The role of patient advocacy organisations in neuromuscular disease R&D – the case of the Dutch neuromuscular disease association VSN

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Abstract:

This article investigates to what extent patient advocacy organisations play a role in influencing R&D and policymaking for rare neuromuscular diseases. The Dutch Neuromuscular disease organisation VSN is studied in depth. A brief history of the VSN is sketched along with the international embedding of the organisation. Then, a more general perspective is provided on the reasons and extent of the involvement of patient organisations (and especially the VSN) in innovation processes. Lastly, internal mechanisms are presented that can best be applied by these organisations. The VSN adheres to a rare, long-term vision on drug innovation that requires long-term planning and policy and vision creation and steering the direction of science and technology. At the same time, other actors like scientific organisations and science policymakers and managers can benefit from these lessons to learn how to deal with patients and patient organisations in the future.

Keywords: patient organisations; orphan drugs; pharmaceutical R&D

1. Introduction

Neuromuscular diseases are a heterogeneous group of life-threatening or chronically-debilitating conditions. None of these diseases have a prevalence above 5 out of 10,000 inhabitants of the European Union. As such, they are examples of so-called rare diseases. These ailments are subject to huge challenges: despite the urgent health needs of persons with rare diseases, drugs for these diseases are known as ‘orphans’ because companies and scientists are not eager to ‘adopt’ them. The small amount of patients does not offer enough potential for economic profitability or scientific prestige.

Of course these perspectives are too shallow and black-and-white. Not in the least because companies, like Genzyme and Shire, proved that orphan drugs can be the basis of a viable business model, and a large range of scientists keep emphasising that research on rare diseases can function as a scientific model system for other, more prevalent diseases [1].

In the light of these challenges and opportunities, a wide range of actors continue to stress the importance of investing in rare diseases [2, 3]. Especially two public initiatives form prominent examples of this emphasis. Firstly, the Orphan Drug Act in the US (since 1983) and the EU Orphan Drug Regulation (since 2000) were decreed, in the context of which medicines can obtain an Orphan Drug Designation that guarantees, amongst other incentives, market exclusivity and protocol assistance. Secondly, a WHO/EU project called ‘Priority medicines for Europe and the world’ aimed to construct, in consultation with scientists, industry and patient groups, a list of diseases that should be the cornerstone of public investment in drug R&D [4]. Drugs for rare diseases were designated as a priority in this report.

Despite these initiatives, rare neuromuscular diseases inherently imply a small basis for support. The stakeholders with the strongest incentives to stimulate R&D are patients. Therefore, some authors claim that patients and their representative organisations more actively stimulate and steer others to work on R&D in comparison with patients (organisations) focussing on more common diseases [5, 6]. These organisations should take the lead in these disease areas because other players would be less willing to do so. For example, patient organisations can serve as “lubricating oil in the difficult relationship between industry and science” [7].

This article investigates to what extent patient advocacy organisations play a role in influencing R&D and policymaking for rare neuromuscular diseases, and if so, what kind of internal mechanisms can best be applied by these organisations. These insights can be helpful for patient organisations to optimise stimulating and steering neuromuscular disease R&D. Moreover, it might increase the understanding of other stakeholders, such as scientific and medical professional groups and businesses, as to how to benefit from patient involvement. Lastly, concerning the scientific relevance, we build on literature about patient advocacy groups [8, 9], which has mushroomed from the 1990s onwards [10].

A prominent Dutch example that is presented here is the Dutch Neuromuscular disease organisation (Vereniging Spierziekten Nederland, VSN).

This historical report proposes to follow the VSN’s efforts in neuromuscular disease research, by studying the activities, documents, statements of the patient organisation and the actors with which it has interacted over these 40 years. This is based

on a study done by Boon [6]. The topics that were taken into account were amongst others biomedical research, diagnostics, innovative therapies, and patient registries.

2. History of the VSN and its related international networks

The Dutch Neuromuscular disease organisation is a patient organisation founded in 1967 by two parents with children who suffered from a neuromuscular disease. Objectives included taking care of the welfare of and communication to patients and parents, setting-up mutual help groups for different neuromuscular diseases, and stimulating research into neuromuscular diseases.

