Demand articulation in intermediary organisations: The case of orphan drugs in the Netherlands

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Abstract

Several aspects of a technology are uncertain when it is in its emerging phase, e.g. the demand for a technology. Demand articulation processes are regarded as important, but till now it is often treated as a black box. We present a conceptual framework for the analysis of demand articulation processes inside intermediary organisations, and in interaction with other stakeholders. The empirical basis of this framework is provided by a case study involving an event history analysis, in which the occurrence and the contents of demands are followed over time. We studied the processes within the 'Dutch Steering Committee Orphan Drugs', an intermediary organisation that supports new and emerging technologies in the context of orphan drugs. Our results show that due to the activity of the intermediary organisation demand articulation occurred, that interactions exist between the demands and the organisation's underlying values, and that in interaction with other actors a debate on the reimbursement of new drugs is settled. The major contribution of this paper lies in the design of a framework for studying demand articulation processes in intermediary organisations and the resulting impacts on the development of emerging technologies. In addition, the paper provides insights in the possibilities to reinforce the role of the intermediary organisation studied.
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1. Introduction

Co-evolutionary approaches in innovation aim to open the black box of the interaction between technology and society in order to understand the development and domestication of technology as a co-

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construction process. The importance of including users in the analysis of innovation processes is widely acknowledged and has led to a broad and diverse range of user involvement literature in innovation studies, organisational studies, and science and technology studies [1–9]. A better mutual understanding of needs, visions, goals, and ethical issues empowers involved actors and increases the chances on successful adoption and implementation of innovations. Moreover, utilising users' creative potential might improve the innovations themselves and even lead to new innovations. User involvement also contributes to the democratic content of decision-making on innovation: users are better equipped to decide on important aspects of their lives [10].

User involvement and user–producer interactions prove to be even more poignant when looking at so-called *emerging technologies*, i.e. technologies that are in an embryonic phase of their development. This phase is characterised by high uncertainties and need for flexibility. These uncertainties include the possible technological options, their applications, the acceptability of these applications, related ethical, legal and social aspects, the definition of production and maintenance networks, and demands. These aspects are specified through so-called articulation processes [11,12], which are partially carried by the expectations of users and other stakeholders, and interactions between them. The Collingridge dilemma [13] states that for stakeholders it is difficult to specify different elements of an emerging technology, while technology and society are still plastic and fluid. In later stages, by contrast, this fluidity is waning because of increasing vested interests, but actors know far better what they want. So, although actors know better how they want to intervene, in later stages options to do so are decreasing. Therefore, it is desirable to support stakeholders to articulate their demands[1] as early as possible.

In innovation literature the importance of *demand articulation* has been emphasised, but whether demand articulation occurs and what its dynamics are have remained unexplored. In this article we attempt to open this black box by proposing a framework with which demand articulation is studied. Demand articulation is defined here as: *…an iterative, inherently creative process in which stakeholders try to unravel preferences for and address what they perceive as important characteristics of an emerging innovation.* Demand articulation takes place when thoughts of stakeholders, in terms of content and position (in favour or against), are made explicit, in such a way that it prompts other actors to (re-)act. Articulation of demand is a learning process that will take time. In the early phase of technology development stakeholders only have 'vague' ideas. These ideas have to be developed further in the course of the demand articulation process. Results of this process include changes in awareness, perceptions, ideas, needs, expectations, and visions.[2]

We pay special attention to the dynamic character of demand articulation processes and the variety of opinions and stakeholders involved. By doing so, we do not only want to contribute to studying demand articulation in emerging technologies, but also want to offer useful pointers for organisations how to analyse their own demand articulation processes, based on which they can think of improvements, e.g. concerning the communication interfaces with other actors or how to enter a debate over technology issues.

In this article we particularly concentrate on *intermediary organisations* as a group of actors that mediate between users, producers, designers, etc. Especially in the health care sector in the Netherlands,[3] where we carried out our case study, these stakeholders channel their demands through representative agents, such as patients' organisations and other kinds of intermediary organisations [15].

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[1] It should be stressed at the outset that the term 'demand' refers to market and societal demand.

[2] In this context the term 'latent demand' was introduced [14].

[3] Whether the case study reveals country-specific dynamics will be discussed in the last section.

Fig. 1 shows the structural set-up of an intermediary organisation, the way in which internal demand articulation processes function (D_{in}), and the way in which demands are communicated through interfaces to other actors. Also the demand articulation with these 'interacting partners' is depicted ($D_{between}$).

The figure illustrates on which elements of the demand articulation processes we want to focus and leads to the following research questions:

1. Do demand articulation processes occur inside intermediary organisations dealing with emerging technologies, and if so, how (D_{in})?
2. How did the demand articulation processes develop through the interaction between the intermediary organisation and its interacting partners ($D_{between}$)?
3. What characteristics do the interfaces have through which demands are communicated?

A case study on orphan drugs is used as an illustration of the framework. Orphan drugs are medicines developed for treatment of rare diseases. They concern a heterogeneous group of conditions that are life threatening or chronically debilitating and have a prevalence of not more than five out of 10,000 inhabitants of the European Union. A large proportion ($\sim 80\%$) of these rare diseases has a genetic origin. Therefore, it is not surprising that therapies mostly come from emerging technology fields related to genetics, such as biotechnology, gene therapy or pharmacogenomics. Moreover, it is claimed that rare diseases serve as a model for studying more prevalent diseases, because disease mechanisms appear in a magnified form [16]. Here we focus on two essential aspects of the drug research and development pipeline that affect the shaping of these emerging technologies, viz. reimbursement of orphan drugs, and orphan drugs research and development. Both are potentially problematic, because of the small numbers of patients involved: companies' return on investment of R&D costs is not guaranteed, and to balance the low sales numbers they need to ask high prices of which reimbursement is uncertain. In this vein, we concentrate more on demand articulation around policy-related issues rather than on user involvement in the development of a specific technology like in Von Hippel's work.

In the following we focus on three important aspects of these articulation processes. In Section 2 we conceptualise demand articulation processes inside intermediary organisations (D_{in}; research question 1), Section 3 deals with demand articulation through interactions between the intermediary and other actors ($D_{between}$; research question 2), and in Section 4 we look at the characteristics of interfaces through which demands are communicated (research question 3). We will illustrate this conceptual framework with a case study of a Dutch intermediary organisation in the health care sector involved in the development of emerging orphan drug technologies (Sections 5 and 6). Section 7 draws conclusions and discusses the results.
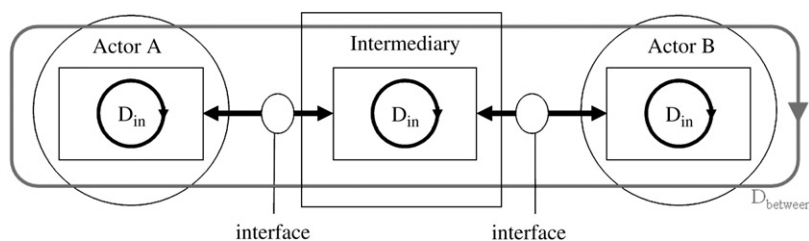

Fig. 1. Demand articulation within (D_{in}) an intermediary organisation and its interacting partners (A and B), and demand articulation in interaction ($D_{between}$) through interfaces.

2. Demand articulation inside intermediary organisations

2.1. The role of intermediary organisations

Intermediaries can be seen as organisations that manage the relationship between two or more actors (see Fig. 1). They feature in social network theory [17], principal-agent theory [18], and theory on market brokerage [19]. In the context of the innovation systems literature, intermediary organisations form the links between firms, research and educational institutes, the demand side, and the infrastructure of the innovation system [9,20]. In the last decades they have become more important, because of an increase in different sorts of actors involved in the innovation process [21], for example through strategic alliances, spin-offs, joint ventures, innovation centres, incubators, science parks, knowledge transfer, etc. This is reinforced by a differentiation and division of the innovation system in parts, such as companies and research institutes, which have their own evaluation routines and accountability structures. Most prominently, intermediary organisations translate, coordinate and broker between these disconnected parts. There is a wide variety of functions that are ascribed to intermediaries ranging from representative agent, liaison, gatekeeper, coordinator, agenda-builder, etc. [22,23]. Users and producers come from different backgrounds and their interaction can be facilitated by intermediary organisations [3,24].[4] A shift in focus of these intermediaries has been observed in recent years from short-term activities such as knowledge translation and brokerage to more upstream activities in the innovation process, such as scoping and strategic intelligence [26]. This means that demand articulation has become an integral part of intermediary organisations. When dealing with emerging technologies and their related uncertainties, intermediaries need to learn about using strategic intelligence and organising their demand articulation processes.

