be studied. Fortunately, as expected from the conceptual model, the indicators applied in this study are mutually associated, implying a high degree of

construct validity. However, some indicators, for example, '(knowledge of) subsidiary payments for research and use' and '(knowledge of) facilitating registration' contain multiple observable aspects. These indicators should be further refined in future research to improve the validity (cf. Riley, 1963).

Third, only small numbers of people are involved in orphan drug development and even fewer are well informed and knowledgeable in this field. This excludes the possibilities of large-scale research and the use of appropriate statistical tests based on probability theory of the formulated hypotheses. To overcome this problem, some robust, small sample, statistical measures of association have been developed in this study. The results obtained provide good estimates of the associations between indicators, but the confidence intervals cannot be estimated. This implies that the estimated associations between indicators hold for the interviewed respondents but that they cannot yet be generalized.

In summary, when biopharmaceuticals in general and orphan drugs in particular are produced and used on a larger scale in the future, research into orphan drug development can be further improved as there will then be a history on which the research can be based. At present, this is not yet an option.

7. Conclusions

This study attempted to identify innovation system barriers to orphan drug development within the Netherlands. On the basis of the conceptual model of the adoption of innovations (Tornatzky and Klein, 1982; Rogers, 1995; Tidd et al., 2001) and by operationalizing the concepts in this model for three different actor groups involved in orphan drug development (producers, regulators, and consumers), a multi-actor approach of analysis is adopted in this study. The data derived from interviews with key actors in each actor group have been analyzed by means of simple descriptive statistics, due to the few respondents involved. The results of the analyses highlight the empirical relationships among the indicators and between the indicators and the concepts they represent (Fig. 5), and also indicate the conditions via the (ordinal) values of their indicators that hamper the willingness to develop orphan drugs to rise from the level of good intentions to the level of active involvement. These conditions are thresholds in the innovation system of orphan drug development, and include: omissions in the knowledge about the pathogenesis of orphan diseases; a lack of suitable animal models; problems with conducting sufficient clinical trials; the uncertainty about

achieving orphan designation; problems with the registration of orphan drugs; the enormous costs of orphan drug development; and the expected small revenues from orphan drug use.

To improve these conditions, concerted actions by the identified actor groups of producers, regulators, and consumers are needed. This requires the regulators (especially governmental agencies) to take a leading role in planning and coordinating these actions. However, as long as the actor groups do not have a shared view on the importance of these conditions and the urgency to improve them, the willingness of producers to develop orphan drugs within the Netherlands will not increase.

This shows that cooperation on innovation in networks of actors with complementary but different competences, responsibilities and interests within and between organizations is only a necessary condition for innovation. Cooperation may take various forms, not all of which guarantee successful coordinated actions of the actors involved and resulting in successful product innovations. To initiate orphan drug development, which is a prerequisite for a biopharmaceutical industry to develop within the Netherlands, governmental agencies in particular must take a leading role in coordinating, not steering the development of at least three additional conditions:

(1) Develop a shared definition of the innovation problem that takes into account all individual actors' competencies, responsibilities, and interests.
(2) Develop an agreed plan of concerted action in time, for example, a road map of innovation policies, management and activities to be pursued by the various actors involved.
(3) Increase the mobilization of patients with rare diseases within and outside the Netherlands for participation in clinical trials and future market access.

The results presented in this study should be regarded as only tentative due to the exploratory nature of the research carried out. Further research should be conducted along two lines of investigation. First, the same research can be conducted in other Western countries. The results obtained from these investigations could be combined with those from the Netherlands to carry out a statistically more reliable international comparative study. Second, if in the future various orphan drugs are introduced to the international market, orphan drug development trajectories can be compared and the barriers to the trajectories can be statistically tested. Hence, statistically better grounded confirmatory research of barriers in orphan drug development can be conducted in the next future.

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