The VSN soon put research that would improve the diagnosis of neuromuscular diseases on their agenda. To this effect, the patient organisation established contact with several medical professionals, scientists, and charity funds. Under the adage that scientists working on rare diseases needed to share their work to be effective, the VSN co-founded the European Alliance of Neuromuscular Disorders Associations (EAMDA) in 1971. EAMDA's objectives included coordinating and stimulating international research, and setting up comparative quantitative data inventories on therapy, diagnostics, research, and prevalence. For example, a 1984 international workshop on Duchenne muscular dystrophy resulted in a coordinated research effort that led to finding the gene responsible for the disease. This also marked the start of the VSN's interest into translating this genetic information into diagnostics and therapy, amongst others by stimulating the set-up of patient registries.

In the 1980s two other science collaborations were co-founded by the VSN: the Dutch Foundation for Neuromuscular Research (SONMZ; 1985) together with doctors and researchers, and the European Neuromuscular Centre (ENMC; 1988) together with other patient organisations, such as the Association Française contre les Myopathies. The ENMC stimulated international research, notably through the organisation of scientific workshops, an information gateway, and a clinical trial network. To date nearly 2000 scientists have taken part in more than 160 workshops. Issues that were discussed during these workshops included criteria for diagnostics, standardising clinical trials, and gene location [11, 12]. The effectiveness of these workshops is underlined by the fact that workshop reports are amongst the most cited articles in NMD. The workshops now embrace wider issues around patients' lives and well-being as well. A programme of practical care workshops, which will run alongside the science workshops, is planned.

In 1998, the VSN reflected on its research steering and stimulating role, and widened its attention to include therapy. One of the diseases for which this was topical at that time was Pompe disease. Once again the VSN thought that this could best be done on an international level and it initiated the International Pompe Association.

In the 2000s the VSN widened their perspective to include advocacy efforts, emphasising awareness of other actors in the medical, health care and scientific sector; empowering patients; and attracting the attention of policymakers and the media. The organisation was actively engaged in all phases of biomedical and clinical R&D. Box 1 illustrates this by showing the major contributions of VSN with regard to therapy.

Box 1: major contributions of VSN to

gene therapy: following scientific developments, informing patients

stem cell therapy: following scientific developments, validating new therapies

exon-skipping: setting-up science networks, following scientific developments

enzyme replacement therapy: animal rights debates, clinical trials, compassionate use, reimbursement, newborn screening

idebenone and TCH346: propagating clinical trials, informing patients

All in all, the VSN is a representative patient organisation that has a strong focus on R&D stimulation and steering. The VSN pursued this by investing in collaborative networks of scientists (see Figure 1) who worked on gene location, gene identification, gene product identification, and productive enzyme therapy. Later, from the 1990s onwards the emergence of actual therapies resulted into including advocacy efforts, e.g. regarding compassionate use and reimbursement.

Insert Figure 1 about here.

3. Involvement of patient organisations in biomedical and pharmaceutical R&D

In the pharmaceutical sector the innovation process is frequently characterised as a linear 'drug research and development pipeline'. The strictness of the model and its phases is created and emphasised by regulatory requirements and its accompanying milestones. Since the 1980s, several authors [13, 14] have begun to claim that the linear layout of pharmaceutical innovation processes could be enhanced by feedback and feedforward

steps. These interactions occur between different stages in which also other stakeholders, such as small high-tech companies and university hospitals are involved. Figure 2 illustrates both the linear and the interactive models.

Insert Figure 2 about here.

One category of external actors with whom pharmaceutical companies interact are the patient organisations, such as the VSN. In science, technology and innovation studies these representative user groups have been investigated over the last three decades [15, 16]. The involvement of these organisations in innovation processes can be beneficial for several reasons [17]. These reasons are illustrated by examples taken from the history of the VSN:

1. *Overcoming market failure:* in the case of rare neuromuscular diseases the market does not adequately meet all societal problems and companies refrain from developing products that are commercially unattractive. For example, the VSN stimulated R&D on neuromuscular diseases by forming national and international networks of scientists.
2. *Employing knowledge of the users and their creative potential:* the VSN tried to gain access to the agenda-setting of scientific research by creating (inter)national networks of researchers. In this way they not only organised an efficient and effective knowledge exchange between scientists but also tried to convey the wishes, 'experiential knowledge' and priorities of patients.