2.2. Learning processes inside intermediary organisations

Intermediary organisations take stock of the heterogeneous set of demands that originate from other stakeholders as well as from internal members. These demands are aggregated and combined as they are put on the internal agenda. Entries on an actor's agenda are statements that are actively taken into consideration, weighed, discussed and eventually pursued. If pursued, these demands are in turn issued to other stakeholders. This internal articulation of demands is a learning process about characteristics of innovations. Demands are defined here as: ...*explicit, univocal statements of actors on how it regards (the future concerning) a technology and which issues regarding this technology should be included or addressed by other stakeholders*. Demands include:

– Science fictions, (guiding) visions, 'Leitbilder', expectations or promises[5] are real-time representations of future technological situations and capabilities [27]. They include statements on the future ('we expect...', 'we anticipate...', etc.). Visions are "mental images of an attainable future *shared* by a collection of actors; they *guide* the actions of and interactions between those actors" [28].

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[4] In the context of innovation systems, Geurts [25] speaks of four gaps: between practical policy processes and science, different (scientific) disciplines, administrators and citizens and between experts and laymen, and between the producers and the users of knowledge.

[5] The distinction between expectations and visions is not clear. Therefore, we treat these two categories as partially overlapping.

– Perceptions of problems and obstacles with existing products or situations. Ideas and solutions: the
  actor acknowledges a problem, knows a direction for solutions, and has some concrete ideas about how
  this end state should be reached.
– (Concrete) needs for existing and non-existing products.
– Concerns about ethical, legal and social implications (ELSI).

Changes in demands for innovations and the related agenda entries are part of a cognitive (trial-and-
error) loop of identified problems and proposed solutions in the context of certain norms, which result in
learning about these innovations. In this paper we perceive changes in demand statements and agenda
entries as first-order learning[6] [29]. Second-order learning occurs when organisations reflect on their and
other organisation's strategies, objectives and norms. Leeuwis et al. [32] define this second-order learning
as follows: *We speak of second-order learning when actors change their goals and/or the norms and
values on the basis of which they evaluate problems and situations.*

Second-order learning involves changes in the values that are underlying first-order statements
(demands and agenda entries). These underlying assumptions are a complex of organisational norms and
values that frame the day-to-day decisions on strategies, operations and demands. They consist of two
aspects [33]. Firstly, appreciative systems and overarching theories that form the reasoning behind
operations, strategy, demands and problem solving ('how to get from the current to the perfect end
situation'). They resemble the paradigms [34] or evaluation routines [35] that shape scientific or
professional practice, but also include objectives and starting points for organisations. Secondly, ultimate
preferences, being the desired identity or attitude, desired social order or desired position in the field
('perfect end situation').

Second-order learning can change the process of demand articulation and resulting demands. For
intermediary organisations this is particularly important, because they have a constant need to position
themselves towards others [36]. Therefore, explicating and reflecting on underlying assumptions is
crucial for these kinds of organisations.

All in all, we study demand articulation as learning processes on two levels, taking into account
demand statements and agenda entries (first-order learning), and underlying assumptions (second-order
learning; cf. Fig. 2). Changes in one of these elements indicate that learning takes place.

3. Demand articulation in interaction between actors

Demand articulation processes within organisations are complemented and influenced by articulation
processes within other organisations. A converging 'force' is needed to counterbalance[7] the diversity of
actors involved and the diverging of demand statements. Converging is an important feature of the demand

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[6] According to Argyris and Schön [29] first-order learning *connects detected outcomes of action to organisational strategies
and assumptions which are modified so as to keep organisational performance within the range set by organisational norms.
The norms themselves […] remain unchanged.* Second-order learning concerns *those sorts of inquiry which resolve
incompatible organisational norms by setting new priorities and weightings of norms, or by restructuring the norms themselves
together with associated strategies and assumptions.* Originating from psychology, organisational sciences and policy studies,
these concepts have been applied in technology and innovation studies before [30,31].

[7] For example because involving more actors is not always better. It can even have a counterproductive impact on the
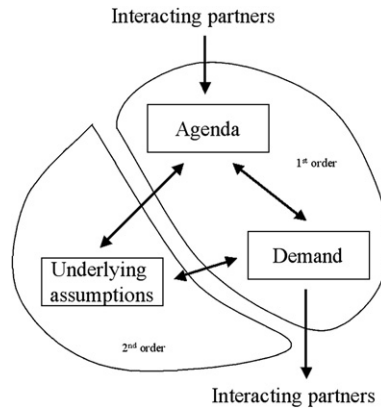innovation process: resistance might arise or increase.

Fig. 2. First- and second-order learning mutually influence each other within an intermediary and with their interacting partners.

articulation process: the variety of demand statements becomes more and more focused and concrete through time. This means that an important role of intermediaries is to use the available information to effectively narrow-down demand options. At the same time, the increase in information and number of actors involved may result in more uncertainty and in different coalitions of ideas. Ultimately, these coalitions might also show convergence and closure in the form of a dominant design or, in contrast, reach stalemate, i.e. a situation in which demand articulation leads to the intensification of contrasts.

Grin et al. [37] call these processes *joint construction*: *a synthesis between the participants' different beliefs*. It is reached through first-and second-order learning processes, which occur in interaction with other actors. In this way, learning takes into account the reactions of other actors, which can take the form of statements on demands or specifications embedded within a technology. Demand articulation in interaction is influenced by agreement or disagreement between intermediaries and their 'interacting partners' on the level of demands and agenda entries, or on the level of underlying assumptions. This results in four different combinations of agreement and disagreement, which relate to four different situations of joint construction of demand, so-called 'construction states' (Fig. 3). If actors agree on both first-and second-order elements they agree both on the contents of the demand statement and the values
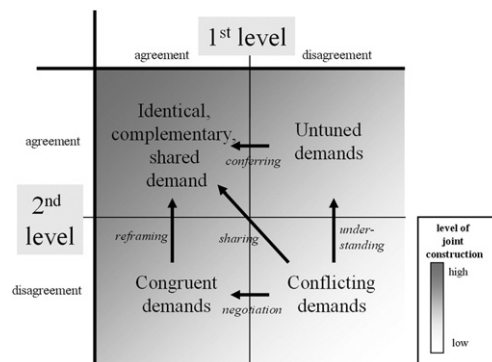

Fig. 3. Four states of demand and related level of joint construction. The arrows show the joint construction enhancing learning shifts between the states. The terms accompanying these arrows are examples of describing these shifts.

underlying them. The demand is 'complementary, shared or even identical'. At the other end, if actors do not agree on both levels, they have clear 'conflicting' demands. The two states in between describe a situation in which actors agree on their underlying assumptions but nevertheless disagree on the first-order demands. These demands are therefore seen as 'untuned'. And a situation in which actors have different values, but still can work together on the first-order level ('congruent' demands).

4. Communication of demands through interfaces

Intermediary organisations are by definition positioned at a central node of a network of actors (Fig. 1), at least this is the 'perfect end situation' of an intermediary. Furthermore, they do not only pass on information from one actor to another, but also add value, for example by translation of knowledge, prioritisation of options, aggregation and selection of information from different sources into a message that is comprehensible for others. This requires a lot of the information collection and dissemination capabilities of an organisation. Intermediary organisations collect and disseminate information through so-called interfaces or media of interaction. The characteristics and dynamics of these interfaces will be analysed by using the following typology based on Mayer [38]:

– Consultation: relevant information is generated and clarified;
– Education: understanding is raised and knowledge is shared;
– Presenting, advocating: points of view are brought forward;
– Mediation: conflicting ideas are aligned (also: negotiating);
– Coordination: different interests and opinions are tuned;
– Deliberation: same as coordination but without having a predefined topic from the start;
– Anticipation: different future options are explored and assessed (if it is about current options, it can be called prioritisation);
– Co-production: activities or projects are taken up together with other actors.

After conceptualising demand articulation inside intermediary organisations, between different stakeholders, and the communication of demands through interfaces, we now turn to the case study, in which the three research questions are put central.

5. Case study design and methodology

5.1. Design of the case study and event history analysis

The case study focuses on the 'Dutch Steering Committee Orphan Drugs' (Stuurgroep Weesgenees-middelen, from now on referred to as WGM). WGM is an intermediary organisation that aims at stimulating the development of orphan drugs, and improving the cure and care of patients with rare diseases.

An analysis of demand articulation processes in intermediary organisations imposes the importance of time ordering and changing entities that are studied over time [39]. These processes are marked by so-called 'events'. We used the 'event history analysis' based on Poole et al. [40] to study these processes. These events included decisions taken, projects started, reports published. They were measured by studying notes of meetings, contacts with other stakeholders, circular letters published, etc. It is important to mention that the events themselves only tell that something has happened. Within the processes of

Fig. 4. Following the three central subjects and relevant external events over time.

demand articulation it is also relevant to look into the related dynamics of the content of demand. Regarding the events and statements, three central subjects were followed over time (Fig. 4): demands, agenda entries, and underlying assumptions, as well as relevant events occurring outside the intermediary.

Events and statements were found in notes, reports, etc. by using strict indicators (Table 1). When identified, they were included into a database that at the end consisted of over 1000 entries. These entries were subsequently coded[8] according to the dimensions shown in Table 1. Dimensions reflect different aspects of the subjects that are of particular interest, e.g. demands include needs, problems, ideas, etc. The time covered by the analysis (from April 1997 to June 2006) roughly runs parallel to the existence of the WGM.

Uncovering these events along the lines of the three central subjects required the application of a triangulation of methods, i.e. (1) doing archival research, studying reports, press releases, minutes of meetings, (2) interviewing employees and representatives of these organisations, and (3) observation during key events within the interfaces, e.g. during expert meetings. The last two methods were specifically needed when studying the underlying assumptions (asking 'why-questions'). All the events and statements represented on the time axis (Fig. 4) were discussed with members of WGM.

Demand articulation processes are concerned with explicating, concretising and narrowing-down of the contents and directions of demand statements. These processes take the shape of cycles. We focused on two cycles of events. An event cycle comprises a series of events that revolve around one topic, span a substantial amount of time, and are thematically coherent. The first cycle treats the end stages of a pharmaceutical innovation process (reimbursement), while the second one deals with the earlier stages of research and development. Besides the events themselves, also the content of these events was recorded in order to distinguish changes in demands, agenda entries and underlying assumptions. These two cycles were chosen because they were prominently present in the resulting event database. Moreover, related topics featured in the assignment on which WGM was founded. Furthermore, experts within WGM acknowledged them as important.

5.2. Operationalisation of the three research questions

The first research question is whether demand articulation occurred within WGM, and if so, how the demand articulation processes take shape inside intermediary organisations (D_{in}). While studying the two event cycles, we looked whether demand statements increased or decreased in number and whether their focus was converging or diverging in relation to their content (becoming more/less concrete) and direction

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[8] This coding exercise took methodological issues, such as interrater reliability and face validity, into account.

Table 1
Operationalisation of central subjects

Central subject	Dimensions	Indicators	
		Presence of statements	Content of statements
Agenda entries	– Decisions on agenda entrance – Weighing of entries – Selecting (prioritising) them	Y/N	See Section 2.2
Underlying assumptions	– Appreciative systems and overarching theories – Ultimate preferences	Y/N	See Section 2.2
Demands	– Science fictions, visions, 'Leitbilder'/'guiding visions', expectations, promises – Problems, obstacles – Ideas, solutions, applications – Needs – Ethical, legal and social concerns	Y/N	See Section 2.2

(for/against). Two aspects were then studied to address the internal organisation of the demand articulation processes. Firstly, the agenda-setting process was investigated. What kinds of issues were put on the agenda of an intermediary and how? Did underlying assumptions, external parties, etc. influence them? For this we examined all agenda entries in the database. Secondly, we studied first-order and second-order learning and looked whether changes occurred on demand statements, agenda entries, and underlying assumptions. Most prominently, we also investigated whether the changes in these elements influenced each other. To keep the study manageable, we confined our analysis of the second part of this research question to one event cycle.

To answer the second research question, about the demand articulation as part of an interaction process with other actors ($D_{between}$), we followed first- and second-order learning for the intermediary and a few other actors on one of the event cycles. For the intermediary this had already been done in the context of research question 2. To uncover the changes in first- and second-order statements of the interacting partners who did play a role in the event cycle, we conducted interviews with representatives of these partners. To minimise problems that respondents might have with stating their underlying assumptions connected to past events,[9] we used an event time line as a mnemonic device. We then examined whether the first- and second-order statements of all actors (intermediary and interacting partners) were in agreement or disagreement. That is, we compared demand statements, agenda entries and underlying assumptions of actor A with those of actor B on a particular point of time on the event time line, and analysed whether they corresponded to or correlated with each other. This gave us hints in which joint construction state these actors could be positioned and whether changes between the four construction states occurred (see Fig. 3).

The third research question concerned the characterisation of the interfaces. Part of the events is linked with the instruments and methodologies that form the interfaces between the different actors. The typology of interfaces, which was discussed in Section 4, is again presented in Table 2. It is supplemented with indicators that link them to the events and statements.

The next section will present the results of the WGM case study.

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[9] Such as problems with remembering precise details, giving non-nuanced views on past issues using the benefits of present insights, etc.

Table 2
Typology of interfaces

Types of interface	Indicators
Consultation: relevant information is generated and clarified	One-way communication (to intermediary) aimed at obtaining relevant information on certain subjects through, for example, questionnaires and interviews
Education: understanding is raised and knowledge is shared	One-way communication (from intermediary) aimed at informing others and teaching them things.
Presenting, advocating: points of view are brought forward	One-way communication (from intermediary) aimed at presenting results or points of view. For example by publications, mission statements, press announcements, etc.
Mediation: conflicting ideas are aligned (also: negotiating)	Other parties have conflicts of interest and these are managed by the intermediary through, for example, alignment meetings, discussions, a series of one-to-one conferences.
Coordination: different interests and opinions are tuned	Alignment of current and future activities without there necessarily being conflicts of interests. Examples: distribution of resources, distribution of media attention, presenting the spectrum of possible interests and opinions.
Deliberation: same as coordination but without having a predefined topic from the start	Meeting with no preconceived agenda.
Anticipation: different future options are explored and assessed (if it is about current options, it can be called prioritisation)	Distant futures are explored by deploying strategic intelligence instruments. Results include technology assessments, foresight studies, scenarios, etc. Differences of interests and opinions are summed up as well as weighed and compared.
Co-production: activities or projects are taken up together with other actors	Organising things together, such as workshops, conferences, publishing of reports, etc.

6. Case study results

To set the scene, Fig. 5 presents a social map in which WGM acts as an intermediary organisation. It shows the most prominent interacting partners of WGM. The inner circle consists of members of WGM coming from different organisations[10] and disciplines. The top boxes are filled out with organisations that often take part in events together with WGM or feature in statements made by WGM. The lower boxes include more indefinite groups of actors that are often cited. Also as an introduction, Fig. 6 shows the most prominent events in which WGM took part or which were important to WGM, e.g. the invitational conference they organised at the start and the evaluation they went through in 2004.

6.1. Does demand articulation occur, and if so, how?

The question whether demand articulation processes are occurring is answered by studying two event cycles on orphan drugs reimbursement and research and development.