3. *Enhance effectiveness (and speed) of the innovation process:* the VSN provided boundary conditions that contributed to the effectiveness of innovation processes. Some of its efforts focused on creating awareness and communicating information about new technologies, but it also included assisting with and initiating clinical trials, the management of expectations, representing patients towards regulatory agencies, and creating research projects. Moreover, the VSN also participated in the debate on the reimbursement of expensive biotechnology drugs.
4. *Ethical and social debates in society:* this is achieved by addressing contested issues around a technology and in this way making sure that the interests of patients have an impact, or at least broaden and enrich debates. One example refers to the debate on the use of transgenic animals to manufacture pharmaceuticals. Apart from the interests of animal rights groups also those of patients were taken into account during the debate. The VSN functioned as a 'rhetoric champion' within this debate.
5. *Increase democratic value of innovation processes:* the VSN actively tries to involve patients in their board, committees, and activities. Legally the association is governed by its members, but in practice only some of them influence the organisation's decision-making.

These five reasons show that it can be beneficial to include patient organisations in innovation processes[1]. The next section delves deeper into which internal mechanisms the VSN applied while trying to influence these innovation processes.

[1] We are aware of potential downsides to this, such as the financial investments and time needed to set-up this involvement, the potential knowledge gaps because of the esoteric nature of biomedicine, the institutional arrangements governing biomedical R&D, differences in norms, possible inflated expectations,

4. Mechanisms within the VSN

In this section three mechanisms are discussed to illustrate how the VSN attempted to articulate their wishes and needs in relation to biomedical innovations[2].

a. Management of expectations

Emerging technologies, such as stem cell and gene therapy, induce enthusiasm, promises and expectations. Patients with no hope of recovery intensify this prophecy in their despair. The VSN has been aware of the risks of 'being ahead of the pack': its respectability is at stake and it might jeopardise scientific developments because too much resistance is created. On the other hand, constantly downplaying new developments might result in less (financial or scientific) attention. Therefore, the VSN aimed to strike a balance and did this by aligning with scientific advisors and internalising the ability to assess scientific knowledge. Hereto it continuously kept track of scientific developments, annotated them, tried to clarify them, and reported about them using disclaimers. They always left the choice to patients, and if they wanted to adopt a new therapy, they encouraged measurement of safety and efficacy data.

b. Active case-building

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and the potentially suspicion towards interactions between the pharmaceutical companies and patient organisations [18].

[2] There were of course more mechanisms discerned but we restricted ourselves to the three most dominant ones [6].

The VSN started to put issues on the policy agenda, such as the reimbursement of expensive drugs. Case building requires a thorough synthesis of needs and preferences, which includes in some cases even producing full-blown consultations, reports and figures. This usually involves cooperation with other actors. Case building results into demands that are not easy to dismiss, although it requires a lot of resources (knowledge, professionalism) that secure empowerment to produce these results.

c. Network building

The VSN initiated the formation of (inter)national networks of scientists and, later, other stakeholders. It had an overview of the field and the problem at hand, and envisaged that some actors needed to be brought together in order to work on the problem. This mechanism largely concerns aligning other actors to achieve some longer-term solutions. Implementing this mechanism not only requires these intermediaries to have an abstract idea of which route to take and which topic to handle, such as the guiding idea to travel from gene location to therapy, but also calls for excellent contacts and interaction skills.

5. Conclusions and repercussions

All in all, the VSN is a patient organisation that maintains contact with a large variety of actors and is able to use these contacts to articulate their demands. The VSN co-founded some of these actors, most of which are concerned with scientific research into neuromuscular diseases. Stimulating scientific research has been one of the most

prominent objectives of the VSN since its foundation in the 1960s. This involvement in basic and later clinical drug R&D is quite unique, at least for Dutch patient organisations.

By this, the VSN adheres to a rare, long-term vision on drug innovation. It regards research as something that requires long-term planning and policy, and finds it important to be involved in vision creation and proactively steering the direction of science and technology. Especially for the uncertain and controversial aspects of emerging technologies, like the orphan drugs future or ethical aspects of stem cell therapy, it would be useful to take a longer-term perspective and provide room for discussion with other stakeholders in a proactive way, without necessarily having a predefined agenda or specific problems.