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[10] BioFarmind and Nefarma (biotechnology and pharmaceutical company representatives), VSOP and CG-Raad (umbrella organisations of patient groups), CVZ (the National Health Care Insurance Board), CBG (Dutch Medicines Evaluation Board), two medical specialists, a pharmacist, a scientist, and a representative of a health care insurance company (since 2005). VWS (Dutch Health Ministry) and the Dutch member of the Committee on Orphan Drugs/EMEA have an observatory role.
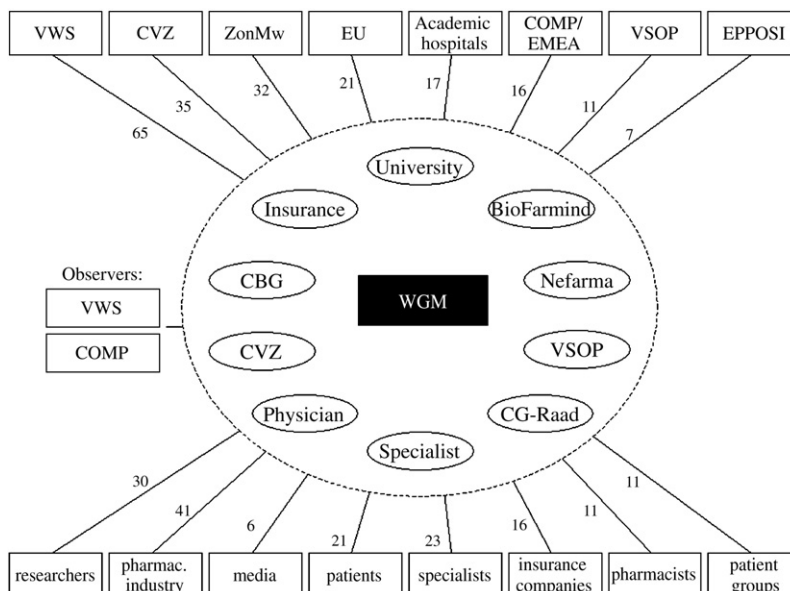
Fig. 5. Social map of the Dutch Steering Committee Orphan Drugs and their interacting partners (figures indicate the number of times that they are mentioned in the database).
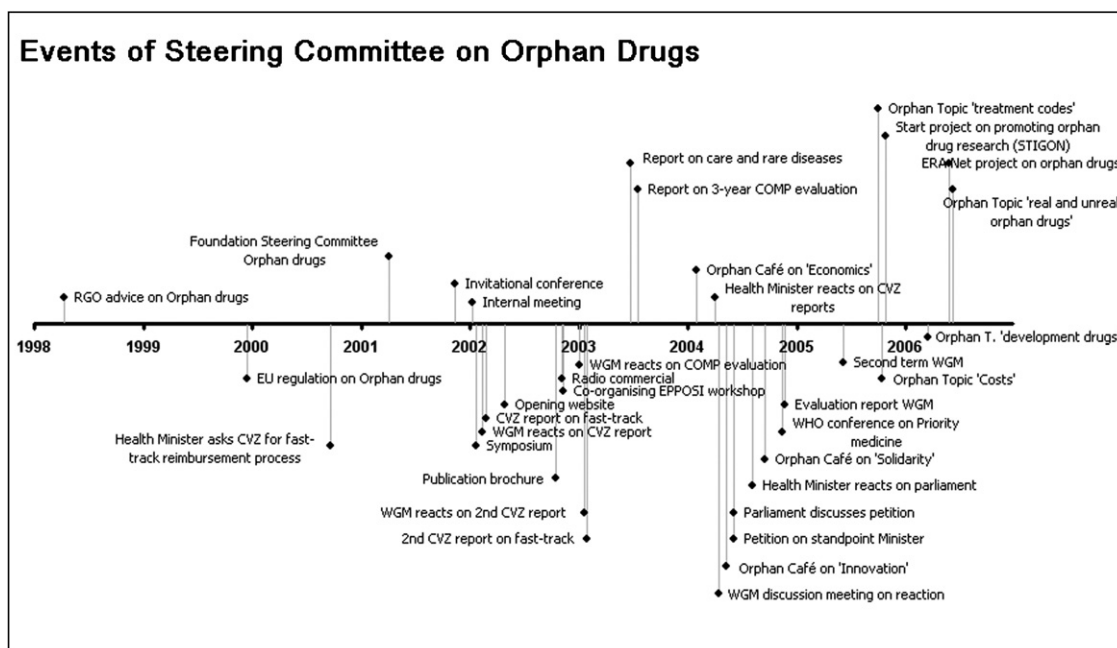

Fig. 6. Most prominent WGM events (1998–2006).

6.1.1. The reimbursement event cycle

The first event cycle, which is fully presented in Appendix A, is about the reimbursement of orphan drugs by public and private health insurance schemes. Orphan drugs have a few disadvantages; most notably, some of them are relatively expensive and because of the low prevalence of rare diseases there are few patients available for clinical trials required for product approval and reimbursement decisions. The Dutch Health Minister acknowledged these drawbacks and asked the National Health Care Insurance Board (CVZ) to investigate possibilities to alleviate them. Direct pressures to deal with the reimbursement issue included the European Union requesting the organisation of the reimbursement of orphan drugs and the actual availability of the first orphan drugs on the Dutch market (two medicines for the treatment of Fabry's disease). Over the next two and a half years (2000–2003), CVZ produced two reports on this issue. WGM got the opportunity to react on concept versions of both CVZ reports and in this way influenced the recommendations. One of the most important recommendations was to finance these medicinal products through the hospitals' research budget. WGM, CVZ and Members of Parliament feared a trade-off between economic and medical benefits and requested another solution, e.g. financing through a *special reimbursement rule* that pays the drugs straight out of the public or private reimbursement scheme. Despite this resistance, the Minister stuck to his opinion of using the hospitals' research budget. A petition initiated by WGM and supported by a large variety of parties, amongst others representatives of hospitals, was filed to the Parliament. The Parliament had a discussion with the Minister following which he commissioned an investigation on the problems expected by the actors in the health care arena. During this investigation he consulted WGM and other stakeholders. In turn, these parties started an exploration of the ways in which rare diseases were treated and orphan drugs administered in academic hospitals. One finding was the growing centralisation of rare disease treatment. Several stakeholders underlined that this would be beneficial to the quality of care of rare disease patients, as had been experienced in the context of haemophilia and Gaucher's disease. Hospitals would be less willing to specialise in a few rare diseases with related expensive drugs, when they were forced to draw on their research budget to finance them.[11] The Minister proved to be amenable to this argument, but because of different reasons, amongst others economic efficiency. He subsequently decided in favour of the special reimbursement rule.

Fig. 7 shows the occurrences of the three central subjects, demands, agenda entries and underlying assumptions, over time. Moreover, the amount of external events is depicted as well. Especially the number of demand statements increases steeply. Furthermore, within the central subject 'demand statements', one can discern the five dimensions coming from Section 2.2 and Table 1: expectations, problems, needs, ideas, and ethical, legal and social impacts (ELSI). The occurrence of these five aspects of demand statements is shown in Fig. 8. Most notably, there are five moments in the cycle when the leaps in demand statements are striking (they are numbered I–V in Fig. 7). Table 3 below illustrates the content of these *demand leaps*. To reflect upon the articulation of demand when following these five leaps, the table also illustrates whether they became more or less concrete and whether there was a change in orientation towards the topic, e.g. in favour of or against a solution for the reimbursement problems of orphan drugs.

The figures and table show that the number of demand statements increased steeply. The demand statements became more focused in the sense that only one aspect of the reimbursement problem became

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[11] It should also be noted that WGM and other stakeholders see this centralisation process more as a bottom-up development, rather than something that should be steered.
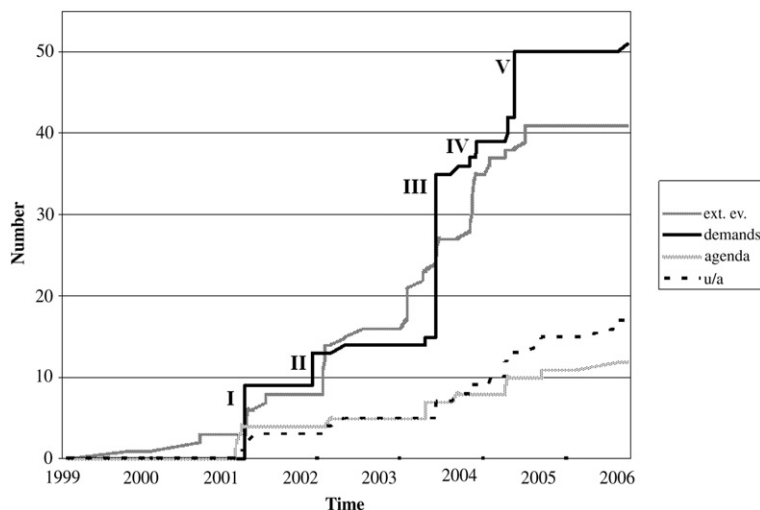
Fig. 7. Cumulative amount of events and statements in the event cycle on reimbursement. Striking demand leaps are denoted with numbers I to V.

central, i.e. financing of orphan drugs that are used in hospitals (intramural). In a petition of June 2004 several solutions and ideas were proposed, e.g. concerning monitoring of rare diseases and setting-up a European co-operation, while in December 2004 only the special reimbursement rule remained and the relating argument of expert centres was added. All the other problems and solutions became supportive of this rule. For example, monitoring of the benefits of orphan drug treatment legitimises its reimbursement and illuminates the existence of centralised expert centres that could become overburdened with orphan drug costs. Moreover, Table 3 shows that within this topic of intramural reimbursement, at first a narrowing-down of ideas took place (leap I to III: special reimbursement rule). Later, under the influence
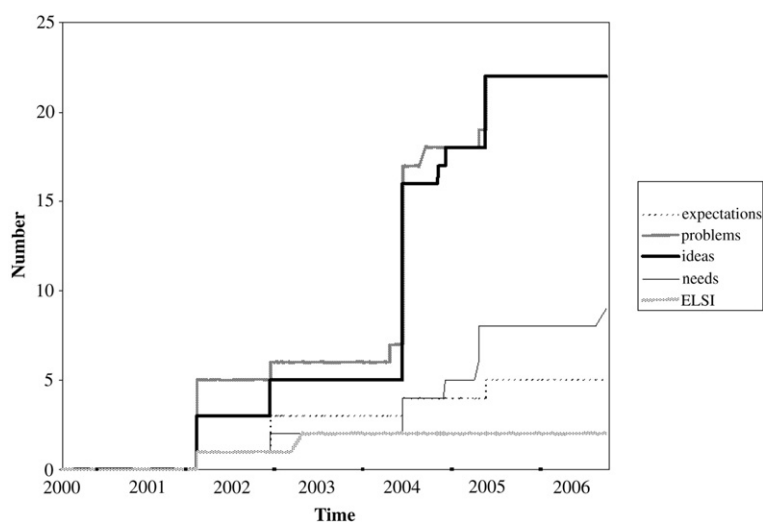

Fig. 8. Cumulative amount of different demand statements.