Besides being proactive, to be regarded as a serious interaction partner, patient organisations need to reflect on their position. They need to balance the interests of the organisation, and speak on behalf of its members and picture their demands in a representative way, at the same time taking an impartial or professional stance in interactions. If patient organisations can overcome the challenges of being proactive and positioning, they can (continue to) play a central and crucial role in the co-production of neuromuscular R&D.

Figures

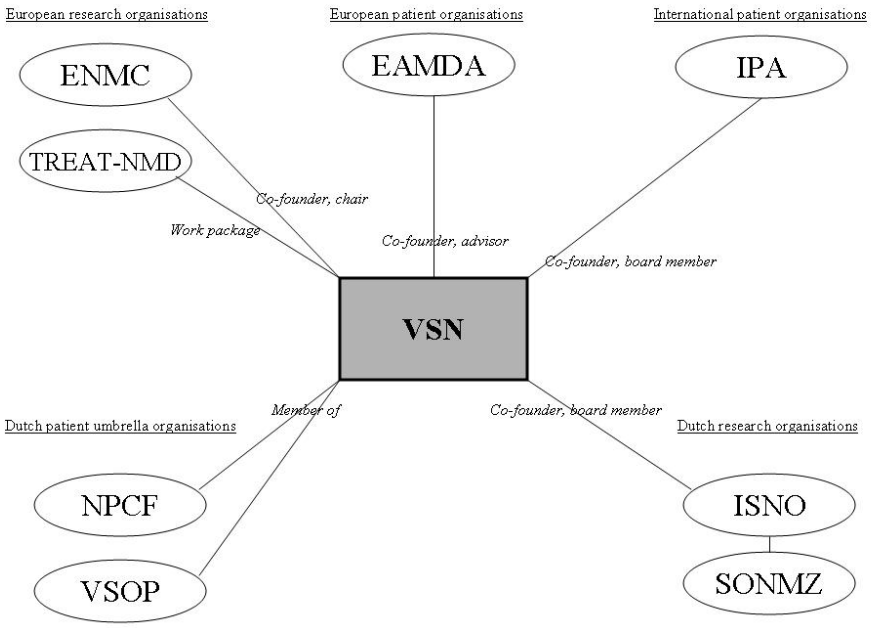

Figure 1: network of national and international partners in which the VSN operates.

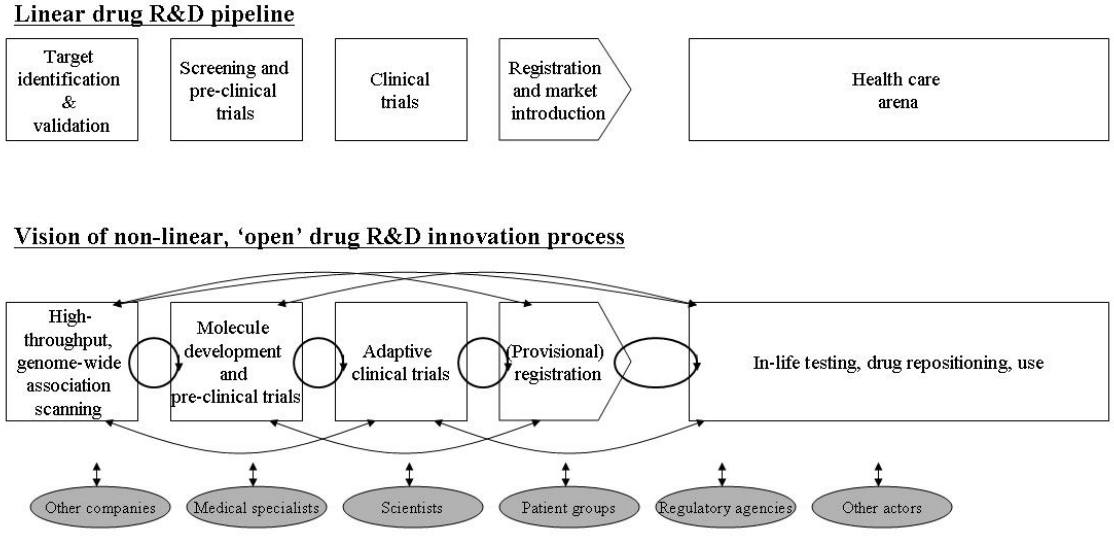

Figure 2: linear model of the drug innovation process as compared to a more interactive representation.

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