Table 3
Changes in concreteness and direction of demand statements

Leap	Context	Topics of demand statements	Content more/less concrete	Change in direction
I	WGM reaction first CVZ report	Adequate care and equal rights to quality (solidarity)	–	–
		Problems: clinical evidence, alternative treatments, costs, definitions, procedures that turn out bureaucratic and non-transparent, medicines with no Dutch registration, differences between treatment in and outside hospitals	–	–
		Ideas: stakeholder participation, cooperation with European parties (COMP)	–	–
II	WGM reaction second CVZ report	Reimbursement of intramural medicines through separate reimbursement rule, otherwise: high costs for expert centres	More	No
		Idea: involve academic hospitals in deliberation	More	No
		Transparency is important	Less	No
		Stakeholder participation	No change	No
III	Petition	Separate reimbursement rule: choice of administering drug should not be a financial one	More	No
		Slow availability of drugs, amongst others due to lack of transparency	More	No
		Monitoring benefits of treatment	New	No
		Early tuning of stakeholders' wishes	More	No
		Cooperation with European parties: e.g. through Priority Medicine project	More	No
		Minister wants every doctor to be able to treat patients with rare diseases. However, treatment is not standardised and knowledge is not well diffused. This calls for concentration of treatment.	More	No
IV	Information for debate in Parliament	Solutions for reimbursing intramural orphan drugs: adjust current reimbursement rules, introduce new orphan drug reimbursement rule, appoint expert centres that get special budgets for rare disease treatment, add rare diseases to group of special cases (haemophilia and HIV/AIDS) that have special arrangements	Less	No
V	WGM answers questions asked by Health Ministry	Reimbursement through expert centres with special budgets or through special orphan drug reimbursement rule. Adjusting current reimbursement rules or using academic research budgets are no solution because of steep rising of costs in the future and concentration of treatment.	More	No

of consultation and deliberation with other parties, the scope of this was widened (leap IV: e.g. special financing of expert centres). Since the preparation of the petition, WGM has been more involved with other stakeholders, such as representative bodies of hospitals and insurance companies, as a *spider in the web* (as one WGM member remarked during a meeting). Finally, a special reimbursement rule was selected again (leap V). Also the statements themselves became more focused: in the first instances *the*

Steering Committee wants to be involved in the discussion on the reimbursement of orphan drugs, later it concerned *the design of a separate reimbursement rule for orphan drugs* [as opposed to a more generic one that is valid for all drugs]. Lastly, the orientation of demands showed no changes. To sum up, the demand statements were increasing in number and showed a growing convergence of content. The orientation of demand statements remained the same. Therefore, it can be concluded that in this event cycle demand articulation did occur. In addition, Fig. 8 also gives insight into demand articulation dynamics. While the expectations, ELSI impacts and needs evinced a moderate growth, the ideas and problems seemed to propel each other as they spiralled to a progressive increase. In the statements this surfaced as the constant and explicit linking of problems with ideas.

6.1.2. The R&D event cycle

The second event cycle focuses on research and development of orphan drugs (Appendix B). Programming research was an important issue when installing the WGM. In the report by the Advisory Council on Health Research (RGO), which instigated WGM, the need for coordination, prioritisation and stimulation of this research was mentioned. It was legitimised by stating that orphan drugs would hardly be developed by commercial parties because of small markets and related commercial unattractiveness. The prioritisation of orphan drug R&D was dropped very soon, because it would mean that the government could *de facto* exclude research on certain rare diseases.[12] Meanwhile, other parties kept stressing the importance of coordination and stimulation. From the start, WGM decided to spend the funds that were at their disposal on their primary tasks. What was left was used for small projects that either focused on care of patients with rare diseases or on stimulating research into rare diseases. For the duration of the event cycle, three external pressures were put on WGM that steered the direction of this cycle. Firstly, WGM was approached by European partners to participate in attempts to start a pan-European initiative on rare diseases and orphan drugs. This was inspired by the notion that *orphan drugs could be defined as a volume problem. The solution therefore lies in scaling-up research through European co-operation*. Secondly, two public research funding Dutch institutes (ZonMw and Top Institute Pharma) said that they also wanted to allocate part of their research budget for rare diseases. Thirdly, the STIGON programme, which was intended to stimulate the translation of basic research results into the development of innovative therapies, had one part of its funds specifically allotted to rare and chronic diseases. Because of a lack of success of the rare disease-dedicated part of this programme, WGM decided to submit two proposals to enhance this situation. It consisted of a PhD project on collecting information on orphan drugs and rare disease research in the Netherlands, which could serve as input for setting up a national research subsidy programme, and an 'orphan drug developer' project stimulating companies to work on orphan drugs and rare diseases. The Health Ministry approved these two projects provided that the development of orphan drugs is directly stimulated. Figs. 9 and 10 show the cumulative amount of demand statements for the event cycle on R&D of orphan drugs, in total and subdivided into the different dimensions of demand.

Figs. 9 and 10 show a sharp increase of demands (mostly ideas) and agenda entries. However, contrary to the former event cycle on reimbursement, no clear leaps in statements are visible, with the exception of a leap in ideas around the evaluation of the WGM in 2004. When analyzing the statements themselves, it becomes clear that although the number of demand statements obviously grew, the content remained more

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[12] Although it kept shimmering in the background: during the evaluation some patient groups indicated that they would favour WGM to prioritise between rare diseases.
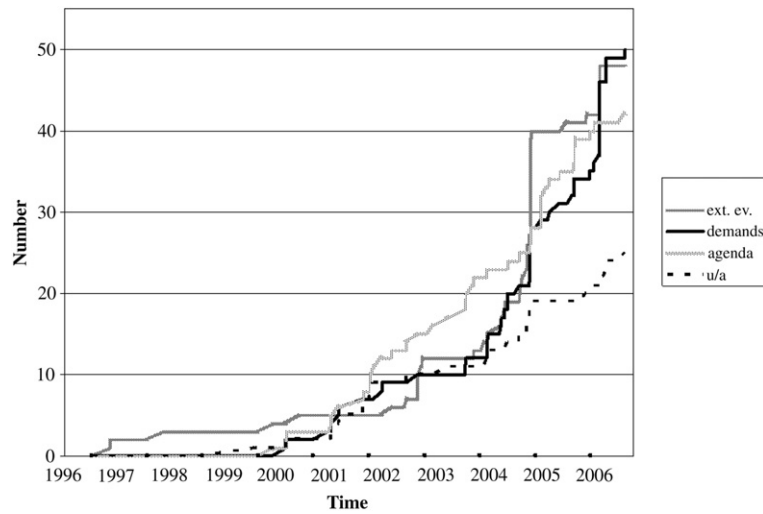
Fig. 9. Cumulative amount of events and statements in the event cycle on R and D of orphan drugs.

or less the same. Thus, the prioritisation of orphan drug R&D was not favoured at the start and did not enter the discussions again. Financial measures to stimulate orphan drugs R&D were discarded at the outset as well. Other stimulating options were attempts to set up (European) networks, which at last resulted in the cooperation in an ERA-Net project. Furthermore, three times an inventory of Dutch orphan drug research was made: in the context of the RGO advice report, a European initiative, and the STIGON-project. At least the last inventory can be seen as a starting point for a national research programme for orphan drug R&D. Such a programme has been an objective from the beginning of WGM as part of the coordination of orphan drug R&D. The programme has often been put on the agenda, but has so far not resulted in concrete results.
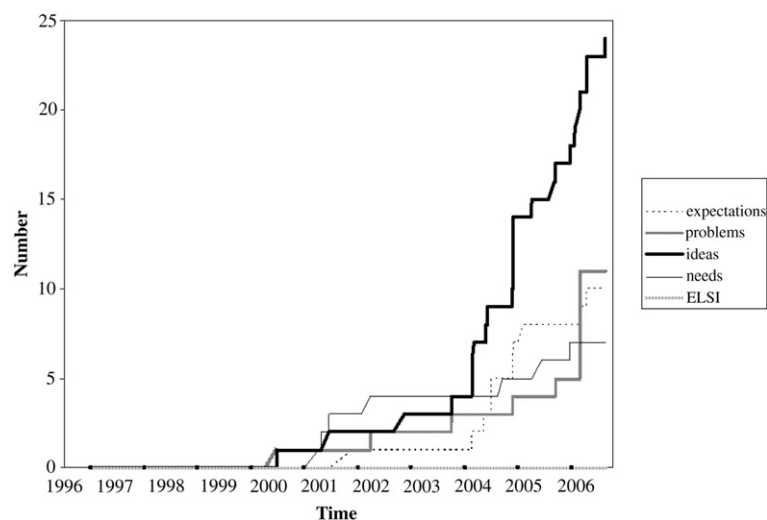

Fig. 10. Cumulative amount of different demand statements.

It can be concluded that although the amount of demand statements steadily increased, it did not lead to a more concrete and convergent focus and orientation. Furthermore, agenda-setting is more prominently present in this event cycle because for a long time WGM knew what to do in the context of research and development, but it did not result into concrete output, e.g. a research programme.

6.1.3. How do demand articulation processes take shape?

Table 3 and Fig. 7 illustrated the five moments in the reimbursement event cycle during which there was a concentration of demand statements. Fig. 11 shows these five leaps (I–V) in the format that was proposed in Fig. 4. In this way, it illustrates the mutual influencing of demand statements, agenda entries, underlying assumptions, and external events.

First-order learning is partially initiated by external parties (a). Clear examples are academic hospitals and patient groups that supported the information contribution to the debate in Parliament in January 2005. Table 3 shows that this contribution led to a widening-up of alternative solutions for financing intramural treatment of rare diseases (leap IV). The influence of external parties shaped the internal agenda of WGM. Developments are mostly introduced to the daily board of WGM (chairman and secretary) that decides to take immediate action (through appointments, letters), puts it on the agenda of the next meeting, or discards it. Sometimes a discussion in a meeting results in agenda entries for the next meeting. The initiators of new agenda entries in the first four years of WGM most of the time were the members of the Steering Committee themselves. They encountered problems in their environment or problems were brought to their attention. But from 2005 onwards, external parties explicitly put forward issues and asked WGM to take action: *In the beginning the Steering Committee did a lot of sowing and rousing, but now a lot of actors come to us. Expectations also increased* (interview result). This can be
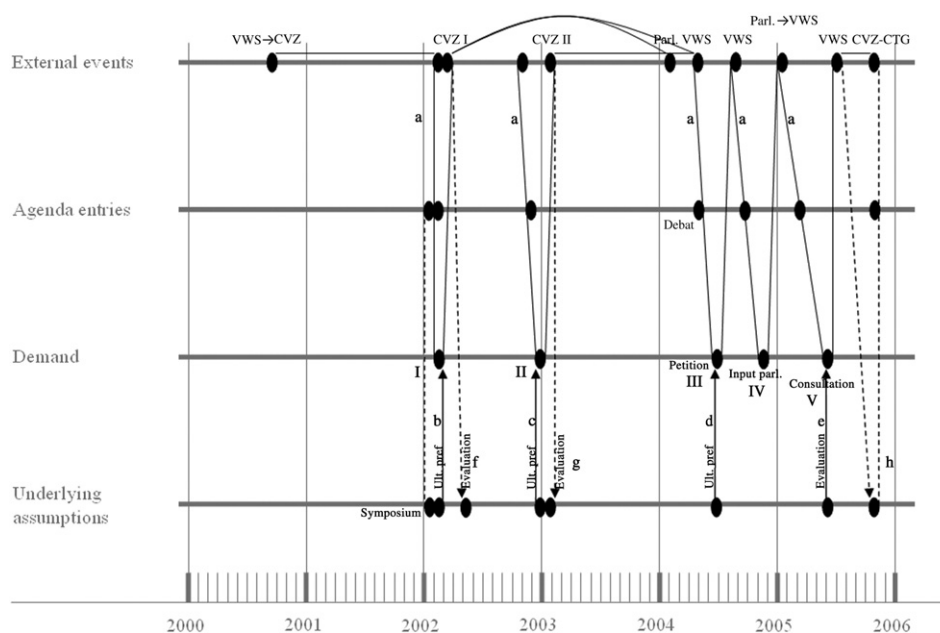

Fig. 11. The interaction between external events, agenda entries, demand elements and underlying assumptions related to the reimbursement event cycle.

seen as a sign of the maturing of WGM as an intermediary organisation. It should be added that this large influence of external parties on the first-order learning of WGM is far from a one-way process. WGM often solicits other parties to give their opinion on a subject; for example, when preparing the input document for the Parliament. Also in the case of the petition, external parties were explicitly approached. Thus, external events/actors (initially) triggered first-order learning.

The underlying assumptions supported the demand statements and agenda entries that were presented above. In this sense, demands were *legitimised* (b–e). The demand statements in the petition run very closely to the underlying preferences of WGM (d), namely that patients and the improvement of their quality of life are central, that people with rare diseases have the same right of treatment as people with more prevalent diseases (solidarity principle), and that new treatments should be available to patients as soon as possible. Furthermore, WGM evaluated and reflected on its contributions and the subsequent impacts. WGM was satisfied with the way in which its opinions were taken up in the first CVZ report (f), while in the second CVZ report WGM's input should have been treated more dominantly according to members of WGM (g). Moreover, WGM found the discussions in Parliament (h) too focused on financial arguments rather than on patient-centred ones, and they considered the input to the consultation round as *a very important operation that could strengthen the role of the Steering Committee* (notes of WGM meeting). Members of WGM also view results of this cycle, of which the special reimbursement rule for orphan drugs is the most notable, as one of their main achievements so far. All in all, the underlying assumptions were highly visible in this event cycle, but they did not change in concreteness, orientation or regarding the content.

In conclusion, the first-order learning influences second-order learning and vice versa, because the same topics are mentioned on different levels. External actors initially trigger this first-order learning and demands are shaped accordingly. This shaping is legitimised by relatively stable ultimate preferences, goals, and objectives of organisations,[13] which tend to change not too often. Frequent changes would amount to a disruptive operation resulting in a repositioning of the organisation, and new foci and priorities.

6.2. Demand articulation in joint construction processes?

The analysed demand articulation processes within WGM did not occur in isolation. Apart from the first-and second-level statements that had already come out of the documents studied, we interviewed representatives of several interacting partners of WGM and asked them about their demands and underlying assumptions on different stages in the event cycle on reimbursement. This led to conclusions on the 'construction states' in which WGM together with other interacting partners were in, on a particular moment in time (Fig. 3).

The event cycle on reimbursement consists of several stages. We focused on five of them that correspond roughly to the five 'leaps' that were present in Table 3.[14] The most prominent interacting partners in this cycle were taken into account and include the Dutch Health Ministry (VWS), the Parliament (Parl), and the National Health Care Insurance Board (CVZ). Fig. 12 below illustrates the states of agreement and disagreement between the first- and second-order levels of WGM, and the three interacting partners in four phases of the reimbursement event cycle.

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[13] Which are closely linked to the reasons for WGM to be established.
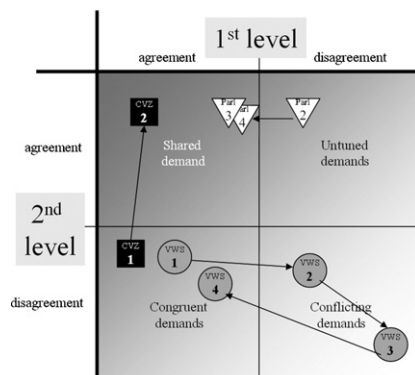[14] We combined leap four and five, because they share the same outcomes.

Fig. 12. Shifts in the level of joint construction between WGM and VWS/Parliament/CVZ (first- and second-order statements of Parliament in stage 1 were not specific to the event cycle, while CVZ explicitly did not have an opinion on the later two stages of the cycle).

Fig. 12 shows that CVZ and the members of Parliament move towards a 'construction state' that can be characterised as shared demand: they agree on both first-and second-order level with WGM at the end. The Health Ministry moves from a congruent demand state to a conflicting demand state and back again. For all three interacting partners, just as for WGM, the demands became more and more articulated over time in the event cycle. This might explain the detour of VWS into the conflicting demand state: the first-and second-order statements were in the first stage not well articulated and therefore, not differentiated enough to be conflicting. Later the differentiation and related conflicts on both levels became more visible (stage 2 and 3). The last stage does not imply another turn of articulation, but a change in orientation on the first-order level: VWS now embraced the idea of a special reimbursement rule for orphan drugs, but used a different legitimisation for this.

Several difficulties of sketching the level of joint construction became clear as well. Firstly, the agreements and disagreements between WGM and the three interacting partners separately, are underlined well in Fig. 12. At the same time no attention is paid to the differences and similarities between the three interacting partners. For example, in stage 1, CVZ and VWS did have conflicting demand statements (first-order). Secondly, the ultimate preferences that are part of the second level were assimilated very well in the analysis. Several parties mentioned solidarity as an important principle that should be the basis of orphan drugs reimbursement policy. Nevertheless, the evaluative second-order statements turned out to be of less value: they are organisation-specific and naturally, a comparison on the level of agreement would not yield interesting results. Thirdly, we did not include 'not-articulating articulations'. In other words, when actors do not address an issue, deliberately or not, and others do, then a comparison on the level of agreement on that issue turns out to be complex. For example, when the Health Ministry finds the principle 'value for money' very important and WGM does not touch this subject, because it stresses 'solidarity' as significant, this indicates either that WGM does not appreciate the former as VWS does, or that they find it of value but they just forgot to mention it.

6.3. What characteristics do the interfaces have?

The third research question deals with the different types of interfaces through which the intermediary organisation communicates with other parties. The methods that are found to be used within these

Table 4
Interface types used and relating methods deployed

Interface type	Times applied	In reimbursement cycle	In R&D cycle	Methods used (only prominent ones)
Consultation	23	2	1	Interviews, letters
Education	7	1	0	Meetings, letters
Presenting, advocating	39	6	0	–
Mediation	9	0	0	Meetings
Coordination	8	5	7	Meetings
Deliberation	26	7	5	Meetings
Anticipation	5	1	0	Conferences, meetings, workshops
Co-production	29	0	5	–

interfaces are diverse and range from promotional activities, such as brochures and a website, to interviews, meetings and scenario studies. The most prominent ones include meetings, writing letters, producing plans and reports, and organising symposia or workshops.

Table 4 shows which interface types were most often deployed, also for the two event cycles separately. Moreover, the table shows which types of methods were used within these interfaces.

7. Conclusions and discussion

This part will provide answers to the three questions introduced in Section 1.

7.1. Do demand articulation processes occur in intermediary organisations dealing with emerging technologies, and if so, how?

In the first (reimbursement) event cycle within WGM, the amount of demand statements rose steeply and converged to one particular problem related to reimbursement. During this process the ideas for solutions narrowed down further in one particular direction, and WGM did not change its orientation (propose versus oppose) towards the options for reimbursing orphan drugs. The second event cycle on orphan drug R&D also showed an increase in the amount of demand statements, but far less convergence regarding the content or orientation.

The reimbursement cycle showed a constant iteration between the problems and ideas from WGM to solve these problems. This is illustrated by the upward spiralling of problems and ideas in Fig. 7. In the R&D cycle the major focus lay on putting problems on the agenda, but ideas to solve related problems were lacking or proved to be problematic. Accordingly, in the reimbursement cycle, articulation of demands is clear, while in the R&D cycle demands are voiced and put on the agenda, but no development and convergence of ideas occurred.

The analysis of first- and second-order learning in the reimbursement cycle yields two important conclusions. Firstly, learning on both levels is interrelated. Secondly, as could be expected from the nature of these types of learning, second-order learning indeed progresses at a less rapid pace than first-order learning. The way in which underlying assumptions, including tasks and functions of an organisation, are outlined, and the way in which issues enter the agenda of an organisation, may reflect the stage of development ('maturity') of an intermediary organisation. Thinking about the underlying assumptions of an organisation, this becomes more important when confronted with an evaluation and a reconsideration of objectives in the light of achievements so far. One major achievement is that actors in the Dutch health

care sector are now more aware of the presence of WGM, partially due to information provision by WGM. This resulted in other parties attempting to put issues on the WGM agenda, whereas in the first four years this had not been observed.

7.2. How did the demand articulation processes develop through the interaction between the intermediary organisation and its interacting partners?

Fig. 12 illustrates that several parties concurred with each other at the beginning and at the end of the reimbursement event cycle. In the meantime the demand statements became more and more articulated and for two of the three interacting partners (CVZ and the Parliament) this implied a move to (more) shared demands. These two actors agree with WGM on both first-and second-order statements. At the same time, through articulation the third actor, the Health Ministry, moved away from a state of congruent demands to a state in which disagreement exists on both first-and second-order issues (state of conflicting demands). Later on, the Ministry moved back to the former state. We conclude that articulation of demands resulted in a temporary growing disagreement on first-and second-order level, followed by a state of increasing (congruent demand) agreement.

7.3. What characteristics do the interfaces have through which demands are communicated?

The analysis of the interfaces used by WGM revealed that giving presentations and lobbying are most prominent in organising communication with other parties. This one-way communication is complemented with consultation (again a one-way type of communication) and co-production and deliberation. The latter two are more focused and offer better opportunities for interactive communication. Anticipation and coordination, which are the most promising ways of organising interfaces for the articulation of long-term oriented demands, is not employed much. This seems to be in line with the observation that the focus of WGM is more on short-term issues, such as reimbursement and regulation; as a consequence in the longer term focused R&D event cycle, these two kinds of interfaces are more present.

7.4. Discussion

In innovation studies, co-construction of technology and society, the related roles of broader sets of involved actors (including intermediaries), and articulation processes of heterogeneous actors, become ever more important. In this paper we conceptualised demand articulation processes in intermediary organisations dealing with emerging technologies. The aim of our study was to develop and apply a conceptual framework to obtain more insights into the role of intermediary organisations in demand articulation concerning emerging technologies. By this we gained an increasing insight into how the actions and interactions of the various actors shape, develop and change emerging technologies.

In an illustrative case study of the Dutch Steering Committee Orphan Drugs (WGM), we analysed demands statements, agenda setting elements, their underlying assumptions, and the type of interfaces used by applying event history analysis methodology. The results of the case study show that the framework and methodology help to understand the dynamics of demand articulation resulting from user involvement through intermediary organisations in innovation processes dealing with emerging

technologies. Till now, demand articulation is often treated as a black box. As a result, many studies in this field wind up with the conclusion that demand articulation is necessary, but do not answer the question how demand articulation could be stimulated. This methodology provides intermediary organisations involved in innovation processes with insights and ideas to play a more effective role in this process, e.g. when uncovering other actors' underlying assumptions and make use of that knowledge in a debate like the one about reimbursement. In particular the methodology proves to be useful to uncover and unravel demand articulation processes within intermediaries in the emerging phase of a technology and reveal how these processes take shape on two levels. In this regard, special attention is paid to (internal) learning about demands and how these demands are based on – or legitimised by – underlying assumptions, such as organisational norms. This was shown in the reimbursement event cycle. By following events and statements over time and look to what extent their content changes, we emphasised the dynamic character of this specific type of learning, and thereby, the demand articulation processes. Furthermore, this internal learning process is supplemented with learning as part of a debate with other stakeholders. It also provides information on how to communicate with them. Besides this analytical part, the framework might also give pointers as to how to improve these processes in intermediary organisations. Important directions include deliberate attempts to change first- and second-order learning, being more reflective about their underlying assumptions and reconsidering agenda-building and/or the communication through interfaces.

The case study also shows that the framework helps WGM to get a better view on its position vis-à-vis other actors in the 'innovation game'. It helps WGM to make clear whether or not, and by whom, WGM is positioned as a valuable stakeholder in this game. Especially knowledge of other stake-holders' underlying assumptions alongside their demands can be of strategic use in a debate. Moreover, as a result of this improved insight, WGM is in a better position to – if necessary – redefine its mission and strategy and make its approaches more effective. What works, what does not? How to put issues on the agenda? In this way WGM is better equipped for the development of a more proactive approach of dealing with emerging technologies and to contribute to attempts to bypass the Collingridge dilemma. A possible result of this enhanced insight and resulting more effective approach could be that WGM is taken (even) more seriously and by this will be able to strengthen its position in the nearby future.

Concerning the joint construction of demands in the interplay between the intermediary and its interacting partners, uncovering the assumptions underlying the second-order learning loop, still needs more attention. Although we took care of most methodological pitfalls, interviewees might have had biased views on the past or are reluctant to admit to unfavourable opinions on past behaviour. A solution is to discuss these issues in a more interactive way, for example in the context of focus groups. Focus groups can also be used to tackle the problem of 'not-articulating articulations': demands that are deliberately not mentioned by actors.

Regarding the interfaces through which communication takes place, we concluded that WGM – at least in the reimbursement case, which closely followed parliamentary decision-making – did not use interface types that had a strategic, long-term focus. Especially for uncertain and controversial aspects of new and emerging technologies, like the orphan drugs future or ethical aspects of stem cell therapy, it is useful to take a longer term perspective and make room for discussions with other stakeholders in a proactive way, without necessarily having a predefined agenda or concrete problems. In this respect, second-order learning takes a more central position. Strategic intelligence methods, such as (constructive) technology assessment [41], are helpful in this regard. They can provide information for deciding on future actions rather than just using one-way communication and internal deliberation. A

lack of (unexpected) demands and visions from others does not result in learning and can even lead to counterproductive results.[15] Moreover, from a methodological stance, there is still room for improvement of the studying interfaces. Informal communication in the present research only is taken along when it is attached to a more formal way of communicating, i.e. when informal demands were stated during a (formal) meeting. Furthermore, the different methods are not all just as expensive, e.g. writing a letter is cheaper than organising a workshop. Although most methods can be used in every interface type, we must admit that some are more prone to be employed in one type than in another. For example, anticipation typically involves conferences and workshop, while consultations imply using questionnaires or interviews.

Other suggestions for refining the developed conceptual framework are the following. Firstly, while studying demand articulation, more – potentially relevant – actors should be included. In this way, it becomes possible to analyse the development of coalitions that hold the same first- and second-order opinions. It would be interesting to see how demand articulation processes between and within these coalitions develop. Secondly, concerning the types of interfaces studied, attention should be paid to the precise nature of these interfaces and to the question whether they are used efficiently. This could, for example, be done by investigating the impact of different interfaces through interviewing the actors with which is communicated through these interfaces, and ask them how they perceive these communication efforts.

With regard to further research, the same analysis could be carried out focusing on other Dutch intermediary organisations starting from a different perspective, such as patient advocacy groups and pharmaceutical industry representatives. The results from these other case studies should be compared with each other, e.g. to compare demand articulation processes in different intermediary organisations. Secondly, while doing this we could focus on intermediary organisations that – in contrast to WGM, which was more focussed on policy-related boundary conditions for a class of emerging technologies – deal with direct influencing and shaping of an emerging technology. Thirdly, the concept of demand articulation in intermediary organisations sketched in this paper presupposes a democratic, deliberative politico-economic tradition and governance culture that is supportive to discourse-based decision-making procedures, both in the public and the private sector, like in the Netherlands. Questions can be asked about the usefulness of this approach in different political cultures. It would be assumed that in advanced technological areas, characterised by complexity and unexplored potential and risk, concerning diverse groups of stakeholders, discourse-based deliberation as described in this paper, is a necessary precondition for successful and competitive innovation trajectories. In this respect the approach explored in this paper might bear relevance beyond the Netherlands.

Acknowledgments

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[15] In this particular case, WGM took up our recommendation and will use strategic intelligence methods, such as focus groups, to help them preparing for an evaluation and a related prospective vision document.

Appendix A. Event cycle of WGM concerning reimbursement of orphan drugs

Date	Event	Statement
20-9-2000	Health Minister asks Health Care Insurance Board (CVZ) to look into reimbursement of orphan drugs	Rare diseases have small patient populations and safety might be difficult.
15-2-2002	WGM reacts on concept version of CVZ report (letter)	The definitions and procedures have not been well defined yet: WGM fears bureaucracy and delays. WGM asks for direct stakeholders to be involved in the procedures. WGM calls for a European-wide reimbursement scheme.
28-2-2002	CVZ report	Reimbursement admission requirements for orphan drugs are the same as for non-orphan ones, but allowances are made for the special characteristics of orphan drugs.
20-11-2002	WGM reacts on concept version of 2nd CVZ report (in an internal meeting)	The solution of paying intramural orphan drugs through the research budget of academic hospitals is seen as unwanted: soaring costs can lead to unwanted trade-offs between economic and health benefits. Transparency and continuous character of policy should be propagated, as well as advising role for stakeholders in regulatory and reimbursement decisions. WGM advises to consult other parties as well (e.g. the academic hospital representative).
12-12-2002	WGM reacts on concept version of 2nd CVZ report based on the discussion in the internal meeting (letter)	Same as above.
30-1-2003	2nd CVZ report	Discusses necessity of pharmaco-economic studies for orphan drugs and details of reimbursement process of orphan drugs. CVZ recognises potential financial problems when rare diseases are treated concentrated in a few hospitals and if these should be financed through their research budget. There should be a separate reimbursement rule for rare diseases that guides financing by national health reimbursement scheme instead of through academic hospital research budgets.
28-1-2004	Parliament discusses orphan drugs	MPs emphasise their preference to a separate reimbursement rule. The Minister does not react, while the official response of the Ministry on the two CVZ reports is in preparation.
7-4-2004	Health Minister reacts on CVZ reports	The Minister's opinion is in broad outlines in correspondence with the proposed reimbursement strategy for orphan drugs. Notable difference: he refuses to deploy the separate rule and opts for finance through the more standardised codes and the research budget of academic hospitals.
19-4-2004	WGM discussion meeting on Minister's standpoint	Initially the COMP report should have been discussed during the meeting, but in advance it was chosen to focus the attention to the Health Minister's reactions on the CVZ reports. It is discussed whether it would be useful to present the Parliament a petition. WGM decides in favour of this.
8-6-2004	Petition	WGM supported by other organisations calls for a separate rule, more European collaboration on research,

Appendix A (*continued*)

Date	Event	Statement
		reimbursement and regulation, monitoring of benefits of orphan drugs, and more coordination of parties involved.
11-8-2004	Health Minister reacts on petition (letter)	The Minister rebounds a few points (monitoring and coordination can be a good task for WGM), dismisses the points on the separate rule, and indicates that European collaboration is devised through a special program.
27-1-2005	Parliament discusses reimbursement orphan drugs	Again the separate rule and the research budget of hospitals are brought to the fore. The Minister refuses to change his plans, but will investigate the matter in consultation with stakeholders.
4-4-2005	Consultation of WGM and other actors on reimbursement orphan drugs	WGM (and representatives of academic hospitals and insurance companies) are consulted. WGM and the academic hospital representatives perform additional investigations. It includes the notion that (bottom-up) centralisation of care for some rare diseases is taking place and that this can be beneficial to the quality of care (as appeared to be the case in the context of, for example, haemophilia and Gaucher's disease). In this context, the drawback of making use of the research budget is even more striking.
29-6-2005	Health Minister reacts on parliamentary discussion based on consultation (letter)	The Health Minister acknowledges the latter point, but more from an economic point-of-view and chooses for a separate reimbursement rule for orphan drugs.

Appendix B. Event cycle of WGM concerning R&D of orphan drugs

Date	Event	Statement
28-4-1997	Minister asks RGO for advice on orphan drugs	Coordination, prioritisation, stimulating research. Content wise, organisational and commercial aspects. Special attention to US Orphan Drug Act.
10-4-1998	RGO advices	National structure, European committee that prioritise orphan drugs (OD), financial stimulating measures
1999 and 2000	Preparation of national structure for orphan drugs (i.e. Steering Committee)	Coordinate and stimulate (infrastructure for) research, inventory of OD research, point of contact network, inventory is difficult, financial stimulation is necessary. The government does not support tax cuts for orphan drug R&D.
16-11-2001	Invitational conference	One of the six important objectives of WGM should be paying attention to research and development of orphan drugs
24-11-2001	WGM subsidises projects	WGM decides to use its total budget on its primary tasks. The remaining amount of money is then spent on projects that deepen patients' knowledge and stimulate scientific projects on orphan drug and rare disease research.
25-1-2002	Symposium	The results of the invitational conference and WGM's internal deliberation reinforce focus on stimulating orphan drug R&D.

Appendix B (*continued*)

Date	Event	Statement
11-11-2002	European Programmes for 6th Framework	WGM participates in two initiatives (French and Italian) for the founding of Networks of Excellence for Orphan Drugs. These initiatives did not succeed.
14-11-2003	ZonMw and Health Ministry give WGM money for projects on orphan drug R&D	Programme for stimulation of innovative drug R&D in the Netherlands (STIGON) allocated some funds for stimulating orphan drug R&D. The health research-funding agency ZonMw and the Dutch Health Ministry decide to fund two pilot projects set up by WGM. WGM chooses for a project on making an inventory of orphan drug R&D as a starting point of setting up a research subsidy programme, and a project that stimulates the development of orphan drugs proactively (an 'orphan drug developer'). Uncertainty on subsisting of WGM during the evaluation delays the start of these projects.
18-11-2004	WHO conference on 'Priority Medicines for Citizens of Europe and the world'	Objectives centred on the public prioritisation of drug research and development achievements. Orphan drugs become a crosscutting theme. WGM contributes to the discussion by publishing a background paper.
22-11-2004	Evaluation of WGM	The gap between research and clinical application is one of the main problems with OD. WGM have emphasised the availability of OD, while R&D of these kind of drugs is somewhat neglected. The Health Ministry therefore indicates that WGM should pay more attention to this. This should lead to a subsidy programme for orphan drug research.
4-2-2005	WGM reacts on evaluation	WGM subscribes to the views as put forward in the evaluation report. It emphasises that stimulation and monitoring of R&D is important, while coordination is impossible.
1-12-2005	ZonMw and WGM co-apply for a part in an ERA-Net Project	The EU honours the ERA-Net Project on rare diseases (E-Rare) in its second attempt. WGM is responsible for the work package on bridging fundamental and applied research.
23-2-2006	WGM deliberates with several boards of academic hospitals on a research programme for orphan drugs	Question marks are placed over national coordination of research, the viability of rare disease research, and the appropriateness of a research subsidy programme as the right innovation measure.

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